Annex 8: Evidence tables

PART A: Ovarian response testing

1. Pre-stimulation management

KEY QUESTION: IS THE ASSESSMENT OF THE PREDICTED RESPONSE TO OVARIAN STIMULATION SUFFICIENTLY RELIABLE?

P	I	C	O
Women undergoing IVF/ICSI	AFC AMH Basal FSH Inhibin B Basal oestradiol Age BMI	Compare against - other tests - age alone	Test Accuracy for predicting Poor response Hyper-response ROC curves Cut-offs False positive/false negative results

1.1 ANTRAL FOLLICLE COUNT (AFC)

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Diagnostic test evaluated Reference standard test Include: Time interval and treatment	Prevalence	Accuracy (Se, Sp, PPV, NPV, LR+, LR-)	Reproducibility	Authors conclusion	Comments
Broer, S. L., Dolleman, M., van Disseldorp, J., Broeze, K. A., Opmeer, B. C., Bossuyt, P. M., Eijkemans, M. J., Mol, B. W. and Broekmans, F. J. Fertil Steril. 2013; 100 (2): 420-9.e7. (23721718)	SR	1023 patients (32 studies)	Ovarian response testing in combination with patient characteristics for prediction of excessive response		The ROC analysis showed high accuracy for AMH (AUC 0.81, 95% CI 0.76–0.87) and for AFC (AUC 0.79, 95% CI 0.74–0.84), but only a moderate accuracy for FSH (AUC 0.66, 95% CI 0.60–0.73). a model incl. age, AFC, and AMH (AUC 0.85) had a significantly higher predictive accuracy than a model based on age alone (AUC 0.61; P<.001).		Both AFC and AMH clearly add value to female age alone in the prediction of excessive response. AMH and AFC in concert have high predictive accuracy, even without adding female age. The results also indicate that the performance of the ORTs may vary across patient subgroups, as determined by female age especially.	
Broer, S. L., van Disseldorp, J., Broeze, K. A., Dolleman, M., Opmeer, B. C., Bossuyt, P., Eijkemans, M. J., Mol, B. W. and Broekmans, F. J. Hum Reprod Update. 2013; 19 (1): 26-36. (23188168)	SR	5705 patients (28 studies)	Ovarian response testing in combination with patient characteristics for prediction of poor response and nonpregnancy		high accuracy for AMH (AUC 0.78: 95% CI 0.72–0.84) and for AFC (AUC 0.76: 95% CI 0.70–0.82) in predicting poor response, but only a moderate accuracy for FSH (AUC 0.68: 95% CI 0.61–0.74; Table III). In predicting pregnancy after IVF, all three ORT had only a very small or no predictive effect (Table II). The AUC were 0.53, 0.50 and 0.55 for FSH, AFC and AMH, respectively (Table III).		Both AFC and AMH clearly add value to female age in the prediction of poor ovarian response in IVF. Comparably good predictions can be made with either AMH or AFC alone, without using female age. Age was the strongest single predictor of pregnancy after IVF, with moderate accuracy (AUC 0.57).	

Arce, Jc, Marca, A, Mirner, Klein B, Nyboe, Andersen A and Fleming, R. Fertil steril. 2013; 99 (6): 1644-53. (23394782)	RCT CS	Secondary analysis of the Megaset trial 749 women treated with 150 IU FSH + GnRH antagonist fixed scheme control	AMH and AFC were measured with the DSL kit and ultrasound respectively		AFC auc for poor and hyper response were 0.741 and 0.636 resp.		AMH was superior to AFC in predicting extremes of ovarian response	Secondary analysis of RCT, cohort in this sense.
Kwee, J., Elting, M. E., Schats, R., McDonnell, J. and Lambalk, C. B. Reprod Biol Endocrinol. 2007; 5 9. (17362511)	RCT CS	110 women performing an IVF cycle	AFC, ovarian volume, EFORT, Clomiphene challenge test were measured by ultrasound. AFC was considered the total number of 2-10 mm Poor was < 6 and hyper > 20 oocytes		AFC ROCauc for POR prediction was 0.83. at the best cut-off (<6) the sensitivity41% was the specificity was 95% and the PPV 75%. For hyper response the ROCauc was 0.92. The best cut-off 14 was associated to sensitivity, specificity and PPV as follows: 82,89 and 58%		AFC performs well as a test for ovarian response being superior or at least similar to complex expensive and time consuming endocrine tests, probably most applicable in general practise	Secondary analysis of RCT, cohort in this sense.
Lan, V. T., Linh, N. K., Tuong, H. M., Wong, P. C. and Howles, C. M. Reprod Biomed Online. 2013; 27 (4): 390-9. (23953069)	RCT CS	N=348 aged <40 years body mass index <28 kg/m2), early follicular phase (day 2–4) basal FSH serum concentrations <12 IU/l,	AFC and AMH measured. Methodology for both two measurements was not specified. Poor was < 3 and hyper > 20 oocytes		Area under the curve (AUC) values and 95% confidence intervals (CI) for AFC for predicting hyporesponse to ovarian stimulation was 0.80 (0.73–0.89) (P < 0.0001). For the prediction of hyperresponse (>20 oocytes retrieved), AUC values and 95% CI were statistically significant for AFC (0.81, 0.74–0.88) Cut off values were 6 and 125 respectively		With subtle differences, both AMH and AFC appear to have the ability to predict poor ovarian response and guide the starting dose of rFSH	Secondary analysis of RCT, cohort in this sense.

Oehninger, S, Nelson, Sm, Verweij, P and Stegmann, Bj. Reproductive Biology and Endocrinology. 2015; 13 (1): (26520396)	RCT CS	infertile women aged 35–42 years (n = 694). Pursue trial. Infertile women aged 35–42 years with a body weight of ≥50 kg and body mass index (BMI) ≥18 and ≤32 kg/m2	AFC and other biomarkers were measured before corifollitropin administration Low response defined as < 6 oocytes, High response as >18 oocytes. AMH was measured with Gen II. Not specified the AMH methodology		Prediction of low: ROCauc 0.88. Prediction of high: ROCauc 0.88 They developed a combined model including age, AFC, AMH, FSH and cycle length		in women aged 35 to 42 years undergoing ovarian stimulation with corifollitropin alfa in a GnRH antagonist protocol, AMH, AFC and age at the start of stimulation were prognostic for both high and low ovarian response, in addition to FSH for high ovarian response and menstrual cycle length for low ovarian response.	Secondary analysis of RCT, cohort in this sense.
Bancsi, L. F., Broekmans, F. J., Eijkemans, M. J., de Jong, F. H., Habbema, J. D. and te Velde, E. R. Fertil Steril. 2002; 77 (2): 328-36. (11821092)	CS	120 women (112 conventional IVF, 18 ICSI Incl.: [1] a regular spontaneous menstrual cycle; [2] presence of both ovaries; [3] no evidence of endocrine disorders Accepted to 45 years Subdivided also to in further analysis on: poor (26) and normal responders (n=84) and on: age<41, and/or FSH<15 (n=92) age>41, and/or FSH>15 (n=28) Setting: One center,	The number of antral follicles and the total ovarian volume by ultrasound, basal levels of FSH, E2, and inhibin B on cycle day 3. The poor response was defined as: [1] collection of fewer than four oocytes at retrieval or [2] cycle cancellation because of impaired follicular reaction (< 3 follicles) in response to exogenous gonadotropins. High response was defined as the collection of >20 oocytes at retrieval		The antral follicle count appeared to have the best discriminative potential for poor response, expressed by the largest ROC AUC of 0.87, FSH 0.04, Inhibin B 0.77		1.The number of antral follicles is the best basal marker of ovarian reserve in terms of predicting poor response in IVF. 2.Addition of basal FSH and inhibin B levels to a logistic model with the antral follicle count significantly improved the prediction of poor response;	Addition of FSH to AFC improves prediction of poor response
Bancsi, L. F., Broekmans, F. J., Looman, C. W., Habbema, J. D. and te Velde, E. R. Fertil Steril. 2004; 81 (1): 35-41. (14711542)	CS	130 women All patients met the following criteria: [1] regular spontaneous menstrual cycle (25–35 days); [2] presence of both ovaries; [3] no evidence of endocrine disorders (normal levels of TSH, T, androstenedione (A), and PRL)	Poor response: <4 oocytes at retrieval		1st cycle AFC: ROC-AUC: 0.87 Mean AFC: ROC-AUC: 0.87		ultrasound-based antral follicle counts seem to be a reliable tool for the assessment of ovarian reserve and studies on the prediction of poor ovarian response to exogenous gonadotropins	

Elgindy, E. A., El-Haieg, D. O. and El-Sebaey, A. Fertil Steril. 2008; 89 (6): 1670-6. (17658520)	CS	33 women, Age <38y D3 FSH <10IU/L BMI: 18-29 kg/m2	AMH, FSH and LH, AFC, mean ovarian volume	9/33 poor responders	ROC-AUC 0.94 (95% CI 0.85-1.018) for poor response			
Jayaprakasan, K., Al-Hasie, H., Jayaprakasan, R., Campbell, B., Hopkisson, J., Johnson, I. and Raine-Fenning, N. Fertil Steril. 2009; 92 (6): 1862-9. (18973895)	CS	141 patients entering IVF programme, under 43 years with FSH < 12 IU/L	Ultrasound measurement. No definition of AFC Poor response was defined as < 4 oocytes		41 patients were PORs AFC had a ROCauc 0.88. At the best cut-off (AFC=11) the sensitivity, specificity and positive likelihood ratio were 83%,83% and 4.9 respectively		AFC had a very good performance in predicting POR	
Jayaprakasan, K., Campbell, B., Hopkisson, J., Johnson, I. and Raine-Fenning, N. Fertil Steril. 2010; 93 (3): 855-64. (19046583)	CS	Prospective study on 150 patients in an IVF clinic	Hormonal and endocrine markers were measured		AFC AUC 0.935 for prediction of poor response		AMH and AFC were the most useful predictors of retrieved oocytes	
Khairy, M., Clough, A., El-Toukhy, T., Coomarasamy, A. and Khalaf, Y. Reprod Biomed Online. 2008; 17 (4): 508-14. (18854104)	CS	148 women entering IVF	Ultrasound measurement of follicles Between 2 and 10 mm POR defined as < 4 oocytes		23 women had POR The AFC prediction of POR: ROCauc 0.79 The best cut-off was < 11, with a Likelihood ratio of 5.4 (post-test probability of POR 50%)		AFC had a good performance in predicting POR. No relevant contribution of adding other variables	
Mutlu, M. F., Erdem, M., Erdem, A., Yildiz, S., Mutlu, I., Arisoy, O. and Oktem, M. J Assist Reprod Genet. 2013; 30 (5): 657-65. (23508679)	CS	192 patients entering IVF cycle Prospective study	AMH and AFC predictive value on ovarian response after stimulation in IVF programs and live birth rates compared with age and basal FSH		Age was related to ovarian response. The ROCauc prediction of poor response was 0.76 (0.68-0.84). OR was 1.21 (1.12-1.3) Sensitivity 30.6%, specificity 96.5% AMH and AFC were superior to AFC		AFC is better than AMH in predicting ovarian response; they although show both limitations in predicting live births; age is the best predictor for live birth rates (OR 0.92 (0-86-0.99)	

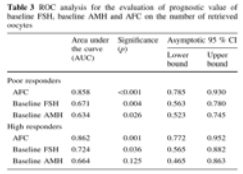
Penarrubia, J., Peralta, S., Fabregues, F., Carmona, F., Casamitjana, R. and Balasch, J. Fertil Steril. 2010; 94 (7): 2590-5. (20400077)	CS	104 women in the IVF programme (25-41 yrs.) healthy and regular cycles	Ultrasound biomarkers measurement (AFC 2-10mm) + some hormonal markers (Inhibin B, FSH and oestradiol). Poor response defined as < 4 oocytes or cancellation for low follicular growth		AFC predicted POR (ROC auc 0.9). Sensitivity 80.7% Specificity 83.3%		AFC and inhibin b have the same, good, performance of predicting ovarian response	
Soldevila, P. N., Carreras, O., Tur, R., Coroleu, B. and Barri, P. N. Gynecol Endocrinol. 2007; 23 (4): 206-12. (17505940)	CS	327 patients entering IVF program Prospective study	Predictive value of AFC on ovarian response to stimulation and pregnancy, and its comparison with other predictive parameters of ovarian reserve such as basal FSH and age		AUC of AFC: 0.73 (95% CI 0.67-0.77) for prediction of poor response.		AFC correlates negatively and statistically significantly with age, basal FSH and LH.	
Tolikas, A., Tsakos, E., Gerou, S., Prapas, Y. and Loufopoulos, A. Hum Fertil (Camb). 2011; 14 (4): 246-53. (22088130)	CS	Prospective study on 90 women	AMH, FSH and AFC were measured. AMH was measured by DSl assay. No specification for AFC. Poor was for <4 oocytes. High response was for > 12 oocytes		AFC predicted POR better than AMH (ROC auc 0.8 vs 0.7) A cut-off value of AFC=4.50 gives 72.4% sensitivity, 80.3% specificity, 63.6% PPV (positive predictive value) and 86% NPV (negative predictive value) for prognosis of poor response		AFC was a good predictor of ovarian response	
Tsakos, E., Tolikas, A., Daniilidis, A. and Asimakopoulos, B. Arch Gynecol Obstet. 2014; 290 (6): 1249-53. (25001569)	CS	Prospective study on 105 women. 25-45 years of age, regular cycles. Entering IVF	Markers were measured				AFC has better diagnostic performance than AMH and age in predicting the extremes of ovarian response	

Table 3 ROC analysis for the evaluation of prognostic value of baseline FSH, baseline AMH and AFC on the number of retrieved oocytes

	Area under the curve (AUC)	Significance (p)	Asymptotic 95 % CI	
			Lower bound	Upper bound
Poor responders				
AFC	0.858	<0.001	0.785	0.930
Baseline FSH	0.671	0.004	0.563	0.780
Baseline AMH	0.634	0.026	0.523	0.745
High responders				
AFC	0.862	0.001	0.772	0.952
Baseline FSH	0.724	0.036	0.565	0.882
Baseline AMH	0.664	0.125	0.465	0.863

1.2 ANTI-MÜLLERIAN HORMONE (AMH)

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Diagnostic test evaluated Reference standard test Include: Time interval and treatment	Prevalence	Accuracy (Se, Sp, PPV, NPV, LR+, LR-)	Reproducibility	Authors conclusion	Comments
Broer, S. L., Dolleman, M., van Disseldorp, J., Broeze, K. A., Opmeer, B. C., Bossuyt, P. M., Eijkemans, M. J., Mol, B. W. and Broekmans, F. J. Fertil Steril. 2013; 100 (2): 420-9.e7. (23721718)	SR	N 4786 patients (32 studies) Model building (all ORT 1023 patients) Study characteristics and assays differed per study but corrected for in random intercept logistic regression models.	IPD meta-analyses Ovarian response testing in combination with patient characteristics for prediction of excessive response Excessive response > 15 oocytes	Normal responders N= 3892 Excessive responders N= 894	AMH OR 1.61 (1.48-1.76), p value < 0.001 The ROC analysis showed high accuracy for AMH (AUC 0.81, 95% CI 0.76–0.87) A model incl. age, AFC, and AMH (AUC 0.85) had a significantly higher predictive accuracy than a model based on age alone (AUC 0.61; P<.001).		Both AFC and AMH clearly add value to female age alone in the prediction of excessive response. AMH and AFC in concert have high predictive accuracy, even without adding female age. The results also indicate that the performance of the ORTs may vary across patient subgroups, as determined by female age especially.	
Broer, S. L., van Disseldorp, J., Broeze, K. A., Dolleman, M., Opmeer, B. C., Bossuyt, P., Eijkemans, M. J., Mol, B. W. and Broekmans, F. J. Hum Reprod Update. 2013; 19 (1): 26-36. (23188168)	SR	5705 patients (28 studies) 4170 patients for poor response analysis Model building (all ORT 617 patients) Study characteristics and assays differed per study but corrected for in random intercept logistic regression models.	IPD meta-analysis Ovarian response testing in combination with patient characteristics for prediction of poor response and nonpregnancy Poor response ≤ 4 oocytes	Poor response N= 893 (21%) Normal response N = 3277 (79%)	AMH OR 0.50 (0.41-0.60), p value < 0.001 The ROC analyses showed high accuracy for AMH (AUC 0.78: 95% CI 0.72–0.84) A model including age, AFC and AMH had a significantly higher predictive accuracy than a model based on age alone (AUC 0.80 vs 0.61; P < 0.001). This model is not better than single use of AMH or AFC.		Both AFC and AMH clearly add value to female age in the prediction of poor ovarian response in IVF. Comparably good predictions can be made with either AMH or AFC alone, without using female age.	

Andersen, An, Witjes, H, Gordon, K and Mannaerts, B. Human reproduction (Oxford, England). 2011; 26 (12): 3413-23. (21954280)	RCT CS	442 patients Age 18-39 years BMI ≤ 32 kg/m2 Regular cycle 24-35 days No endocrine abnormalities FSH levels ≤ 12 IU/L rFSH 200 IU/day GnRH antagonist Randomized for pre-treatment with OC or no pre-treatment AMH assay DSL	RCT for OC or no OC pre-treatment. For this question cohort study AMH, AFC, FSH in the prediction or ovarian response Poor response < 6 oocytes Excessive response > 18 oocytes	Incidence low and excessive response not stated	Low response Total group: AUC 0.84 OC group: 0.84 Non-OC group: 0.88 High response Total group: 0.77 OC group: 0.74 Non-OC group: 0.82		AMH appeared to be an important predictor for the number of oocytes retrieved.	Secondary analysis of RCT, cohort in this sense.
Arce, Jc, Marca, A, Mirner, Klein B, Nyboe, Andersen A and Fleming, R. Fertil steril. 2013; 99 (6): 1644-53. (23394782)	RCT CS	749 women, (n=375 recombinant FSH, n=374 hp-HMG) aged 21 to 34 years, serum follicle-stimulating hormone (FSH) level 1–12 IU/L and antral follicle count (AFC) >10. mild male factor or unexplained fertility	Relation: AMH at start of stimulation and ovarian response and treatment outcome.	IVF population	AMH accounted for 85%, FSH for 14%, and inhibin B and AFC for <1% each of the explained variation in oocyte yield. Multiple regression model revealed that AMH (P<.001) and FSH (P<.001) were statistically significant predictors of the number of oocytes retrieved, but AFC (P=.125) and inhibin B (P=.706) were not		AMH is the best predictor for identifying patients with poor and high ovarian response	Secondary analysis of RCT, cohort in this sense.
Lan, V. T., Linh, N. K., Tuong, H. M., Wong, P. C. and Howles, C. M. Reprod Biomed Online. 2013; 27 (4): 390-9. (23953069)	RCT CS	382 patients Age < 40 years BMI < 28 kg/m2 FSH ≤ 12 IU/L GnRH agonist protocol rFSH individualized dosage between 150 – 375 IU/day. AMH assay?	RCT comparing dose algorithms with AMH or AFC. Cohort for prediction of ovarian response Poor response < 3 oocytes Excessive response > 20 oocytes	Incidence total group not stated	Poor response AMH: AUC 0.88 (0.81-0.95), Excessive response AMH AUC 0.76 (0.69-0.83)		AMH is a good predictor of poor ovarian response.	Secondary analysis of RCT, cohort in this sense.

Oehninger, S, Nelson, Sm, Verweij, P and Stegmann, Bj. Reproductive Biology and Endocrinology. 2015; 13 (1): (26520396)	RCT	686 patients, Age 35-42 yrs. BMI ≥18 and ≤ 32 kg/m2 PCOS excluded GnRH antagonist 150 ugr corifollitropin alfa or rFSH 300 IU/day AMH assay gen II	RCT comparing corifollitropin alfa vs rFSH, cohort study for predicting ovarian response with AMH, AFC and FSH. Poor response < 6 oocytes Excessive response > 18 oocytes	Low response N = 159 (23.2%) Excessive response N = 97 (14.1%)	Low response OR 0.19 (0.12-0.28), P < 0.0001 AMH AUC 0.871 High AMH OR 1.93 (1.58-2.36) P < 0.0001 AMH AUC 0.864		In older women AMH is a significant predictor of ovarian response	
Elgindy, E. A., El-Haieg, D. O. and El-Sebaey, A. Fertil Steril. 2008; 89 (6): 1670-6. (17658520)	CS	33 women, Age <38y D3 FSH <10IU/L BMI: 18-29 kg/m2	AMH, FSH and LH, AFC, mean ovarian volume	9/33 poor responders	ROC-AUC 0.9 (95% CI 0.8-1.006) for poor response			
Heidar, Z., Bakhtiyari, M., Mirzamoradi, M., Zadehmodarres, S., Sarfjoo, F. S. and Mansournia, M. A. J Endocrinol Invest. 2015; 38 (9): 1007-15. (25981081)	CS	188 women No endocrine disease No PCOS GnRH agonist uFSH AMH assay GEN II	Prospective cohort study of AMH in ovarian response Poor ovarian response ≤ 3 oocytes Excessive ovarian response ≥ 12 oocytes	No ovarian response N 15 (7.8%) Poor response N = 22 (11.4%) Excessive response N = 53 (28.2%)	Poor response AMH OR 0.36 (0.19-0.68) AUC 0.76 (0.66-0.86) Sensitivity 0.72 (0.63-0.81) Specificity 0.81 (0.60-0.93) Excessive response AMH OR 1.71 (1.09-2.7) AUC 0.69 (0.60-0.77) Sensitivity 0.57 (0.43-0.69) Specificity 0.73 (0.63-0.81)		AMH levels showed to be a good test to discriminate between different ovarian responses.	
Jayaprakasan, K., Campbell, B., Hopkisson, J., Johnson, I. and Raine-Fenning, N. Fertil Steril. 2010; 93 (3): 855-64. (19046583)	CS	Prospective study on 150 patients in an IVF clinic Age: <41y First cycle IVF	FSH, LH, E2, inhibin B, AMH Poor response <4 oocytes AMH assay: MIS/AMH ELISA		ROC-AUC 0.91 for prediction of poor response		AFC and AMH are the most significant predictors of the number of oocytes retrieved and of poor ovarian response.	

Li, R, Gong, F, Zhu, Y, Fang, W, Yang, J, Liu, J, Hu, L, Yang, D, Liang, X and Qiao, J. Reproductive biomedicine online. 2016; 33 (4): 506-512. (27502068)	CS	615 patients Normal ovulatory cycles No PCOS GnRH agonist rFSH (+rLH) AMH assay gen II	Prospective cohort study for AMH as ovarian response predictor. Poor ovarian response ≤ 5 oocytes Excessive ovarian response > 15 oocytes		Poor response OR 0.61 AUC-ROC 0.70 (0.60-0.80). cut-off value 1.1 ng/ml sensitivity: 52.27%, specificity: 87.23% Excessive response: OR 1.65 AUC-ROC curve is 0.76 (0.72-0.80) Cut off 2.6 ng/ml with sensitivity: 81.28%, specificity: 59.51%.		serum AMH concentration was positively correlated with the number of oocytes and AMH concentration could predict the ovarian response.	
Mutlu, M. F., Erdem, M., Erdem, A., Yildiz, S., Mutlu, I., Arisoy, O. and Oktem, M. J Assist Reprod Genet. 2013; 30 (5): 657-65. (23508679)	CS	192 patients entering IVF cycle Prospective study Age: 18-44y No endocrine disorders	AMH and AFC predictive value on ovarian response after stimulation in IVF programs and live birth rates compared with age and basal FSH		AMH AUC-ROC: 0.86 (95% CI 0.80-0.92) for discriminating between poor and normal response		ROC analysis revealed that AFC was the most accurate of all tests in predicting poor response to ovarian stimulation; AUC for AMH was lower than AFC but better than basal FSH and age.	
Tolikas, A., Tsakos, E., Gerou, S., Prapas, Y. and Loufopoulos, A. Hum Fertil (Camb). 2011; 14 (4): 246-53. (22088130)	CS	Prospective study on 90 women. Age: 25-45y no serious endocrinology disorders BMI: 19-30	AMH, FSH and AFC were measured. AMH was measured by DSl assay. No specification for AFC. Poor was for <4 oocytes. High response was for > 12 oocytes		Baseline AMH ROC: 0.7 (95% CI 0.58-0.82) D5 AMH: AUC 0.682 (95% CI 0.57-0.80) For prediction of poor response		baseline serum AMH level is a good predictor of poor ovarian response but mid-stimulation (day 5) AMH serum levels do not offer better prediction of response in stimulated IVF and ICSI cycles.	
Tsakos, E., Tolikas, A., Daniilidis, A. and Asimakopoulos, B. Arch Gynecol Obstet. 2014; 290 (6): 1249-53. (25001569)	CS	105 women Age 25-45 yrs. No endocrine disorders BMI 19-30 kg/m2 r/uFSH individualized dose GnRH antagonist AMH assay DSL	Prospective cohort study predictive value of AMH in ovarian response Poor response < 4 oocytes Excessive response > 12 oocytes	Poor response N = 35 Excessive response N = 8	Poor <4oocytes AMH AUC 0.634 (0.523-0.745), P 0.026 High response > 12 oocytes AMH AUC 0.664 (0.465-0.863), p 0.125		AFC, baseline AMH and baseline FSH are good predictors for the outcome of ovarian stimulation in GnRH-antagonist cycles	

1.3 Basal Follicle Stimulating Hormone (FSH)

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Diagnostic test evaluated Reference standard test Include: Time interval and treatment	Prevalence	Accuracy (Se, Sp, PPV, NPV, LR+, LR-)	Reproducibility	Authors conclusion	Comments
Broer, S. L., Dolleman, M., van Disseldorp, J., Broeze, K. A., Opmeer, B. C., Bossuyt, P. M., Eijkemans, M. J., Mol, B. W. and Broekmans, F. J. Fertil Steril. 2013; 100 (2): 420-9.e7. (23721718)	SR	4786 patients (32 studies)	Ovarian response testing in combination with patient characteristics for prediction of excessive response		ROC-AUC of 0.64 (95% CI 0.61-0.67) for the prediction of an excessive response			
Broer, S. L., van Disseldorp, J., Broeze, K. A., Dolleman, M., Opmeer, B. C., Bossuyt, P., Eijkemans, M. J., Mol, B. W. and Broekmans, F. J. Hum Reprod Update. 2013; 19 (1): 26-36. (23188168)	SR	5705 patients (28 studies)	Ovarian response testing in combination with patient characteristics for prediction of poor response and nonpregnancy		ROC-AUC of 0.66 (95% CI 0.62-0.69) for the prediction of a poor response			

Arce, Jc, Marca, A, Mirner, Klein B, Nyboe, Andersen A and Fleming, R. Fertility and sterility. 2013; 99 (6): 1644-53. (23394782)	RCT CS	749 women, ivf population, (n=375 recombinant FSH, n=374 hp HMG) aged 21 to 34 years, serum follicle-stimulating hormone (FSH) level 1–12 IU/L and antral follicle count (AFC) >10. mild male factor or unexplained fertility	Relation: AMH at start of stimulation and ovarian response and treatment outcome.		FSH accounted for 14% of the explained variation in oocyte yield. Multiple regression model revealed that AMH (P<.001) and FSH (P<.001) were statistically significant predictors of the number of oocytes retrieved ROC-AUC of 0.73 for the prediction of poor response and an ROC-AUC of 0.71 for high response after hp-hMG stimulation, and an ROC-AUC of 0.72 for poor response and an ROC-AUC of 0.73 for high response after rFSH stimulation		AMH is the best predictor for identifying patients with poor and high ovarian response AMH+ FSH for prediction both low and high response AUC for values were not significantly higher in comparison to those obtained for AMH only.	Secondary analysis of RCT, cohort in this sense.
Kwee, J., Elting, M. E., Schats, R., McDonnell, J. and Lambalk, C. B. Reprod Biol Endocrinol. 2007; 5 9 (17362511)	RCT CS	110 patients: 56 CCCT, 54 EFFORT before first IVF aged 18–39 years Incl.: idiopathic for >3 years and/or due to a male factor and/or cervical hostility Excl.: severe male factor and PCOS	AFC, basal ovarian volume (BOV), the exogenous FSH ovarian reserve test (EFORT) and the clomiphene citrate challenge test (CCCT), in prediction poor and hyperresponders		1.Univariate logistic regression bFSH ROC-AUC = 0.83 2.Multiple logistic regression analysis did not produce a better model in terms of improving the prediction of poor response.		FSH were similar as AFC in the prediction of poor response.	Secondary analysis of RCT, cohort in this sense.
Oehninger, S, Nelson, Sm, Verweij, P and Stegmann, Bj. Reproductive Biology and Endocrinology. 2015; 13 (1): (26520396)	RCT CS	infertile women aged 35–42 years (n = 694). Pursue trial. Infertile women aged 35–42 years with a body weight of ≥50 kg and body mass index (BMI) ≥18 and ≤32 kg/m2	AFC, AMH, age and basal FSH were measured before corifollitropin administration Low response defined as < 6 oocytes, High response as >18 oocytes.		Prediction of high response: ROCauc 0.88. They developed a combined model including age, AFC, AMH, FSH and cycle length		in women aged 35 to 42 years undergoing ovarian stimulation with corifollitropin alfa in a GnRH antagonist protocol, AMH, AFC and age at the start of stimulation were prognostic for both high and low ovarian response, in addition to FSH for high ovarian response and menstrual cycle length for low ovarian response.	Secondary analysis of RCT, cohort in this sense.

Bancsi, L. F., Broekmans, F. J., Eijkemans, M. J., de Jong, F. H., Habbema, J. D. and te Velde, E. R. Fertil Steril. 2002; 77 (2): 328-36. (11821092)	CS	120 women (112 conventional IVF, 18 ICSI Incl:[1] a regular spontaneous menstrual cycle ; [2] presence of both ovaries; [3] no evidence of endocrine disorders Accepted to 45 years Subdivided also to in further analysis on: poor (26) and normal responders (n=84) and on: age<41, and/orFSH<15 (n=92) age>41, and/orFSH>15 (n=28) Setting: One center,	The number of antral follicles and the total ovarian volume by ultrasound, basal levels of FSH, E2, and inhibin B on cycle day 3. The poor response was defined as: [1] collection of fewer than four oocytes at retrieval or [2] cycle cancellation because of impaired follicular reaction (< 3 follicles) in response to exogenous gonadotropins. High response was defined as the collection of >20 oocytes at retrieval		The antral follicle count appeared to have the best discriminative potential for poor response, expressed by the largest ROC AUC of 0.87, FSH 0.04, Inhibin B 0.77		1.The number of antral follicles is the best basal marker of ovarian reserve in terms of predicting poor response in IVF. 2.Addition of basal FSH and inhibin B levels to a logistic model with the antral follicle count significantly improved the prediction of poor response;	Addition of FSH to AFC improves prediction of poor response
Elgindy, E. A., El-Haieg, D. O. and El-Sebaey, A. Fertil Steril. 2008; 89 (6): 1670-6. (17658520)	CS	33 women, Age <38y D3 FSH <10IU/L BMI: 18-29 kg/m2	AMH, FSH and LH, AFC, mean ovarian volume	9/33 poor responders	ROC-AUC 0.85 (95% CI 0.66-1.05) for poor response			
Jayaprakasan, K., Al-Hasie, H., Jayaprakasan, R., Campbell, B., Hopkisson, J., Johnson, I. and Raine-Fenning, N. Fertil Steril. 2009; 92 (6): 1862-9. (18973895)	CS	141 women, IVF population first cycle, two groups poor responders n=41, normal responders n=100 Incl.: age< 43, FSH<12 Excl.: history of ovarian surgery or were found to have an ovarian cyst or follicle measuring 20 mm or more in diameter setting: one centre	Ovarian vascularity indices (VI, FI, and VFI), ovarian volume (OV), and antral follicle count (AFC)		prediction of poor ovarian response: FSH OR 1.295, 95 % CI 1.050-1.597, P<0.05, AUC 0.685		AFC and basal FSH were the only significant predictors of poor ovarian response on multiple regression analysis	

Khairy, M., Clough, A., El-Toukhy, T., Coomarasamy, A. and Khalaf, Y. Reprod Biomed Online. 2008; 17 (4): 508-14. (18854104)	CS	148 women entering IVF POR defined as < 4 oocytes	Performance of different variables in the prediction of poor ovarian response: Age BMI AFC FSH Oestradiol		23 women had POR The AFC prediction of POR: ROCauc 0.69		AFC had a good performance in predicting POR. No relevant contribution of adding other variables	
Mutlu, M. F., Erdem, M., Erdem, A., Yildiz, S., Mutlu, I., Arisoy, O. and Oktem, M. J Assist Reprod Genet. 2013; 30 (5): 657-65. (23508679)	CS	192 women normoresponders 143-poor responders 49 Inclusion: : age between 18 and 44 years, regular menstrual cycles (21–35 days), no endocrine disorders	Basal levels of AMH, FSH and antral follicle prior to IVF treatment. The predictive value of these parameters in terms of 1.retrieved oocyte number 2.live birth rates		ROC-AUC of 0.75 (95% CI 0.66-0.85) for prediction of poor and normal ovarian response		1. AFC is better than AMH and these two are better than FSH in predicting poor response 2. The only significant predictor of the probability of achieving a live birth was age.	
Penarrubia, J., Peralta, S., Fabregues, F., Carmona, F., Casamitjana, R. and Balasch, J. Fertil Steril. 2010; 94 (7): 2590-5. (20400077)	CS	98 women, IVF population 72 normal responders and 26 poor responders. age range: 25 to 41 years, undergoing their first ART cycle and fulfilling our inclusion criteria. All patients were infertile but otherwise healthy women, had both ovaries with no previous ovarian surgery	D-5Inhibin B, AFC		ROC-AUC of 0.62 (95% CI 0.51-0.71) for prediction of ovarian response		1.Basal FSH and day-5 inhibin B have similar predictive properties for ovarian response in assisted reproduction cycles	
Soldevila, P. N., Carreras, O., Tur, R., Coroleu, B. and Barri, P. N. Gynecol Endocrinol. 2007; 23 (4): 206-12. (17505940)	CS	327 women; first IVF cycle, one center 107 low response, 206 normal response. Incl. crit.: first IVF cycle Excl. crit.: Exclusion criteria incorrect viewing of the ovaries and the presence of organic ovarian pathology.	AFC, basal FSH, age, BMI, E2, LH		1.Predictive value for poor response OR 95% CI FSH 0.93 (0.87-0.98) 2. Predictive value of follicle-stimulating hormone (FSH) for poor response ROC-AUC: 0.629 (95% CI 0.57-0.68) for prediction of poor response		1. The AFC has predictive value for ovarian response in an IVF cycle, with a cut-off value of 7 follicles above which there are more chances of normal response. Its predictive value is higher than that of basal FSH 2.. The number of antral follicles is shown as an independent marker of poor response, with an importance comparable with basal FSH and age.	

Tolikas, A., Tsakos, E., Gerou, S., Prapas, Y. and Loufopoulos, A. Hum Fertil (Camb). 2011; 14 (4): 246-53. (22088130)	CS	Prospective study on 90 women. Poor was for <4 oocytes. High response was for > 12 oocytes	AMH, FSH and AFC were measured. AMH was measured by DSl assay.		Prediction of poor response: ROC auc: 0.65		AFC the best predictor of ovarian response, followed by AMH	
Tsakos, E., Tolikas, A., Daniilidis, A. and Asimakopoulos, B. Arch Gynecol Obstet. 2014; 290 (6): 1249-53. (25001569)	CS	Prospective study on 105 women. 25-45 years of age, regular cycles. Entering IVF	Markers were measured		Prediction of poor ovarian response: ROCauc: 0.67 Prediction of high ovarian response: ROCauc: 0.72		AFC has better diagnostic performance than AMH and age in predicting the extremes of ovarian response	

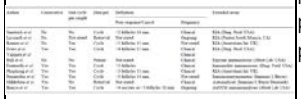
1.4 Inhibin B

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Diagnostic test evaluated Reference standard test Include: Time interval and treatment	Prevalence	Accuracy (Se, Sp, PPV, NPV, LR+, LR-)	Reproducibility	Authors conclusion	Comments
Broekmans, F. J., Kwee, J., Hendriks, D. J., Mol, B. W. and Lambalk, C. B. Hum Reprod Update. 2006; 12 (6): 685-718. (16891297)	SR	(9 studies) Variation among the definitions of poor response and study quality and design characteristics is clearly present but logistic regression analysis revealed that none of the items significantly impacted the predictive performance of the test	Inhibin B for poor response prediction and/or non-pregnancy prediction		Spearman correlation coefficient for poor response: -0.93, for non-pregnancy prediction: -0.94		With the use of basal inhibin B in regularly cycling women, the accuracy in the prediction of poor response and non-pregnancy is only modest at a very low threshold level. At best the test may be used as screening test for counselling purposes or to direct further diagnostic steps	The inhibin B is not good marker as the other specified in prediction of poor response.
Arce, Jc, Marca, A, Mirner, Klein B, Nyboe, Andersen A and Fleming, R. Fertility and sterility. 2013; 99 (6): 1644-53. (CN-00872359)	RCT	749 women, aged 21 to 34 years, unexplained infertility or mild male factor infertility and with serum FSH level 1–12 IU/L and AFC >10, BMI of 18 to 25 kg/m2, and regular menstrual cycles of 24 to 35 days.	AMH, FSH, Inhibin B Inhibin B-ELISA (2.6 ng/ml sensitivity)		ROC-AUC of 0.62 for the prediction of poor response and an ROC-AUC of 0.60 for high response after hp-hMG stimulation, and an ROC-AUC of 0.64 for poor response and an ROC-AUC of 0.53 for high response after rFSH stimulation		The inhibin B has the lower AUC in predicting both low and excessive ovarian response in comparison to other tests (FSH, age, AFC)	Secondary analysis of RCT, cohort in this sense.
Kwee, J., Elting, M. E., Schats, R., McDonnell, J. and Lambalk, C. B. Reprod Biol Endocrinol. 2007; 5 9. (17362511)	RCT	110 patients: 56 CCCT, 54 EFFORT before first IVF aged 18–39 years Incl.: idiopathic for >3 years and/or due to a male factor and/or cervical hostility Excl.: severe male factor and PCOS	AFC, basal ovarian volume (BOV), the exogenous FSH ovarian reserve test (EFORT) and the clomiphene citrate challenge test (CCCT), in prediction poor and hyperresponders		ROC-AUC of 0.86 for the increment of inhibin B in the EFORT for the prediction of poor response and an ROC-AUC of 0.93 for the increment of inhibin B in the EFORT for the prediction of hyper response		AFC performs well as a test for ovarian response being superior or at least similar to complex expensive and time consuming endocrine tests	Secondary analysis of RCT, cohort in this sense.

Fawzy, M, Lambert, A, Harrison, Rf, Knight, Pg, Groome, N, Hennelly, B and Robertson, Wr. Human reproduction (Oxford, England). 2002; 17 (6): 1535-43. (12042274)	CT	54 women<39 years	inhibin B, Inhibin A, E2 assessment after 4 days treatment of gonadotropins		ROC-AUC of 0.96 (95% CI 0.86-0.99) for D5 inhibin B for predicting poor response (<8 mature oocytes)		women with inhibin B< 400 pg/ ml in d-5 have a poor response to ovarian stimulation and are less likely to conceive compare to women with inh B>400 pg/ ml Day 5 inhibin B was the best predictor of pregnancy (no live births and four cycles cancelled, low inhibin group;	
Hendriks, D. J., Broekmans, F. J., Bancsi, L. F., de Jong, F. H., Looman, C. W. and Te Velde, E. R. Hum Reprod. 2005; 20 (1): 163-9. (15471926)	CS	63 patients	CCCt test (repeated) in comparison to basal FSH, AFC, inhibin B Poor response (<4 oocytes or cancellation due to impaired (<3 follicles) or absent follicular growth) was used as primary outcome measure	IVF population first cycle long rFSH	For basal ans rep CCCT (ROCAUC): FSH cd10 = 0.79, inhibin B cd10 = 0.79, mean FSH cd10 = 0.82 and mean inhibin B cd10 = 0.88). This compared well with the performance of the basal markers (FSH 0.82, inhibin B 0.72 and AFC 0.83). In a multivariate analysis		CCCT (single or repeated) has a rather good ability to predict poor response in IVF. However, it appears that the predictive accuracy and clinical value of the CCCT is not clearly better than that of basal FSH in combination with an AFC.	
Penarrubia, J., Peralta, S., Fabregues, F., Carmona, F., Casamitjana, R. and Balasch, J. Fertil Steril. 2010; 94 (7): 2590-5. (20400077)	CS	98 women: 72 normal responders and 26 poor responders. age range: 25 to 41 years) undergoing their first ART cycle and fulfilling our inclusion criteria. All patients were infertile but otherwise healthy women, had both ovaries with no previous ovarian surgery,	D-5Inhibin B, AFC Inhibin B measurements were performed by an enzymatically amplified two-site-step sandwich immunoassay (enzyme-linked immunosorbent assay) in microtiter plates (Diagnostic Systems Laboratories Inc., Webster, TX). The assay sensitivity was 15 pg/mL, and the intra-assay coefficient of variation was 5.5%. The inter-assay coefficient of variation at low (36 pg/mL) and high (246 pg/mL) concentrations was 12% and 7%, respectively.		For prediction of poor response ROC curves (AUCROC) were 0.91(0.83–0.96) for inh B Odds ratio (95% CI) 1.00 (0.95–1.05) sensitivity, specificity, and diagnostic accuracy of 92.31%, 80.56%, and 91%,		1.Basal AFC and day-5 inhibin B have similar predictive properties for ovarian response in assisted reproduction cycles 2. day-5 inhibin B is a superior predictor of live birth.	

van Rooij, I. A., Broekmans, F. J., te Velde, E. R., Fauser, B. C., Bancsi, L. F., de Jong, F. H. and Themmen, A. P. Hum Reprod. 2002; 17 (12): 3065-71. (12456604)	CS	119 patients, first IVF cycle Age <46 y	D3 measurement of AMH, FSH, oestradiol (E2) and inhibin B In a subset of 23 patients a GnRH agonist stimulation test (GAST) was performed		AFC highest ROC-AUC of 0.86 for poor response, ROC-AUC of inhibin 0.76 for poor response			

1.5 BASAL OESTRADIOL

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Diagnostic test evaluated Reference standard test Include: Time interval and treatment	Prevalence	Accuracy (Se, Sp, PPV, NPV, LR+, LR-)	Reproducibility	Authors conclusion	Comments
Broekmans, F. J., Kwee, J., Hendriks, D. J., Mol, B. W. and Lambalk, C. B. Hum Reprod Update. 2006; 12 (6): 685-718. (16891297)	SR	Systematic review and meta-  analysis of 10 studies including 3911 patients	Basal oestradiol for poor response prediction and/or non-pregnancy prediction Poor response different definitions in different studies, different assays	Not reported	 Spearman correlation coefficient for poor response prediction: -0.50 Sensitivity range 0.03-0.83 Specificity range 0.13-0.98 LR + range from 0.7 – 23.8		The clinical applicability for basal oestradiol as a test before starting IVF is prevented by the very low predictive accuracy, both for poor response and non-pregnancy.	
Kwee, J., Elting, M. E., Schats, R., McDonnell, J. and Lambalk, C. B. Reprod Biol Endocrinol. 2007; 5 9 (17362511)	RCT CS	110 patients: 56 CCCT, 54 EFFORT before first IVF aged 18–39 years Incl.: idiopathic for >3 years and/or due to a male factor and/or cervical hostility Excl.: severe male factor and PCOS	AFC, basal ovarian volume (BOV), the exogenous FSH ovarian reserve test (EFORT) and the clomiphene citrate challenge test (CCCT), in prediction poor and hyperresponders		Prediction of low ovarian response: ROC of 0.75 for the increment of basal oestradiol in the EFFORT Prediction of high ovarian response: ROC of 0.83 for the increment of basal oestradiol in the EFORT		FSH were similar as AFC in the prediction of poor response.	Secondary analysis of RCT, cohort in this sense.
Hendriks, D. J., Broekmans, F. J., Bancsi, L. F., de Jong, F. H., Looman, C. W. and Te Velde, E. R. Hum Reprod. 2005; 20 (1): 163-9. (15471926)	CS	63 women Regular menstrual cycle (25-35 days) No endocrine disorders Age < 46 years GnRH agonist rFSH 150 IU/days	CCCt test (repeated) in comparison to basal FSH, AFC, inhibin B Poor response < 4 oocytes or cycle cancellation	Normal response N=46 Poor response N=17	Normal responders E2 140 pmol/L, Poor responders E2 157 pmol/L, P-value 0.866 ROC-AUC 0.54 (0.36-0.72), p value 0.09		No significant effect of oestradiol in the prediction of ovarian response	

Khairy, M., Clough, A., El-Toukhy, T., Coomarasamy, A. and Khalaf, Y. Reprod Biomed Online. 2008; 17 (4): 508-14. (18854104)	CS	148 patients entering IVF program Prospective study	Performance of different variables in the prediction of poor ovarian response: Age BMI AFC FSH Oestradiol		Prediction of poor response: ROC auc: 0.51		AFC had a good performance in predicting POR. No relevant contribution of adding other variables	dAFC showed to be the single most important predictor of ovarian response amongst the tested variables in this study (age, BMI, basal FSH and oestradiol concentrations)
Penarrubia, J., Peralta, S., Fabregues, F., Carmona, F., Casamitjana, R. and Balasch, J. Fertil Steril. 2010; 94 (7): 2590-5. (20400077)	CS	98 patients Age 25-41 yrs. First IVF cycle Normal ovulatory function GnRH agonist rFSH	Prospective cohort study. Day 3 FSH, LH, oestradiol. AFC and ovarian volume Poor response ≤ 3 oocytes or cycle cancellation	Poor response N = 26 Normal response N = 72	No significant difference between E2 levels of poor and normal responders 34.2 pg/ml vs 40.8 pg/ml, p NS. OR 0.97 (0.95-0.99). Sensitivity 42.31% Specificity 79.17% AUC 0.55 (0.44-0.65)		No significant correlation between E2 and ovarian response. Low accuracy for prediction of ovarian response.	
van Rooij, I. A., Broekmans, F. J., te Velde, E. R., Fauser, B. C., Bancsi, L. F., de Jong, F. H. and Themmen, A. P. Hum Reprod. 2002; 17 (12): 3065-71. (12456604)	CS	119 patients, first IVF cycle Age <46 y	D3 measurement of AMH, FSH, oestradiol (E2) and inhibin B In a subset of 23 patients a GnRH agonist stimulation test (GAST) was performed		Univariate model Prediction of poor response: ROC-AUC of 0.52		a high correlation of AMH with ovarian response, as expressed by the number of oocytes retrieved.	

1.6 AGE

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Diagnostic test evaluated Reference standard test Include: Time interval and treatment	Prevalence	Accuracy (Se, Sp, PPV, NPV, LR+, LR-)	Reproducibility	Authors conclusion	Comments
Broer, S. L., et al. Fertil Steril. 2013; 100 (2): 420-9.e7. (23721718	SR	57 studies included for a total of 4786 women. IPD metanalysis	Comparison of markers for prediction of excessive response		The multivariable analyses demonstrated that a model including age, AFC, and AMH (AUC 0.85) had a significantly higher predictive accuracy than a model based on age alone (AUC .61; P <.001). Interestingly, a single AMH or AFC test had a comparable accuracy (AUC 0.81 and 0.79, respectively).		In conclusion, this IPD meta-analysis shows that AFC and AMH add predictive accuracy to age in the prediction of an excessive response. A model combining these ORTs provides good predictive accuracy, without the necessity of including female age	
Broer, S. L., et al. . Hum Reprod Update. 2013; 19 (1): 26-36. (23188168).	SR	5705 patients from 28 studies (IPD metanalysis)	Comparison of markers for prediction of poor response		The multivariable analyses for poor response prediction showed that a model with age, AFC and AMH had a significantly higher predictive accuracy than a model based on age alone (AUC 0.80 versus 0.61; P≤0.001). The predictive value of the multivariable model, including age and the two ORTs, AMH and AFC, was not significantly better than that of a single ORT		The study demonstrates that the ORTs, AFC and AMH are highly capable of forecasting a poor responder to ovarian hyperstimulation for IVF, even without using female age	
Kwee, J., Elting, M. E., Schats, R., McDonnell, J. and Lambalk, C. B. Reprod Biol Endocrinol. 2007; 5 9 (17362511)	RCT CS	110 patients: 56 CCCT, 54 EFFORT before first IVF aged 18–39 years Incl.: idiopathic for >3 years and/or due to a male factor and/or cervical hostility Excl.: severe male factor and PCOS	Age, AFC, basal ovarian volume (BOV), the exogenous FSH ovarian reserve test (EFORT) and the clomiphene citrate challenge test (CCCT), in prediction poor and hyperresponders		1.Univariate logistic regression age ROC-AUC = 0.63 for prediction of poor response Univariate logistic regression age ROC-AUC = 0.71 for prediction of high response		AFC is able to accurately predict the number of follicles obtained during maximal ovarian stimulation.	Secondary analysis of RCT, cohort in this sense.

Oehninger, S, Nelson, Sm, Verweij, P and Stegmann, Bj. Reproductive Biology and Endocrinology. 2015; 13 (1): (26520396)	RCT CS	infertile women aged 35–42 years (n = 694). Pursue trial. Infertile women aged 35–42 years with a body weight of ≥50 kg and body mass index (BMI) ≥18 and ≤32 kg/m2	AFC, AMH, age and basal FSH were measured before corifollitropin administration Low response defined as < 6 oocytes, High response as >18 oocytes.		Prediction of low response: ROCauc 0.61. Prediction of high response: ROCauc 0.61 They developed a combined model including age, AFC, AMH, FSH and cycle length		in women aged 35 to 42 years undergoing ovarian stimulation with corifollitropin alfa in a GnRH antagonist protocol, AMH, AFC and age at the start of stimulation were prognostic for both high and low ovarian response, in addition to FSH for high ovarian response and menstrual cycle length for low ovarian response.	Secondary analysis of RCT, cohort in this sense.
Bancsi, L. F., Broekmans, F. J., Eijkemans, M. J., de Jong, F. H., Habbema, J. D. and te Velde, E. R. Fertil Steril. 2002; 77 (2): 328-36. (11821092)	CS	120 women entering IVF program	Measurement of the number of antral follicles and the total ovarian volume by ultrasound, and of basal levels of FSH, E2, and inhibin B on cycle day 3		Age did not increase the performance of the predictive model based on antral follicles, inhibin b and serum FSH ROC-AUC of 0.61 for prediction of poor response		the antral follicle count provides better prognostic information on the occurrence of poor response during hormone stimulation for IVF than does the patient's chronological age	
Jayaprakasan, K., Al-Hasie, H., Jayaprakasan, R., Campbell, B., Hopkisson, J., Johnson, I. and Raine-Fenning, N. Fertil Steril. 2009; 92 (6): 1862-9. (18973895)	CS	141 women, IVF population first cycle, two groups poor responders n=41, normal responders n=100 Incl.: age< 43, FSH<12 Excl.: history of ovarian surgery or were found to have an ovarian cyst or follicle measuring 20 mm or more in diameter setting: one centre	Ovarian vascularity indices (VI, FI, and VFI), ovarian volume (OV), antral follicle count (AFC) and age		prediction of poor ovarian response: ROCauc: 0.74		AFC and basal FSH were the only significant predictors of poor ovarian response on multiple regression analysis	
Khairy, M., Clough, A., El-Toukhy, T., Coomarasamy, A. and Khalaf, Y. Reprod Biomed Online. 2008; 17 (4): 508-14. (18854104)	CS	148 patients entering IVF program Prospective study	Performance of different variables in the prediction of poor ovarian response: Age BMI AFC FSH Oestradiol		the accuracy of age was moderate (LR = 5.43) ROC-AUC of 0.71 for prediction of poor ovarian response		AFC had a good performance in predicting POR. No relevant contribution of adding other variables	dAFC showed to be the single most important predictor of ovarian response amongst the tested variables in this study (age, BMI, basal FSH and oestradiol concentrations)

Mutlu, M. F., Erdem, M., Erdem, A., Yildiz, S., Mutlu, I., Arisoy, O. and Oktem, M. J Assist Reprod Genet. 2013; 30 (5): 657-65. (23508679)	CS	192 patients entering IVF cycle Prospective study	AMH and AFC predictive value on ovarian response after stimulation in IVF programs and live birth rates compared with age and basal FSH		Age was related to ovarian response. The ROCauc prediction of poor response was 0.76 (0.68-0.84). OR was 1.21 (1.12-1.3) Sensitivity 30.6%, specificity 96.5% AMH and AFC were superior to AFC		AFC is better than AMH in predicting ovarian response; they although show both limitations in predicting live births; age is the best predictor for live birth rates (OR 0.92 (0-86-0.99)	
Penarrubia, J., Peralta, S., Fabregues, F., Carmona, F., Casamitjana, R. and Balasch, J. Fertil Steril. 2010; 94 (7): 2590-5. (20400077)	CS	98 women, IVF population 72 normal responders and 26 poor responders. age range: 25 to 41 years, undergoing their first ART cycle and fulfilling our inclusion criteria. All patients were infertile but otherwise healthy women, had both ovaries with no previous ovarian surgery	D-5Inhibin B, AFC, age		ROC-AUC of 0.55 for prediction of ovarian response		1.Basal FSH and day-5 inhibin B have similar predictive properties for ovarian response in assisted reproduction cycles	

1.7 Body mass index (BMI)

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Diagnostic test evaluated Reference standard test Include: Time interval and treatment	Prevalence	Accuracy (Se, Sp, PPV, NPV, LR+, LR-)	Reproducibility	Authors conclusion	Comments
Broer, S. L., Dolleman, M., van Disseldorp, J., Broeze, K. A., Opmeer, B. C., Bossuyt, P. M., Eijkemans, M. J., Mol, B. W. and Broekmans, F. J. Fertil Steril. 2013; 100 (2): 420-9.e7. (23721718)	SR	N 4786 patients (32 studies) Study characteristics and assays differed per study but corrected for in random intercept logistic regression models.	IPD meta-analyses Ovarian response testing in combination with patient characteristics for prediction of excessive response Excessive response > 15 oocytes	Normal response N= 3892 (81,3%) Excessive response N= 894 (18.7%)	BMI mean ER 23.4 (18.5-29.4) NR 23.4 (18.6-30.1), p 0.943 Logistic regression model in prediction of excessive response BMI: OR 1.00 (0.97-1.03), p 0.954		BMI not significantly predictive of an excessive response	
Broer, S. L., van Disseldorp, J., Broeze, K. A., Dolleman, M., Opmeer, B. C., Bossuyt, P., Eijkemans, M. J., Mol, B. W. and Broekmans, F. J. Hum Reprod Update. 2013; 19 (1): 26-36. (23188168)	SR	5705 patients (28 studies) 4170 patients for poor response analysis Study characteristics and assays differed per study but corrected for in random intercept logistic regression models.	IPD meta-analyses Ovarian response testing in combination with patient characteristics for prediction of poor response Poor response ≤ 4 oocytes or cycle cancellation	Poor response N= 893 (21%) Normal response N = 3277 (79%)	Mean BMI 23.2 (18.5-30.1) Logistic regression model in poor response prediction. BMI OR 1.03 (0.99-1.06), p 0.114		BMI not significantly predictive of a poor response	
Khairy, M., Clough, A., El-Toukhy, T., Coomarasamy, A. and Khalaf, Y. Reprod Biomed Online. 2008; 17 (4): 508-14. (18854104)	CS	148 patients, 137 patients completed IVF treatment GnRH agonist, individualized rFSH dose	Prospective cohort study, assessing BMI, FSH, AFC, E2 in the prediction of poor response. Poor response < 4 oocytes or cycle cancellation	Mean BMI 26.7 ± 2.6 Normal response N = 125 Poor response N = 23	Non-significant difference in BMI NR 26.9 ±4.6 vs PR 27.8 ± 2.6 OR 1.18 (0.99-1.40), p value 0.05. NS in multivariate analyses ROC-AUC of 0.68 for prediction of poor response		There were no significant differences regarding BMI levels between the two groups Approximately 95% had a BMI in the range 21.5–31.9 kg/m	

2. Additional hormonal assessment at baseline

KEY QUESTION: WHAT IS THE PROGNOSTIC VALUE OF HORMONAL ASSESSMENT AT BASELINE?

P	I	C	O
Women undergoing IVF/ICSI	Baseline progesterone Baseline oestradiol		Efficacy: - cumulative LBR/cycle - Cumulative ongoing pregnancy rate /started cycle (fresh + frozen) - Clinical pregnancy rate/started cycle - Nr of Oocytes/ nr of MII oocyte recovery rate (yield) - number of embryo's (fresh+frozen) Safety - incidence of different grades of OHSS - grade of OHSS - incidence of cycle cancellation for hyper-response (predefined) - Bleeding - Infection - Torsion - Long-term effect on maternal/child health - other adverse events (treatment related) Patient-related outcomes - Compliance - Drop-out rates - Patient burden - QoL - Patient preferences

1.2 BASELINE OESTRADIOL

No relevant studies were identified.

1.3 PROGESTERONE

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Diagnostic test evaluated Reference standard test Include: Time interval and treatment	Prevalence	Accuracy (Se, Sp, PPV, NPV, LR+, LR-)	Reproducibility	Authors conclusion
Hamdine, O., Macklon, N. S., Eijkemans, M. J., Laven, J. S., Cohlen, B. J., Verhoeff, A., van Dop, P. A., Bernardus, R. E., Lambalk, C. B., Oosterhuis, G. J., Holleboom, C. A., van den Dool-Maasland, G. C., Verburg, H. J., van der Heijden, P. F., Blankhart, A., Fauser, B. C. and Broekmans, F. J. Fertil Steril. 2014; 102 (2): 448-454.e1. (24929258)	SR/MA	1052 patients	Progesterone levels at initiation of stimulation (CD2)	6.7% (recalculated properly: 7% 95%CI 4-11)	Sensitivity:0.08 (95%CI: 0.06-0.09) Specificity:0.99 (95%CI: 0.97-1) PPV:0.90 (95%CI:0.83 – 0.97) NPV:0.72(95%CI: 0.70 – 0.75) calculated	RD -0.15 (95%CI: -0.23 to -0.07) This is what is published and is a fixed model although I2=64.8 The application of a random model gives: - RD: 0.165 95%CI -0.297 to -0.033 Or RR: 0.456 95%CI: 0.243 - 0.856, fixed model, I2 = 7.8)	Early elevated P levels are associated with a lower OPR in ovarian stimulation using GnRH antagonists. The incidence of such a condition, however, is 7%. Problems in the meta-analysis: In two of the studies included, an intervention is applied in patients with high P: Kolibianakis: delay of initiation of stimulation by 1-2 days (P cut-off 1.6) Blockeel: administration of GnRH antagonist for three days prior to initiation of stimulation (P cut-off 1.6) Thus, the association observed is valid only when these interventions are applied. In the non-interventional study by Hamdine et al (2014), included patients had GnRH antagonist started either on CD 2 or on CD 6 (P cut-off 1.5). Thus, again extrapolation of the association between baseline P and the probability of pregnancy is restricted to such a setting

Faulisi, S., Reschini, M., Borroni, R., Paffoni, A., Busnelli, A. and Somigliana, E. Gynecol Obstet Invest. 2017; 82 (2): 175-180. (27522226)	CS	312 (143 excluded)	Progesterone levels at initiation of stimulation (CD3) Cut-off 1.6 ng/ml	0.2% (0 - 1.2)	Sensitivity:0.003 Specificity:1 PPV:1 NPV:0.18 LR+/- LR-:0.997 Accuracy:0.19 calculated	Does not offer a result on the cut-off level for which the study was performed. It can be calculated though from the publication, by also including the "excluded patients" RD: -0.185 (95%CI: -0.786 to + 0.416) RR:1.346 (95%CI: 0.121 - 14.960)	Routine day 3 serum progesterone assessment in IVF cycles with the use of GnRH antagonists is not justified. Further evidence is warranted prior to claiming its systematic use.
Panaino, T. R., Silva, J. B., Lima, M. A., Lira, P., Areas, P. C., Mancebo, A. C., Souza, M. M., Antunes, R. A., Souza, M. D. JBRA Assisted Reproduction 2017;21(1):11-14 (28333025)	CS	418 patients 468 ETs	Progesterone levels at initiation of stimulation (CD2) Cut-off 1.5 ng/ml	3.7% (2.3-5.8)	Sensitivity:0.045 Specificity:0.98 PPV:0.76 NPV:0.38 LR+:1.95 LR-:0.98 Accuracy:0.39 calculated	RD: -16.3 95% CI:-37.0 to +4.3 RR:0.59 95%CI:0.25 -1.40	The impact of serum progesterone in the beginning of stimulation and pregnancy outcomes is a matter of concern. Basal elevated levels could help identify patients that will repeat it on hCG day, being probably a marker to help a freeze-all strategy to these cycles. More cycles than patients were analysed without proper adjustment Statistical analysis regarding CP is flawed

3. Pre-treatment therapies

KEY QUESTION: DOES HORMONE PRE-TREATMENT IMPROVE EFFICACY AND SAFETY OF OVARIAN STIMULATION?

P	I	C	O
Women undergoing IVF/ICSI	- oestradiol - progesterone - contraceptive (estradiol + progesterone) (COC) (incl dual suppression) - GnRH antagonist	- No pre-treatment	Efficacy: - cumulative LBR/cycle - Cumulative ongoing pregnancy rate /started cycle (fresh + frozen) - Clinical pregnancy rate/started cycle - Nr of Oocytes/ nr of MII oocyte recovery rate (yield) - number of embryo's (fresh+frozen) Safety - incidence of different grades of OHSS - grade of OHSS - incidence of cycle cancellation for hyper-response (predefined) - Bleeding - Infection - Torsion - Long-term effect on maternal/child health - other adverse events (treatment related) Patient-related outcomes - Compliance - Drop-out rates - Patient burden - QoL - Patient preferences

3.1 OESTROGEN PRE-TREATMENT

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Farquhar C, Rombauts L, Kremer JA, Lethaby A, Ayeleke RO. Cochrane Database Syst Rev. 2017; 5:CD006109. (28540977)	SR	4 RCTs 17B estradiol 4mg: Cédrin-Durnerin 2007; Cédrin-Durnerin 2012; Fanchin 2003	oestradiol pre-treatment vs no pre-treatment in GnRH antagonist protocols	1/ live birth or ongoing pregnancy 2/ clinical pregnancy rate 3/ number of oocytes 4/ OHSS	1/ live birth or ongoing pregnancy OR 0.79 (0.53 to 1.17); 2 RCTs; 502 women; moderate quality 2/ clinical PR OR 0.91 [0.66, 1.24]; 4RCT; 688 women; very low Q 3/number of oocytes mean diff 2.23 (0.71-3.75) p<0.004; 2 RCT; 139 women (Cedrin 2007;Cedrin 2012; normoresponders) 4/ ND	When oestrogen in antagonist cycles was compared with no pre-treatment in either antagonist or agonist cycles, there was no clear evidence of a difference between the groups in rates of live births or ongoing pregnancies or OHSS.	GRADE evidence profile
Shahrokh Tehrani Nejad, E., Bakhtiari Ghaleh, F., Eslami, B., Haghollahi, F., Bagheri, M. and Masoumi, M. Int J Reprod Biomed (Yazd). 2018 (30288488)	RCT	N=210 included but 176 analyzed 18-35 yrs. AMH1-6 <2 IVF attempts OCP (N=53) vs E2 (N=63) vs no prett (N=70) → lost of follow up +++ (different proportion in each group) →unrealistic hypothesis for the calculation of number of patient	OCP start at day 20 for 1à days (6d window before OS) E2 = 4mg/d start day 20 for 10 days (6d window before OS) Exclusion if no menstrual bleeding during the 6d before OS Control start D2 rFSH 150 GnRH antagonist protocol for LH suppression in the 3 groups	1/clinical pregnancy 2/mature oocytes	No statistical diff for clinical PR (42.9% (27/63) vs. 34.3% (24/70)) or number of mature oocytes retrieved (10.71±3.73 vs. 10.40±4.38) no case of OHSS in either group	results of the present study failed to show the statistically significant differences in pregnancy rate in IVF patients who received cycle scheduling with OCP, E2 valerate with a comparison to control group in a randomized clinical trial after 6 days of pretreatment discontinuation in GnRH antagonist cycles	poor quality RCT but more recent one

3.2 PROGESTOGEN PRE-TREATMENT

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Farquhar C, Rombauts L, Kremer JA, Lethaby A, Ayeleke RO. Cochrane Database Syst Rev. 2017; 5:CD006109. (28540977)	SR	7 RCTs Norethisterone 10mg: Cédrin-Durnerin 2007; Ditkoff 1996; Engmann 1999; Hugues 1994 MPA 10mg: Aston 1995 Ethynodiol acetate 4mg: Salat-Baroux 1988 Progesterone inj 100mg: Shaker 1995	Comparisons - progestogen prettt vs no prettt in agonist protocols - progestogen prettt vs no prettt in antagonist protocols - progestogen+Gn vs Gn (no agonist or antagonist): data exclude	1/ live birth or ongoing pregnancy 2/ clinical pregnancy rate 3/ number of oocytes 4/ cyst formation	**P vs no P in agonist** 1/ live birth/ongoing pregnancy OR 1.35 (0.69 to 2.65); 2 RCTs; 222 women; low quality evidence; 2/ clinical pregnancy OR 1.99 (1.20 to 3.28); 3 RCTs (1 with HCG+); 374 women 3/ number of oocyte MD -0.52 NS; 2 RCTs; 222 women; 4/ cyst OR 0.16 (0.08 to 0.32) p ; 3 RCT; 374 women; moderate quality evidence **P vs no P in antagonist** 1/ live birth/ongoing pregnancy OR 0.67 (0.18 to 2.54); 1 RCT; 47 women; low quality evidence; 2/clinical pregnancy OR 0.52 (0.16 to 1.71); 1 RCT; 47 women 3/number of oocyte MD 2.7 NS; 1 RCT; 47 women 4/ND	There was insufficient evidence to determine any differences in rates of live birth/ongoing pregnancy or number of oocyte. There was evidence of more clinical pregnancies in the group pretreated with a progestogen in agonist protocol. In agonist protocol, fewer women had ovarian cyst formation in the group pretreated with a progestogen compared with those who had no pretreatment	GRADE evidence profile

3.3 COMBINED ORAL CONTRACEPTIVE PILL PRE-TREATMENT

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Farquhar C, Rombauts L, Kremer JA, Lethaby A, Ayeleke RO. Cochrane Database Syst Rev. 2017; 5:CD006109. (28540977)	SR	17 RCTs EE 30µg/ desogestrel 150 EE 30µg/ levonorgestrel 150 EE 20µg/ levonorgestrel 100 EE 35µg/ cyproterone acetate 2 mg 2 low responders (Kim 2011; Daly 2002) 1 PCOS (Hwang 2004): OCP 3 consecutive cycles	Comparisons - OCP prettt vs no prettt in GnRH antagonist protocols - OCP prettt vs no prettt in GNRH antagonist protocol, low responders	1/ live birth or ongoing pregnancy 2/ clinical pregnancy rate 3/ number of oocytes 4/ OHSS 5/ ovarian cyst	**OCP vs no OCP in antag** 1/ live birth/ongoing pregnancy OR 0.74 (0.58 to 0.95); 6 RCTs; 1335 women; moderate quality evidence; 2/clinical pregnancy OR 0.85 (0.63 to 1.15); 5 RCTs; 740 women 3/number of oocyte MD 0.44 NS; 6 RCT; 1077 w 4/OHSS OR 0.98 (0.28 to 3.40); 2 RCTs; 642 women; low quality evidence 5/cyst OR 0.47 (0.08-2.75); 1 RCT 64 women very low Q **low responders** no difference for live birth/ongoing pregnancy rate (1 RCT, OR 1.71, 95% CI 0.61-4.79) or number of oocytes (1 RCT, MD 0.70, 95% CI -0.11 to 1.51)	In antagonist protocol, the rate of live birth/ongoing pregnancy was lower in the OCP pretreatment group compare to no pretreatment. There was insufficient evidence to determine the effect on OHSS or cyst formation.	GRADE evidence profile

Shahrokh Tehrani Nejad, E., Bakhtiari Ghaleh, F., Eslami, B., Haghollahi, F., Bagheri, M. and Masoumi, M. Int J Reprod Biomed (Yazd). 2018 (30288488)	RCT	N=210 included but 176 analyzed 18-35 yrs. AMH1-6 <2 IVF attempts OCP (N=53) vs E2 (N=63) vs no prett (N=70) → lost of follow up +++ (different proportion in each group) →unrealistic hypothesis for the calculation of number of patient	OCP start at day 20 for 1à days (6d window before OS) E2 = 4mg/d start day 20 for 10 days (6d window before OS) Exclusion if no menstrual bleeding during the 6d before OS Control start D2 rFSH 150	1/clinical pregnancy 2/mature oocytes	No statistical diff for clinical PR (39.6% (21/53) vs. 34.3% (24/70)) and number of oocytes (10.55±3.38 vs. 10.40±4.38)	results of the present study failed to show the statistically significant differences in pregnancy rate in IVF patients who received cycle scheduling with OCP, E2 valerate with a comparison to control group in a randomized clinical trial after 6 days of pretreatment discontinuation in GnRH antagonist cycles	poor quality RCT but more recent one

3.4 GnRH ANTAGONIST PRE-TREATMENT

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Aflatoonian, A., Hosseinisadat, A., Baradaran, R. and Farid Mojtahedi, M. Int J Reprod Biomed (Yazd). 2017; 15 (4): 231-238. (28835940)	RCT	POR Bologna N=60 (30+30) Randomized (no number of patient calculation) Control older 40y vs 38y (NS p 0.07)	Control E2 prett antag Study E2 prettt than antag 7 days for delayed start	1/ OCPR 2/Number oo	1/ OCPR 2/30 vs 1/30 2/Number oocytes 3.6 vs 5.1 p 0.14	There is no significant difference between delayed-start GnRH antagonist protocol versus GnRH antagonist protocol in POR Bologna	Very low quality evidence (60 patients) E2 prettt in both group
Blockeel, C., Riva, A., De Vos, M., Haentjens, P. and Devroey, P. Fertil Steril. 2011; 95 (5): 1714-9.e1-2. (21300334)	RCT	69 patients Pilot study (no patient number calculation) N=36 control N=33 study normogonadotropic women < 36y basic characteristics not shown	N=36 control rFSH D2 150-225 and fixed antagonist D7 N=33 study Antagonist D2-D5 stop and then same rFSH and fixed antagonist	1/ ongoing pregnancy rate 2/ number of oocyte (primary outcome)	1/ Ongoing pregnancy rate study group 42% control 33% MD 9.1% [13-30] p= 0.59 2/ Number of oocyte study group 12.8(7.8) control 9.9 (4.9) MD 2.9 [0.2,6.0] p=0.07	In antagonist fixed protocol there is a trend toward a higher number of retrieved oocytes with early follicular use of antagonist pretreatment compare to no intervention but does not yield significantly higher pregnancy rates	Very low quality evidence (69 patients)
DiLuigi, Aj, Engmann, L, Schmidt, Dw, Benadiva, Ca, Nulsen, Jc. Fertil steril 2011; 95(8): 2531-3 (21324455)	RCT	POR N=54	Microdose agonist flare up Vs E2+antag prettt in antagonist protocol	1/LBR 2/OCPR 3/Number oocytes	NS	Same results with luteal phase ganirelix protocol but low number of patients	

Maged, Am, Nada, Am, Abohamila, F, Hashem, At, Mostafa, Wa and Elzayat, Ar. Reproductive sciences (thousand oaks, calif.). 2015; 22 (12): 1627-1631. (26045549)	RCT	RCT (4 centers) Poor responders: Bologna criteria 160 women comparable groups	OCP D5-25 + E2 D21-28 Then rando to - D2 rFSH300+ HMG150 + flexible antag or - D2-8 antag stop and start same stimulation	1/ clinical pregnancy 2/ number of oocyte	1/ clinical pregnancy/cycle study group 30% control 10% p=0.003 2/ number oocyte study 4.3(2.5) control 2.4(2.1) p=0.02	Delayed start protocol significantly improved clinical pregnancy rate and IVF cycle parameters in PORs	Low quality evidence, no ongoing pregnancy rate Prettt with OCP followed by oestradiol in both groups (confusion?)

PART B: LH suppression and ovarian stimulation

4. Ovarian stimulation protocols

KEY QUESTION: ACCORDING TO PREDICTED RESPONSE-BASED STRATIFICATION, WHICH STIMULATION PROTOCOL IS MOST EFFICIENT AND SAFE?

A. HIGH RESPONDER

P	I	C	O
Women undergoing IVF/ICSI with predicted **HIGH** ovarian response	Stimulation protocol - Clomiphene citrate - GnRH-antagonist - GnRH-agonist - Reduced dose-FSH - Anti-oestrogens - Natural cycle IVF or MNC	Compare against one another	Efficacy: - cumulative LBR/cycle - Cumulative ongoing pregnancy rate /started cycle (fresh + frozen) - Clinical pregnancy rate/started cycle - Nr of Oocytes/ nr of MII oocyte recovery rate (yield) - number of embryo's (fresh+frozen) Safety - incidence of different grades of OHSS - grade of OHSS - incidence of cycle cancellation for hyper-response (predefined) - Bleeding - Infection - Torsion - Long-term effect on maternal/child health - other adverse events (treatment related) Patient-related outcomes - Compliance - Drop-out rates - Patient burden - QoL - Patient preferences

4A.1 GnRH ANTAGONIST VERSUS GnRH AGONIST

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Lambalk CB, Banga FR, Huirne JA, Toftager M, Pinborg A, Homburg R, van der Veen F, van Wely M. Hum Reprod Update. 2017;23(5):560-579. (28903472)	SR	PCOS women: Nine trials including 1294 couples from a PCOS population (for the primary outcome OPR)	GnRH antagonist vs GnRH agonist protocols in women with high ovarian response	LBR OPR CPR OHSS Number of oocytes	ANTAGONIST vs AGONIST -**Ongoing pregnancy** (RR0.97, 95% CI 0.84–1.11), I2=0% 9 trials (1294 women) - **Live birth** RR 0.90 (CI 0.69–1.19) 3 trials, 363 patients -**clinical pregnancy** (RR 1.01,95% CI 0.86–1.19) 10 trials, 1086 patients -**OHSS** (RR 0.53, 95% CI 0.30–0.95) 9 trials (1294 women) -**Number of oocytes** RR 040 (0.97-1.77) In PCOS patients, the number needed to prevent one case of OHSS was 14 (95% CI 7 – 50) treatments with antagonist.	In couples with PCOS, we found no evidence for a difference in ongoing pregnancy or clinical pregnancy rate, but again there was a significantly lower OHSS rate in the antagonist group. In PCOS patients, the number needed to prevent one case of OHSS was 14 (95% CI 7 – 50) treatments with antagonist. In women with PCOS and application of the GnRH antagonist as the first choice seems justified.	GRADE evidence profile Meta-analysis per patient type 1.1.2 PCOS patients 1.1.3 poor responders

Shin, J. J., Park, K. E., Choi, Y. M., Kim, H. O., Choi, D. H., Lee, W. S. and Cho, J. H. Clin Exp Reprod Med. 2018; 45 (3): 135-142 (3020274)	RCT	36, randomized across three arms, pilot study. 14 early antagonist 11 conventional antagonist start 11 agonist All three arms OC pretreatment/ All three arms start dosage 150 IU but not fixed by protocol. PCOS acc to Rotterdam	early antagonist start day 1 conventional antagonist start day 5 agonist long suppression start under OC. 1 cycle comparison.	Oocyte number Clinical Pregnancy per ET OHSS rate mod/sev OHSS rate mod/sev in cases with E2 level> 2000 Pg/ml	Oocyte number 16/12/19, NS Clinical Pregnancy per ET 50/11/22%, NS OHSS rate mod/sev 7.7/18.2/27.3% OHSS rate mod/sev in cases with E2 level> 2000 Pg/ml 12.5/40/50%	We found no difference in the number of total oocytes and mature oocytes retrieved, the clinical pregnancy rate, or the incidence of moderate-to-severe OHSS among the three different protocols.	Starting dosage high 150 and over. Power calculated on oocyte number difference: 80 cases. Power not achieved. Biological rationale not clear
Trenkic, M., Popovic, J., Kopitovic, V., Bjelica, A., Zivadinovic, R. and Pop-Trajkovic, S. Ginekol Pol. 2016; 87 (4): 265-70. (27321097)	RCT	PCOS patients 2013-2014 Inclusion criteria: PCOS Rotterdam criteria 18-39 years BMI 18-30kg/m2 Exclusion criteria: Uterine cavity abnormalities Thyroid dysfunction Abnormal prolactin levels Ovarian cyst Severe male factor infertility requiring ICSI	Group 1: Long GnRH agonist N=45 Group 2: Flexible GnRH antagonist N=45	CPR OHSS N MIIs N oocytes	Group 1 vs 2 **CPR** 44.4%(20) 46.7%(21) p=0.832 **OHSS** 15.56%(7) 6.70%(3) p= 0.241 **N MIIs** 9.90± 6.08 7.29±4.95 p=0.035 **Number of oocytes** 13.71± 6.69 10.11± 6.46 p=0.005	The GnRH antagonist protocol in PCOS patients has a pregnancy rate comparable to that of the GnRH agonist protocol. Since this protocol has a lower rate of complications and is more convenient for patients, we believe that the GnRH antagonist protocol should be used as the first-line treatment for PCOS patients in an IVF program.	RCT quality: LOW Randomization mode YES Allocation concealment NO Blinding –NO Incomplete outcome reporting: UNCLEAR Free of other bias: NO No sample size calculation Unclear number of embryos transferred in 2 groups

4A.2 Mild stimulation

4A.2.1 Clomiphene citrate (CC)

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Saleh, Se, Ismail, Mt and Elshmaa, Ns. Middle East Fertility Society Journal. 2014; 19 (1): 51-6. (CN-00988957)	CT	Prospective study with a retrospective controlled section 128 PCOS patients 20-35y	Group I: n=64 Conversion from OI to IVF CC (100mg) CD2-6 +rFSH (75IU) CD 3-6 + GnRH ant (0.25mg) Group II: n=64 Retrospective control group GnRH ant (0.25mg) + rFSH (&50-225IU) Trigger: GnRHa 0.2mg	Number of mature oocytes CPR	Group I vs II No of oocytes retrieved: (7.7± 1.3 vs. 8.1± 1.4), NS No of mature oocytes: (5.7± 1.1 vs. 6.1 ±1.3), NS Clinical PR: 43.8% vs 45.3%, NS	Conversion of high response CC-gonadotropin ovulation induction cycles in patients with PCOS to IVF–ICSI–ET; offers a safe and effective option to avoid cycle cancellation and complications, with comparable implantation and clinical pregnancy rates to those of planned IVF in age-matched PCOS patients, using the GnRH-antagonist protocol, but with a lower cost.	prospective cohort no control group high risk of selection bias
Jiang, S. and Kuang, Y Medicine (Baltimore). 2017; 96 (32): e7540. (28796038)	CS	Retrospective observational study 174 PCOS patients, BMI 25-33kg/m² Mild vs mild with CC Groups comparable at baseline	Control group: n=84 hMG 225 IU/d + MPA 10 mg/d Study group: n=90 CC 50 mg/d +hMG 225 IU/d+MPA 10 mg/d Trigger: GnRHa 0.1mg+ hCG 5000IU Freeze-all		HMG+MPA group vs HMG+MPA+CC group No oocytes retrieved: [13 (0–42) vs 5 (0–30), P=1.644E–6] No mature oocytes: [11 (0–35) vs 4 (0–26), P=3.864E–6] No moderate to severe OHSS in both groups	CC reduced the total dose of HMG, when cotreatment with HMG on the basis of MPA priming. This protocol is more cost-effective and well tolerated than HMG+MPA protocol.	

Lin, Y. H., Seow, K. M., Hsieh, B. C., Huang, L. W., Chen, H. J., Huang, S. C., Chen, C. Y., Chen, P. H., Hwang, J. L. and Tzeng, C. R. J Assist Reprod Genet. 2007; 24 (8): 331-6. (17636445)	CS	Prospective observational study 50 patients with previous excessive ovarian response	CC (100mg/d) CD 3-7 +hMG CD 4,6 and 8 +GnRH ant (2.5mg) protocol Trigger: hCG 10.000IU Control: previous cycle with GnRHa long protocol +hMG (0.25mg/day)		Long vs CC protocol: No of oocytes: 16.6±5.0 vs 12.6±4.3 Moderate OHSS: 16% (8/50) vs 2% (1/50), p<0.05 Severe OHSS: 2% (1/50) vs 0% (0/50), NS Live birth/ongoing pregnancy rate: 0% vs 19/50 Clinical PR (per cycle): 6% (3/50) vs 42% (21/50), p<0.05	This study showed that the CC/hMG/cetrorelix protocol reduced peak E2 levels and the need of coasting and prolonged coasting (≥ 4 days) in women who had excessive ovarian response to the GnRHa long protocol.	Unclear study design (prospective cohort with a retrospective control section) - high risk of selection and attrition bias

4A.2.2 AROMATASE INHIBITORS

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Chen, Y., Yang, T., Hao, C., Zhao, J. Med Sci Monit 2018; 24: 4248-53 (29925074)	CS	Retrospective study 181 PCOS patients Groups comparable at baseline	Long GnRHa protocol Letrozole group n=78 Letrozole was given when E2>4000pg/ml and stopped before day of oocyte retrieval Non-letrozole group n=103 Trigger: 4.000-5.000IU hCG	No of oocytes retrieved No of MII oocytes OHSS rate Clinical PR	Non LE vs LE group **No of oocytes retrieved:** 18.9±6.4 vs 19.9±6.2, NS **No of mature oocytes:** 16.6±6.1 vs 17.8±6.2, NS **OHSS rate:** 7.8% (8/103) vs 2.6% (2/78), NS **Clinical PR:** 47,4% (27:57) vs 60.5 (23/38), NS		

4A.2.3 REDUCED DOSE PROTOCOL

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Oudshoorn, S. C., van Tilborg, T. C., Eijkemans, M. J. C., Oosterhuis, G. J. E., Friederich, J., van Hooff, M. H. A., van Santbrink, E. J. P., Brinkhuis, E. A., Smeenk, J. M. J., Kwee, J., de Koning, C. H., Groen, H., Lambalk, C. B., Mol, B. W. J., Broekmans, F. J. M. and Torrance, H. L. 32(12):2506-2514 (29121269)	RCT	521 expected high responders AFC > 15	255 women to 100IU daily FSH 266 women to 150IU daily FSH	PRIMARY was ongoing pregnancy achieved within 18 months after randomization and resulting in a live birth. SECONDARY occurrence of OHSS and cost-effectiveness OTHER Biochemical pregnancy Clinical pregnancy Ongoing pregnancy Cycle cancellation rate Live birth (fresh only)c CLBR 1st cycle Live birth (fresh and cryo) Time to ongoing pregnancy leading to live birth (days)	100IU vs 150IU Ongoing pregnancy within 18 months of FU resulting in live birth 169 (66.3%) 185 (69.5%) RR 0.953 [0.85–1.07] Clinical pregnancy 180 (70.6%) 207 (77.8%) RR 0.907 [0.82–1.00] NS Ongoing pregnancy 173 (67.8%)e 189 (71.1%) RR 0.955 [0.85–1.07] NS Live birth (fresh only)c 65 (25.7%) 67 (25.2%) NS CLBR 1st cycle Live birth (fresh and cryo) 91 (36.0%) 104 (39.1%) NS Number of OHSS events 24/456 (5.2%) 56/474 (11.8%) p=0.001 Mild 18/456 (3.9%) 40/474 (8.4%) p=0.008 Moderate 0/456 11/474 (2.3%) p=0.001 Severe 6/456 (1.3%) 5/474 (1.1%) p=0.712	In women with a predicted hyper response scheduled for IVF/ICSI, a reduced FSH dose does not affect live birth rates but reduce the incidence of mild and moderate OHSS, but had no impact on severe OHSS. Future studies should therefore also include the effect of prevention measures such as cancellation for hyper response, GnRH-agonist triggering and a freeze-all policy. However, as cycle cancellation occurred twice as often in the first cycle in the reduced dose group, a definite claim advocating FSH dose reduction in predicted hyper responders cannot be made until results from future studies comparing various safety management approaches have become available.	RCT quality: MODERATE/HIGH Randomization mode OK Allocation concealment OK Blinding –none Incomplete outcome reporting: No (number of oocytes were reported per oocyte retrieval) Free of other bias: NO Mixing agonist and antagonist protocols Allowing dose adjustments in 2nd cycle Cycle cancellation in high response should be considered with caution given that this is likely to have happened mostly in Agonist cycles since there is no possibility to trigger with GnRH agonist Freeze all policy was not adopted and this is current clinical practice.

4A.3 Modified natural cycle

No relevant studies were identified

B. NORMAL RESPONDER

P	I	C	O
Women undergoing IVF/ICSI with predicted **NORMAL** ovarian response	Stimulation protocol - Clomiphene citrate - GnRH-antagonist - GnRH-agonist - Reduced-dose FSH - Anti-oestrogens	Compare against one another	Efficacy: - cumulative LBR/cycle - Cumulative ongoing pregnancy rate /started cycle (fresh + frozen) - Clinical pregnancy rate/started cycle - Nr of Oocytes/ nr of MII oocyte recovery rate (yield) - number of embryo's (fresh+frozen) Safety - incidence of different grades of OHSS - grade of OHSS - incidence of cycle cancellation for hyper-response (predefined) - Bleeding - Infection - Torsion - Long-term effect on maternal/child health - other adverse events (treatment related) Patient-related outcomes - Compliance - Drop-out rates - Patient burden - QoL - Patient preferences

Papers selected for this question that were already included in the evidence table of question 6	**Type**
Verpoest, W. M., Kolibianakis, E., Papanikolaou, E., Smitz, J., Van Steirteghem, A. and Devroey, P. Reprod Biomed Online. 2006; 13 (2): 166-72. (16895628)	RCT

4B.1 GnRH ANTAGONIST VERSUS GnRH AGONIST

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Lambalk CB, Banga FR, Huirne JA, Toftager M, Pinborg A, Homburg R, van der Veen F, van Wely M. Hum Reprod Update. 2017;23(5):560-579. (28903472)	SR	26 trials, entailing 7191 couples from a general IVF population Definition of general IVF population:		Ongoing pregnancy rate	Ongoing pregnancy rate (26 RCT, RR 0.89, 95% CI 0.82–0.96, 7191 women)		GRADE evidence profile Meta-analysis per patient type 1.1.1 General

4B.2 Mild stimulation

4B.2.1 Clomiphene citrate (CC)

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Zander-Fox, D., Lane, M., Hamilton, H. and Tremellen, K. J Assist Reprod Genet. 2018; 35 (6): 1047-1052. (29633146)	CS	25 cases vs 50 controls Matched for age and BMI from a Good Prognosis Comparator cohort	Cases: CC 10 mg day 2-6, followed by 100 or 150 mg <60kg> Corifollitropin on day 6, with top up daily rFSH from day 13 if hCG criteria not met	Creation of at least four mature oocytes. Preventing the need of top up daily FSH	Not recorded. Oocyte number 6.4 vs 10.7, P=0.01 44% vs 0%, P not given	Sequential clomiphene CFA protocol does not appear to be an optimal regime for low impact IVF treatment as it does not provide adequate COH from a single CFA injection and results in lower fresh embryo transfer pregnancy rates and fewer embryos for cryopreservation.	Differences in Duration Infertility and Infertility Diagnosis. No RCT

4B.2.2 AROMATASE INHIBITORS

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Mukherjee, S., Sharma, S. and Chakravarty, B. N. J Hum Reprod Sci. 2012; 5 (2): 170-4. (23162355)	RCT	94 women between 25 and 35 years of age without any demonstrable cause of infertility, whose husbands were suffering from azoospermia were chosen for IVF-ICSI following TESA January 2009 to December 2010	Group A Let+rFSH 42 women who received Letrozole 5 mg daily from D3 to D7 +rFSH 75IU from D5 onward till hCG trigger Group B rFSH 52 women rFSH 150- 225IU from D2 antagonist 0.25 ml S/C	CPR Multiple pregnancy OHSS N MIIs N Grade 1 embryos Endo thickness Gonadotropin dose	**Group A vs B** CPR 36% VS 33% P=0.82 OHSS 0 VS 7/52 P=0.01 N MIIs 4.6 (2.5) vs 4.9 (2.3) p=0.55	Adjunctive use of letrozole with gonadotrophin, especially in women where male factor infertility is the sole indication going for IVF-ICSI treatment, may be an effective mean of low-cost IVF therapy. It not only offers a cost-saving stimulation protocol but also reduces unnecessary side effects like OHSS and multiple pregnancies yet maintain a descent success rate. Although, we need more RCTs to come to a conclusion on regular use of such combined protocol.	RCT quality: LOW Randomization mode YES Allocation concealment NO Blinding –NO Incomplete outcome reporting: Unclear Free of other bias: NO No sample size calculation Patient with azoospermia Not clear whether patients were normal responders (lack of ovarian reserve markers data)

Verpoest, W. M., Kolibianakis, E., Papanikolaou, E., Smitz, J., Van Steirteghem, A. and Devroey, P. Reprod Biomed Online. 2006; 13 (2): 166-72. (16895628)	RCT	20 patients 10 letrozole 10 no-letrozole Inclusion criteria were: (i) subfertility for more than 1 year requiring IVF/ICSI, (ii) age younger than 39 years, (iii) first or second IVF/ICSI trial and (iv) use of ejaculated spermatozoa only. Exclusion criteria were: (i) patients belonging to any of the WHO classification groups (I, II or III) of ovulatory disorders, (ii) oligomenorrhoea (menstrual cycle >35 days), (iii) polymenorrhoea (menstrual cycle<21 days), (iv) early follicular phase FSH concentrations ≥15 IU/l, (v) endometriosis AFS grades III and IV, (vi) IVF/ICSI PGD and (vii) BMI ≥28	Group A (n = 10), Letrozole 2.5 mg daily from day 2 until day 6 of the cycle + rFSH starting on day 2 of the cycle Group B (n = 10), rFSH starting on day 2 of the cycle Both groups, a constant daily dose of 150 IU rhFSH was used for stimulation and GnRH antagonist 8-month period from January until September 2003	CPR PR N oocytes	**Group A vs B** Mean no. of oocytes (SD) 13.8 (9.24) vs 9.6 (7.73) Positive HCG rate 50% vs 20% CPR 50% vs 20%	This pilot study supports the idea that aromatase inhibitors can contribute to normal potential of implantation and follicular response, without having negative anti-oestrogenic effects.	QUALITY: LOW/MODERATE Randomization mode – adequate Bias LOW Allocation concealment+ No Bias HIGH Blinding NO Bias HIGH Incomplete outcome data – NO Bias HIGH Selective reporting- NO Bias LOW Other bias: LOW Very small RCT unable to provide any conclusions for pregnancy outcomes.

4B.2.3 REDUCED DOSE PROTOCOL

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Sterrenburg, M. D., Veltman-Verhulst, S. M., Eijkemans, M. J., Hughes, E. G., Macklon, N. S., Broekmans, F. J., Fauser, B. C., Hum Reprod Update 2011; 17(2): 184-96 (20843965)	SR	5 RCT, 960 women	COMPARISON A 100 vs 200 IU/day rFSH	Number of oocytes retrieved CPR OHSS	Number of oocytes retrieved MD -3.5 (95% CI -4.86, -2.27), p<0.05 CPR: OR 0.95 (95% CI 0.69-1.30), NS OHSS OR 0.58 (95% CI 0.18-1.90), NS	This meta-analysis suggests that the optimal daily recFSH stimulation dose is 150 IU/day in presumed normal responders younger than 39 years undergoing IVF. Compared with higher doses, this dose is associated with a slightly lower oocyte yield, but similar pregnancy and embryo cryopreservation rates. Furthermore, the wide spread adherence to this optimal dose will allow for a considerable reduction in IVF costs and complications	QUALITY: MODERATE -Reporting on trials quality (randomization mode, blinding, allocation concealment) -No reporting on other sources of bias -Proper search strategy live Meta-analysis clearly concluding in favor of a dose of 150IUrFSH despite the difference in the number of oocytes retrieved in favor of higher doses. Although it is clear that higher doses do not increase live birth rates in the fresh IVF cycle, we cannot exclude a beneficial effect of higher doses and higher oocyte yield on cumulative live births

Baart EB, Martini E, Eijkemans MJ, Van Opstal D, Beckers NG, Verhoeff A, Macklon NS, Fauser BC. Hum Reprod. 2007;22(4):980-8. (17204525)	RCT	111 patients 44 conventional arm 67 mild arm groups comparable women below 38 years of age, with a regular indication for IVF and with a partner with a sperm count .5 million progressively motile sperm per ml (prior to capacitation)	Conventional stimulation: Long GnRH agonist with fixed daily dose of 225 IU r FSH Mild stimulation: fixed dose of 150 IU rFSH starting on cycle Day 5. GnRH antagonist co-treatment at 0.25 mg per day s.c. was initiated on the day the leading follicle reached a diameter of 14 mm December 2002 to August 2005.	Primary outcome(s) 1. number of oocytes obtained 2. proportion of chromosomally abnormal embryos per patient. This was expressed as the ratio of abnormal embryos on the number of embryos diagnosed per patient.	CONVENTIONAL vs MILD Oocytes retrieved (n) 12.1+5.7 vs 8.3+4.7 p=0.01 Diff (5%CI) 3.7 (1.6–5.9)	Mild ovarian stimulation results in fewer oocytes and a decreased proportion of aneuploid and mosaic embryos. However, based on the current findings, we would like to propose that future ovarian stimulation strategies should not focus on obtaining as many oocytes as possible. Instead, strategies should aim at less interference with ovarian physiology, thus minimizing embryo aneuploidy rate and facilitating selection of the best quality embryo for transfer.	QUALITY: MODERATE Randomization mode – Adequate Bias LOW Allocation concealment+ adequate Bias LOW Blinding NO Bias HIGH Incomplete outcome data – NO Bias HIGH Selective reporting- NO Bias LOW Other bias: LOW PGS study with biopsy of 9 Chromosomes and FISH. Currently outdated technique
Blockeel, C., Sterrenburg, M. D., Broekmans, F. J., Eijkemans, M. J., Smitz, J., Devroey, P. and Fauser, B. C. J Clin Endocrinol Metab. 2011; 96 (4): 1122-8. (21307142)	RCT	Inclusion: regular indication and first treatment cycle of IVF; 18 and 36 yr.; BMI 18 - 29 kg/m2; regular cycle (25–35); FSH (< 12 U/liter); no major uterine or ovarian abnormalities; no endocrine/metabolic abnormalities; no PCOS; no severe endometrioses (≥ grade 3).	GROUP 1 FSH fixed 150 IU/d [D2 - hCG] + ganirelix 0.25 mg [D6] N= 36 GROUP 2 rFSH fixed 150 IU/d [D5 - hCG] + ganirelix 0.25 mg [D6] n=40 2008 - 2009	OPR Positive hCG Total gonadotropin dose Stimulation days	Group 1 vs Group2 OPR 28% vs 25% p=0.78 Positive hCG 36% vs 25% p=0.29 Total gonadotropin dose 1364 (226) vs 1177(295) p <0.01 Stimulation days 9.1(1.5) vs 7.8 (2.0) p <0.01	This study shows that the administration of recFSH starting on d 2 or d 5 of the cycle in a GnRH antagonist protocol for IVF/intracytoplasmic sperm injection patients yields a comparable endocrine profile and follicular development. Future studies should focus on the design of more patient-tailored ovarian stimulation protocols. Whether there is a difference in embryo quality, pregnancy rate, and live birth rate remains to be determined in a larger trial.	QUALITY: LOW Randomization mode –NO Bias HIGH Allocation concealment- NO Bias HIGH Blinding NO Bias HIGH Incomplete outcome data – adequate Bias LOW Selective reporting- NO Bias LOW Other bias: YES Small study. Clinical data based on a small number of events. Severely underpowered to drive conclusions

Hohmann, Fp, Macklon, Ns and Fauser, Bc. The Journal of clinical endocrinology and metabolism. 2003; 88 (1): 166-73. (12519847)	RCT	169 patients randomized Inclusion criteria: 20 - 38 yr; BMI 19- 29; regular cycles (25 - 35); no relavant disease; no severe endometriosis; no ovarian abnormalities; ≤ 3 IVF cycles; no previous POR; no previous OHSS. Exclusion: NA	GROUP 1: Long agonist protocol 150rFSH GROUP 2: Flexible antagonist protocol 150rFSH D2 start GROUP 3: Flexible antagonist protocol 150rFSH D5 start	OPR Positive hCG N oocytes	Group 1 vs 2 vs 3 OPR 8 (18%) vs 8 (17%) vs 8 (16%) p=0.98 Positive hCG 10 (22%) vs 10 (20%) vs 10 (20%) p=0.96 N oocytes 9 (1–25) vs 8 (2–31) vs 7 (1–27) p=0.57	Application of the described mild OS protocol resulted in pregnancy rates per started IVF cycle similar to those observed after profound stimulation with GnRH agonist cotreatment despite shorter stimulation and a 27% reduction in exogenous FSH. A higher cancellation rate before oocyte retrieval was compensated by improved embryo quality concomitant with a higher chance of undergoing embryo transfer. A relatively low number of oocytes retrieved after mild ovarian stimulation distinctly differs from the pathological reduction in the number of oocytes retrieved after profound ovarian stimulation (poor response) associated with poor IVF outcome. The relatively small number of oocytes obtained after mild ovarian stimulation may represent the best of the cohort in a given cycle	QUALITY: LOW Randomization mode – Adequate Bias LOW Allocation concealment- NO Bias HIGH Blinding NO Bias HIGH Incomplete outcome data – adequate Bias LOW Selective reporting- NO Bias LOW Other bias: UNCLEAR

C. LOW RESPONDER

P	I	C	O
Women undergoing IVF/ICSI with predicted **LOW** ovarian response	Stimulation protocol - Clomiphene citrate - GnRH-antagonist - GnRH-agonist - Reduced-dose FSH protocol - Higher dose FSH protocol - Anti-oestrogens - Natural cycle IVF or MNC	Compare against one another	Efficacy: - cumulative LBR/cycle - Cumulative ongoing pregnancy rate /started cycle (fresh + frozen) - Clinical pregnancy rate/started cycle - Nr of Oocytes/ nr of MII oocyte recovery rate (yield) - number of embryo's (fresh+frozen) Safety - incidence of different grades of OHSS - grade of OHSS - incidence of cycle cancellation for hyper-response (predefined) - Bleeding - Infection - Torsion - Long-term effect on maternal/child health - other adverse events (treatment related) Patient-related outcomes - Compliance - Drop-out rates - Patient burden - QoL - Patient preferences

Papers selected for this question that were already included in the evidence table of question 6	**Type**
Ebrahimi, M., Akbari-Asbagh, F. and Ghalandar-Attar, M. Int J Reprod Biomed (Yazd). 2017; 15 (2): 101-108. (28462402)	RCT

4C.1 GnRH antagonist versus GnRH agonist

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Lambalk CB, Banga FR, Huirne JA, Toftager M, Pinborg A, Homburg R, van der Veen F, van Wely M. Hum Reprod Update. 2017;23(5):560-579. (28903472)	SR	6 studies Total cases 780	410 GnRH antagonist vs 370 GnRH agonist	Ongoing PR Clinical PR Oocyte number Live Birth	Ongoing PR OR 0.87 (0.65-1.17) Clinical PR OR: 0.85 (0.66-1.10) Oocyte number: -0.08 (-0.59-0.43) Live Birth (3studies): 0.89 (0.56-1.41)	In poor responders, application of the GnRH antagonist as the first choice seems justified.	GRADE evidence profile GnRH ant vs long GnRHa 1.2.3 poor responder
Xiao, J., Chang, S. and Chen, S. Fertil Steril. 2013; 100 (6): 1594-601.e1-9. (24055048)	SR	7 studies	GnRH antagonist 417 vs Short GnRH agonist 318	Clinical PR Number of oocytes	CPR (7 RCT, 735) OR 1.33 (0.88-2.01) Number of oocytes retrieved (5 RCT, 417) MD -0.54 (-0.98 - -0.10)	Compared with GnRH agonist protocols, the GnRH antagonist protocol is associated with fewer oocytes retrieved, lower E2 levels, and thinner endometrium whereas the clinical pregnancy and cycle cancellation rates are similar.	GRADE evidence profile GnRH ant vs short GnRHa RCT and CCTs included. So overall low to moderate quality
Demirol, A. and Gurgan, T. Fertil Steril. 2009; 92 (2): 481-5. (18990368)	RCT	90 patients Definition poor response 3 criteria baseline (day 3) FSH > 15 mIU/mL <4 oocytes in all previous IVF attempts, A minimum two (range, 2–4) previous IVF cycles with poor ovarian response (E2 concentration on the day of hCG njection < 500 pg/mL or <4 MIIs retrieved).	Group A Microdose flare-up OCP+leuprolide +450IUhMG Group B GnRH antagonist 450IU hMG + Cetrorelix Duration years not specified	CPR MIIs Cancellation rate	A vs B Cancellation rate, n (%) 3/45 (6.7%)vs 5/45 (11.1%) p=0.714 No MIIs retrieved 4.3(2.13) vs 3.1(1.09) p= 0.001 CPR% 12/42 (28.6) vs. 6/40 (15.0) p=0.204	The microdose flare-up protocol seems to have a better outcome in poor-responder patients, with a significantly higher mean number of mature oocytes retrieved and higher implantation rate The results presented in this study indicate better results in terms of total gonadotropin dose used, number of mature oocytes retrieved, and implantation rate when COH is associated with the microdose flare-up GnRH-a compared with the GnRH antagonist for poor responder patients.	RCT quality: LOW/Moderate Randomization mode: OK Allocation concealment OK Blinding – Single Blind Incomplete outcome reporting: NO Free of other bias: NO Low/moderate quality small RCT Sample size was 695 and only 90 patients were recruited because this would take many years according to the authors

Merviel, P., Cabry-Goubet, R., Lourdel, E., Devaux, A., Belhadri-Mansouri, N., Copin, H. and Benkhalifa, M. Reprod Health. 2015; 12 52. (26025412)	RCT	440 women were prospectively randomized, after an interval of less than 4 months Definition: <4 MIIs were retrieved in the first stimulated IVF cycle using the GnRH agonist long protocol (P1 protocol) Groups comparable	GROUP A (220) OCP + flare-up GnRH-agonist GROUP B (220) GnRH-antagonist protocol Between 2004 and 2011 at Amiens University hospital	OPR CPR MIIs COCs	GROUP A VS GROUP B No of oocytes retrieved (per pick-up) 1224 (6.0 ± 4.1) 1218 (6.2 ± 4.9) No of M2 oocytes retrieved 894(4.3±3.7) vs 913(4.6 ±4.1)NS No of cancelled cycles (%) 42 (19.0) vs 51 (23.1) NS CPR% (%) 17.9 vs 15.9 NS OPR % 14.6 vs 14.2 NS	The implantation and ongoing pregnancy rates per embryo transferred were not significantly different with the contraceptive pill + flare-up GnRH-a protocol compared to the multidose GnRH antagonist protocol. It is suggested that current strategies for the management of poor responders be reconsidered in the light of the potential contribution of age and the effect of life style changes on fertility potential. A customized policy of ovarian stimulation in these patients including mild stimulation protocols, sequential IVF cycles, oocytes-embryos freeze all protocols and blastocyst transfers after screening may improve the clinical outcome.	RCT quality: LOW Randomization mode OK) Allocation concealment NO(low) Blinding – NO(low) Incomplete outcome reporting: OK Free of other bias: NO Significantly more embryos transferred in 1 arm Low quality small RCT Sample size calculation: yes for pregnancy - correct

Schimberni, M., Ciardo, F., Schimberni, M., Giallonardo, A., De Pratti, V. and Sbracia, M. Eur Rev Med Pharmacol Sci. 2016; 20 (20): 4354-4361. (27831635)	RCT	250 poor responders in a previous cycle: 2 of the follwing criteria: - Age>40 - FSH>12 - ≤ 3 oocytes in previous IVF - E2 < 1500 in previous IVF Rome Italy, between July 2014 and December 2015	A: 68: CC(100x5) + FSH (450) + antagonist B: 71: FSH 450 + antagonist C; 75: Short agonist + FSH 450 July 2014 to December 2015. All patients comparable for age, BMI, duration of infertility, basal FSH, infertility causes	Clinical PR # oocytes # MII	**A vs B vs C** No. of retrieved oocytes 3.8 ± 2.9 vs 3.41±1.9 vs3.8±2.39 p=0.542 No. MIIs 2.31±2.05 vs 2.3±1.7 vs 3.13±2.13 p=0.015 (C vs. A, C vs. B) Clinical pregnancy rate 5.9% vs 14.1% vs 29.3% p=0.0291 (C vs. B), 0.001 (C vs. A, B vs. A)	The short GnRH agonist protocol with its flare-up effect should be the first choice in poor responder women especially cases of women 40 years old or more, whereas the flexible GnRH antagonist protocol seems to be less effective in these patients. Instead, the association of CC to high doses of gonadotropins in the treatment of poor responder patients should be avoided due to its very low success rate and the high cost per baby born	RCT quality: LOW Randomization mode No (low) Allocation concealment NO(low) Blinding – NO(low) Incomplete outcome reporting: OK Free of other bias: NO Low quality small RCT Sample size calculation: Not clear for which pregnancy % was calculated. Sample-size calculation was based on previous experience on poor responder patients, expecting an observed difference of 20% among the protocols in pregnancy rate for a power of 80% an alpha of 5%, 62 women needed to be recruited into each arm.

4C.2 Mild stimulation

4C.2.1 Clomiphene citrate (CC)

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Bechtejew TN, Nadai MN, Nastri CO, Martins WP. Ultrasound Obstet Gynecol. 2017; doi: 10.1002/uog.17442. (28236310)	SR	4 RCTs 1165 women		Live birth rate	live birth (4 RCT, RR 0.87, 95% CI 0.62–1.22, 1165 women)		CC in stimulation protocol (combined with FSH)
Ragni, G. Levi-Setti, P. E. Fadini, R. Brigante, C. Scarduelli, C. Alagna, F. Arfuso, V. Mignini-Renzini, M. Candiani, M. Paffoni, A. Somigliana, E. Reprod Biol Endocrinol 2012; 10:114 (23249758)	RCT	Randomized 304 Analyzed N=291 Inclusion criteria: 1) indication to IVFICSI; 2) age 18–42 years; 3) day 3 serum FSH > 12 IU/ml on at least two occasions or previous poor response (≤ 3 oocytes with a conventional stimulation protocol) in a previous IVF cycle.	CC versus FSH. 1) CC: Day 3–Day 7: CC 150 mg/ day; The hCG triggering of ovulation (250 mg) was performed when at least one follicle with a mean diameter! 18 mm. 2) GnRH agonist (Triptoreline) (0.1 mg) was injected daily from Day 1/ 2 and r-FSH 450 IU (adjustable) was administered from Day 3 until hCG day	LBR CPR No of oocytes Cancelled cycles	CLOMIPHENE vs. HIGH DOSE FSH Cancelled cycles 21 (14%) vs. 21 (14%) p=1.00 Number of oocytes retrieved 1.1 ± 1.1 vs. 2.0 ± 1.8 p<0.001 PR per started cycle 5% (8/145) vs. 6% (9/146) p=1.00 LBR per started cycle 3% (5/145) vs. 5% (7/146) p=0.77 OR: 0.80 (95%CI: 0.25-2.63). THESE FIGURES ARE AS REPORTED AS FROM THE META_ANALYSIS by SONG! LB: 0.71 (0.22 – 2.29) CP: 0.89 (0.33 – 2.38)	In women with compromised ovarian reserve selected for in vitro fertilisation, ovarian stimulation with clomiphene citrate or high-dose gonadotropins led to similar chances of pregnancy but the former is less expensive.	Sample size not reached: 472. 304 women included, 13 dropped out. Multicenter, registered trial. Non-blinded. Study lacks power to demonstrate a potentially relevant difference in LBR RCT quality: LOW Randomization mode NO Allocation concealment NO Blinding –NO Incomplete outcome reporting: NO(low) Free of other bias: NO

Schimberni, M., Ciardo, F., Schimberni, M., Giallonardo, A., De Pratti, V. and Sbracia, M. Eur Rev Med Pharmacol Sci. 2016; 20 (20): 4354-4361. (27831635)	RCT	250 poor responders in a previous cycle: 2 of the follwing criteria: - Age>40 - FSH>12 - ≤ 3 oocytes in previous IVF - E2 < 1500 in previous IVF Rome Italy, between July 2014 and December 2015	A: 68: CC(100x5) + FSH (450) + antagonist B: 71: FSH 450 + antagonist C; 75: Short agoist + FSH 450 July 2014 to December 2015. All patients comparable for age, BMI, duration of infertility, basal FSH, infertility causes	Clinical PR # MII No of retrieved oocytes	**A vs B vs C** No. of retrieved oocytes 3.8 ± 2.9 vs 3.41±1.9 vs3.8±2.39 p=0.542 No. MIIs 2.31±2.05 vs 2.3±1.7 vs 3.13±2.13 p=0.015 (C vs. A, C vs. B) Clinical pregnancy rate 5.9% vs 14.1% vs 29.3% p=0.0291 (C vs. B), 0.001 (C vs. A, B vs. A)	The short GnRH agonist protocol with its flare-up effect should be the first choice in poor responder women especially cases of women 40 years old or more, whereas the flexible GnRH antagonist protocol seems to be less effective in these patients. Instead, the association of CC to high doses of gonadotropins in the treatment of poor responder patients should be avoided due to its very low success rate and the high cost per baby born	RCT quality: LOW Randomization mode No (low) Allocation concealment NO(low) Blinding – NO(low) Incomplete outcome reporting: OK Free of other bias: NO Low quality small RCT Sample size calculation: Not clear for which pregnancy % was calculated. Sample-size calculation was based on previous experience on poor responder patients, expecting an observed difference of 20% among the protocols in pregnancy rate for a power of 80% an alpha of 5%, 62 women needed to be recruited into each arm.

4C.2.2 AROMATASE INHIBITORS

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Bechtejew TN, Nadai MN, Nastri CO, Martins WP. Ultrasound Obstet Gynecol. 2017; doi: 10.1002/uog.17442. (28236310)	SR	1 RCT 53 women			Live birth rate (1RCT, RR 2.60, 95% CI 0.55-12.22, 53 women)		GRADE evidence profile
Ebrahimi, M., Akbari-Asbagh, F. and Ghalandar-Attar, M. Int J Reprod Biomed (Yazd). 2017; 15 (2): 101-108. (28462402)	RCT	70 poor responders Definition: Bologna criteria Comparable baseline characteristics	GROUP A n=35 letrozole+GnRH-antagonist (LA) GROUP B n=35 placebo+GnRH-antagonist Iran between March and August 2015.	CPR PR Cancellation rate MIIs COCs	Oocyte retrieved (n) 2.80 ± 1.09 vs 2.60±1.51 p=0.81 Metaphase II oocytes (n) 2.03 ± 0.12 vs 2.09 ± 0.13 p=0.84 Total cancellation rate% 20 vs 22.9, p=0.08 Cycle cancellation % 15.6 vs 16.3, p=0.14 Biochemical pregnancy rate (%): 25.7 vs 20, p=0.34 Clinical pregnancy rate (%) 14.3 vs. 11.4, p=0.12	In conclusion, there is insufficient evidence to establish recommendation on the use of low dose letrozole as an adjuvant in ART stimulation protocols of poor responder patients. The use of letrozole in GnRH-antagonist cycles does not improve clinical outcomes in poor responder patients undergoing intracytoplasmic sperm injection.	RCT quality: MODERATE/HIGH Randomization mode OK Allocation concealment OK Blinding –Double blind Incomplete outcome reporting: OK Free of other bias: NO No Sample size Small sample size to derive conclusions on clinical outcomes

Eftekhar, M., Mohammadian, F., Davar, R. and Pourmasumi, S. Iran J Reprod Med. 2014; 12 (11): 725-30. (25709627)	RCT	184 women Definition: one or more previous failed ART cycle in which three or fewer oocytes have been retrieved and had serum ER2R levels ≤500 pg/ml on the day of hCG administration Comparable groups	Group A (n= 80), CC/Gns/ Antagonist Group B (n= 87), Letrozole/Gns/ Antagonist Iran, between March 2009 and May 2011 .	CPR PR	**Group A vs B** Chemical pregnancy n, (%) 10.87 (11.5%) vs 11.80 (13.8%), p=0.816 Clinical pregnancy rate n(%) 7 (8%) vs 9 (11.3%) p=0.601	In mild ovarian stimulation protocol, letrozole and clomiphene have similar value for the poor responder. The optimal treatment strategy for these patients remains debated	RCT quality: LOW Randomization mode OK Allocation concealment NO Blinding –NO Incomplete outcome reporting: Not ok (not ITT) Free of other bias: NO No Sample size calculation Small sample size to derive conclusions on clinical outcomes

4C.2.3 REDUCED DOSE PROTOCOL

No relevant studies were identified

4C.3 HIGHER GONADOTROPIN DOSE

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion
Lensen, Sarah F, Wilkinson, Jack, Mol, Ben Willem J, La, Marca Antonio, Torrance, Helen and Broekmans, Frank J. Cochrane Database of Systematic Reviews. 2017; (6): (29388198)	SR	5 RCTs in predicted low responders. Overall pooling of studies not possible due to variation of gonadotrophin dose in study and control arms.	2 studies comparing 300/ 450 IU daily versus 150 IU daily (Klinkert 2005, van Tilborg 2017). 2 studies comparing 400/ 450 IU daily versus 300 IU daily (Harrison 2001, Batsu 2016). 1 study comparing 600 IU daily versus 450 IU daily (Lefebrve 2015).	Live birth/ ongoing pregnancy rate. Clinical pregnancy Number of oocytes Cycle cancelation for poor response	Live birth or ongoing pregnancy 300/450 IU vs 150 IU: OR (95% CI) 0.71[0.32-1.58] 400/450 IU vs 300 IU: OR (95% CI) 0.77[0.19-3.19] 600 IU vs 450 IU: OR (95% CI)1.33 [0.71-2.52] Clinical pregnancy 300/450 IU vs 150: OR(95%CI) 0.50[0.25-1.00] 400/450 IU vs 300 IU: OR(95%CI) 0.84[0.26-2.69] 600 IU vs 450 IU: OR(95%CI) 1.14[0.66-1.99] Number of oocytes 300/450 IU vs 150 IU: MD(95%CI) 0.69 (0.50 to 0.88). 400/450 IU vs 300 IU: MD(95%CI) -0.03; (-0.30 to 0.88). 600 IU vs 450 IU: MD(95%CI) 0.08; (-0.04 to 0.20). Cycle cancellations for poor response 300/450 IU vs 150 IU OR (95% CI) 0.23[0.11-0.47) 400/450 IU vs 300 IU OR (95% CI) 1.47[0.62-3.49] 600 IU vs 450 IU: OR (95% CI) 0.86[0.50-1.50	Due to differences in dose comparisons, caution is warranted in interpreting the findings of five small trials assessing predicted low responders. The effect estimates were very imprecise, and increased FSH dosing may or may not have an impact on rates of live birth/ ongoing pregnancy, OHSS and clinical pregnancy.

4C.4 MODIFIED NATURAL CYCLE

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Morgia, F., Sbracia, M., Schimberni, M., Giallonardo, A., Piscitelli, C., Giannini, P. and Aragona, C. Morgia Fertil Steril. 2004; 81 (6): 1542-7. (15193474)	RCT	125 women (215 cycles) Definition: <43 years and had undergone a previous IVF cycle at our IVF clinic that resulted in a poor response, that is, three or fewer follicles recruited or cycle cancelled because of no follicle activation. Comparable groups	Group A MNC 55 patients 114 cycles Group B microdose GnRH analog flare 70 women 101 cycles January 2000 and July 2002	PR Cycles with oocytes Cycles with ET	Pregnancy/cycle (%) 6.1 vs 6.9 NS Pregnancy/transfer (%) 14.9 vs 10.1 NS Results also presented for 3 age categories <36, 36-39, >39 but groups are very small	In our study, the use of IVF with a natural-cycle protocol was a valuable alternative to COH in poor responders. In these patients, natural-cycle IVF is at least as effective as COH, especially in younger patients, with a better implantation rate. This alternative should be proposed to poor responders, because the natural cycle is cheaper than hyperstimulation and permits a more "friendly" approach to IVF with results comparable to those with COH, at least in these patients.	RCT quality: LOW/MODERATE Randomization mode OK Allocation concealment OK Blinding – NO(low) Incomplete outcome reporting: Unclear Free of other bias: NO LOW/MODERATE No sample size calculation Results also presented for 3 age categories <36, 36-39, >39 but groups are very small

5. LH suppression regimes

KEY QUESTION: WHICH LH SUPPRESSION REGIMEN IS PREFERABLE?

P	I	C	O
Women undergoing IVF/ICSI	- GnRH agonist (long) - GnRH agonist flare up - GnRH antagonist - Progestin	Compare against one another	Efficacy: - cumulative LBR/cycle - Cumulative ongoing pregnancy rate /started cycle (fresh + frozen) - Clinical pregnancy rate/started cycle - Nr of Oocytes/ nr of MII oocyte recovery rate (yield) - number of embryo's (fresh+frozen) Safety - incidence of different grades of OHSS - grade of OHSS - incidence of cycle cancellation for hyper-response (predefined) - Bleeding - Infection - Torsion - Long-term effect on maternal/child health - other adverse events (treatment related) Patient-related outcomes - Compliance - Drop-out rates - Patient burden - QoL - Patient preferences

5.1 GnRH AGONIST PROTOCOLS

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Siristatidis, C. S., Gibreel, A., Basios, G., Maheshwari, A. and Bhattacharya, S. Cochrane Database Syst Rev. 2015; (11): Cd006919. (26558801)	SR		Long GnRH agonist protocol Short GnRH agonist protocol Ultrashort GnRH agonist protocol	Live birth rate Ongoing pregnancy rate Clinical pregnancy rate OHSS	**Long vs short GnRH agonist protocol** **LBR**: 4 RCT, OR 1.60, 95% CI 0.85-3.03, 295 wome **Long vs ultrashort GnRH agonist protocol** **LBR**: 1 RCT, OR 1.78, 95% CI 0.72-4.36, 150 women **Short vs ultrashort GnRH agonist protocol** **CPR**: 1 RCT, OR 1.33, 95% CI 0.47-3.81, 82 women **Long GnRH agonist protocol, luteal vs follicular start** **LBR/OPR** 1 RCT, OR 1.89, 95% CI 0.87-4.10, 223 women **Long GnRH agonist protocol, continuation vs stopping at start stimulation** **OPR:** 3 RCT, OR 0.75, 95%CI 0.42-1.33, 290 women **OHSS** 1 RCT, OR 0.47, 95% CI 0.04-5.35, 96 women **Long GnRH agonist protocol, continuation vs reducing dose** PR: 4 RCT, OR 1.02, 95% CI 0.68-1.52, 407 women		GRADE evidence profile -Long vs short GnRHa -Long vs ultrashort GnRHa -Luteal vs follicular start -Continuation vs stopping at start stimulation -Continuation vs dose reduction at start stimulation -2 vs 3 weeks administration before stimulation.

Vercellini, P., Consonni, D., Dridi, D., Bracco, B., Frattaruolo, M. P., Somigliana, E. Hum Reprod 2014; 29(5): 964-77 (24622619)	SR	Women with or without adenomyosis	effect of uterine adenomyosis on IVF outcome in the long and the short GnRH agonist protocol	Clinical pregnancy rate	Long GnRH agonist protocol CPR: 2 RCT, RR 1.05, 95% CI 0.75-1.48, 550 women Short GnRH agonist protocol CPR: 4 RCT, RR 0.58, 95% CI 0.38-0.88, 2106 women		
Frydman, R., Parneix, I., Belaisch-Allart, J., Forman, R., Hazout, A., Fernandez, H. and Testart, J. Hum Reprod. 1988; 3 (4): 559-61. (2969005)	RCT	186 patients "normal responders"	- Group 1 (n=94) . Long protocol. Buserilin 300 ug x 2/day from CD2 for 13 days. 150 IU of HMG x 2/day x 5 days starting dose once pituitary suppression proven - Group 2 (n=92). Short protocol. Triptorelin, 0.1 mg/day from CD1. 150 IU of HMG from day 3	Cancellation rate Ongoing PR/cycle Ongoing PR/pick-up Ongoing PR/transfer	Cancellation rate (%): 4.3 vs 1.1 Ongoing PR/cycle (%): 20.2 vs 16.3 Ongoing PR/pick-up (%): 21.1 vs 16.5 Ongoing PR/transfer (%): 27.2 vs 19.0	the use of long or short protocols appears to give similar results but modifications of the treatment may improve results and increase patient comfort. Comparison of these results with those achieved in classically monitored cycles without agonist treatment demonstrates that LHRH agonists should be the systematic choice in IVF.	No inclusion/exclusion criteria defined. Different agonist between groups Higher dose of HMG in group 1 Short protocol seems more simple, but no better cycle outcome achieved.
Ravhon, A., Lawrie, H., Ellenbogen, A., Lavery, S., Trew, G. and Winston, R. Fertil Steril. 2000; 73 (5): 908-12. (10785215)	RCT	150 patients Exclusion of previous low response or fertilization failure No differences for age, BMI, nº previous cycles, indication for IVF	Group 1 (n=70). Long protocol start day 2. Group 2 (n=55). Long protocol start day 21. Group 3 (n=61) short protocol, star CD2 Buserilin 300 ug x 3 or 0.5 mg sc/day. rFSH 100-225 according to age	Clinical Pregnancy rate # oocytes	Group 1 vs 2 vs 3 Clinical Pregnancy rate (%): 19.6/18.6/8.3 #oocytes: 9.5/7.8/8.4	Starting buserelin in the midluteal phase has the advantage of faster down-regulation compared with starting buserelin in the early follicular phase. However, in terms of success rates, the two long protocols are similar	Neither starting the agonist earlier (day 2 of previous cycle) nor later (day 2 of stimulating cycle) , improves cycle outcome compared to day 21 of previus cycle starting. In any how, short sample size

Sbracia, M., Farina, A., Poverini, R., Morgia, F., Schimberni, M. and Aragona, C. Fertil Steril. 2005; 84 (3): 644-8. (16169397)	RCT	220 patients >=40 Similar for age, basal FSH, duration and cause of infertility, January 1999 to July 2001	Group A (n=110) Buserilin 0.4 mg SC/day from CD1 Group B (n=110) Same dose starting day 22-24 of previous cycle 300 UI/day of hpFSH for both groups	Pregnancy rate/cycle Preg rate/transfer # oocytes	Short vs long GnRH agonist protocol Pregnancy rate/cycle 10.9 vs 22.7 (<0.01) Preg rate/transfer 11.5 vs 23.8 (<0.01) No of oocytes retrieved 4.5±3.1 vs. 8.4±5.8, p<0.05	Our data suggest that in older patients the short protocol might be detrimental	No benefit of short protocol in patients >=40

5.2 GnRH antagonist protocol

Long GnRH agonist vs GnRH antagonist

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Al-Inany, H. G., Youssef, M. A., Ayeleke, R. O., Brown, J., Lam, W. S. and Broekmans, F. J. Cochrane Database Syst Rev. 2016; 4 Cd001750. (27126581)	SR	73 RCTs	GnRH antagonist protocol Long GnRH agonist protocol	Live birth rate OHSS	**LBR**: 12 RCT, OR 1.02, 95% CI 0.85-1.23, 2303 women **OHSS** 6% (290/4474) vs. 11% (396/3470); 36 RCT, OR 0.61, 95% CI 0.51-0.72, 7944 women		GRADE evidence profile Long GnRHa vs GnRH ant
Friedler, S., Gilboa, S., Schachter, M., Raziel, A., Strassburger, D. and Ron El, R. Reprod Biomed Online. 2006; 12 (1): 27-32. (16454930)	RCT	78 normovulatory patients < 35 Male or tubal Excluded: PCO, FSH >10, endocrinopathy No differences between groups	July to December 2003 40: Antagonist: rFSH: 225 IU. Antagonist when follicle >= 12 mm 38: Agoinist Napharelin 200 mg x 3/day from mid luteal phase; FSH 225 IU Luteal phase: Micron. P, 100 mg x 3/day from the day after ET	Clinical pregnancy rate	**GnRH antagonist vs GnRH agonist protocol** CPR: 21.6% (8/37) vs. 36.0% (13/36), NS	The similarity of the luteal hormonal profi le and dynamics between the study and control groups may indicate that the use of any GnRH analogue is not playing a major role during the luteal phase, where the LH may also be suppressed by the supraphysiological oestradiol and progesterone concentrations	These findings suggest a comparable endometrial receptivity between both protocols, as the exposure to E2 and P during the implantation window is very similar.

Toftager, M., Bogstad, J., Bryndorf, T., Lossl, K., Roskaer, J., Holland, T., Praetorius, L., Zedeler, A., Nilas, L. and Pinborg, A. Hum Reprod. 2016; 31 (6): 1253-64. (27060174)	RCT	1099 women randomized - < 40 The two groups were similar with respect to; age, BMI, cycle length and the proportion of women with cycle length .35 days (10.4 versus 11.1%), ovarian volume and abdominal girth	January 2009 to December 2013 - Antagonist (n=528): rFSH: 0.25 mg/day Ganireslix from day 6 - Agonist (n=495): nafarelin, 200 ug x3/from day 21day, x2/day from stim day 1. - 150 rFSH if age <=36, 225 if >36. -6500 IU of hCG when 3 follicles >=17	OHSS Ant vs. Ag TOTAL Mild Moderate Severe EARLY Mild Moderare Severe LATE Mild Moderate Severe TOTAL RD (95% CI) Moderate Severe LBR per randomized LPR per started stim LBR per ET	OHSS Ant vs. Ag 32.4 vs 31.9 10.2 vs 15.6 : 5.1 vs 8.9 (<0.01) 31.6 vs 30.9 9.8 vs 15.6 3.2 vs 6.3 (<0.01) 9.8 vs 11.1 2.7 vs 5.3 1.9 vs 4.2 (0.02) -5.3 (-9.6 to -1.0) -3.8 (-7.1 to -0.4) 22.8 vs 23.8 (0.7) 22.2 vs 21.6 27.4 vs 26.2	The on-going discussion on risk of OHSS and reproductive outcome using the two different treatment regimens has come closer to an end with this trial. This study demonstrates a significant reduction in moderate and severe OHSS and the associated complications when a short GnRH antagonist protocol is used, and OPR and LBR are similar in both protocols.	Appropriated sample sized RCT, showing that both protocols are similar in terms of pregnancy outcomes, but being the GnRH antagonist protocol significantly safer.

Toftager, M., Bogstad, J., Lossl, K., Praetorius, L., Zedeler, A., Bryndorf, T., Nilas, L. and Pinborg, A. Hum Reprod. 2017; 32 (3): 556-567. (28130435)	RCT	1050 women allocated, 1023 started treatment - < 40 The two groups were similar with respect to; age, BMI, cycle length and the proportion of women with cycle length .35 days (10.4 versus 11.1%), ovarian volume and abdominal girth January 2009 to December 2013	Embryo transfers of cryopreserved embryos were performed either in hCG-triggered natural cycle by use of 6500 IU hCG at the day the leading follicle was ≥17 mm or, in case of anovulatory infertility, in estradiol and progesterone substituted cycles (oral estradiol 2 mg three times daily from cycle Days 2–3 and vaginal progesterone was added as luteal phase support 3 days prior to embryo transfer of cleavage stage frozen–thawed embryos and 6 days before transfer of vitrified-warmed blastocysts). Embryos were thawed the day before transfer. Up to two viable Day-2 embryos or one or two surviving blastocysts were transferred. In the hCG-triggered FET cycles, no luteal phase support was provided	Cumulative live birth rate Time to live birth	**Antagonist vs agonist** - Live birth*, n (%) 182 (34.1%) vs 161 (31.2%) P=0.32 OR: 1.14 (0.88–1.48) - Time to first live birth (in months), 11.0 (4.0) vs 11.5 (2.9) p<0.01	The chances of at least one live birth following utilization of all fresh and frozen embryos after the first ART cycle are similar in GnRH-antagonist and GnRH-agonist protocols.	The GnRHantagonist protocol is as effective as the GnRH-agonist protocol with lower OHSS risk and should be the first choice of treatment for ART. Subgroups such as women older than 36 years may still benefit from the GnRH-agonist protocol. The data from the present studt reinforce the concept of GnRH antagonist as first line treatment for pituitary suppression.

Verpoest, W., De Vos, A., De Rycke, M., Parikh, S., Staessen, C., Tournaye, H., De Vos, M., Vloeberghs, V. and Blockeel, C. Current pharmaceutical biotechnology. 2017; 18 (8): 622-627. (28786358)	RCT	132 patients undergoing PGD for monogenic diseases os chr.struct abn. <40 Normogpnadotrophic BMI < 30 Regular cycle (25-36) Excluison PCO Endocr. AI diseases Endometriosis III-IV Patients were comparable for age, weight, BMI, parity	GnRH a long protocol (n=62): Triptorelin 0.1 mg/day or Buserilin 600 ug/day from CD 21. HMG: 225/day GnRH antagonist (n=60) Ganirelix 0.25/day from stim day 6. HMG: 225/day	CPR/cycle CPR/transfer # oocytes	**Long GnRH agonist vs. GnRH antagonist protocol** CPR/cycle 49.2 vs 26.2 (0.008) CPR/transfer 58.4 vs 42.1 (NS) Number of oocytes: 13.2±7.3 vs; 12.6±7.1	There is no significant difference in the number of embryos available for PGD on cleavage stage between both protocols	Unexpected higher rate of transferrable embryos in long protocol.

SHORT GNRH AGONIST VS GNRH ANTAGONIST

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Gordts, S., Van Turnhout, C., Campo, R., Puttemans, P., Valkenburg, M. and Gordts, S. Facts Views Vis Obgyn. 2012; 4 (2): 82-7. (24753894)	RCT	160 cycles -1st or 2nd IVF cycle -< 40 Exclusion: - PGD cycles - Testicular sperm extraction Populations comparable for age day of transfer, number of attempt	All patients: OCP previous cycle FSH from day 6 post-pill_ 150 for < 36y; 200 for >=36 Short Agonist group (n=80): Buserilin 3 puffs, 3 x day from day 3 postpill Antagonist group (n=80) Ganirelix from fol>12mm	Live birth rate Ongoing pregnancy rate # oocytes	**GnRH agonist vs GnRH antagonist** LBR 19% vs 20% OPR 21% vs 20% Number of oocytes 11.0 vs 11.2	This prospective randomized study shows that live birth rate, implantation rates and evolutive pregnancy rates are equal for the short agonist protocol and the antagonist protocol in an overall IVF-population	No data on OHSS provided.

Maldonado, L. G., Franco, J. G., Jr., Setti, A. S., Iaconelli, A., Jr. and Borges, E., Jr. Fertil Steril. 2013; 99 (6): 1615-22. (23394779)	RCT	96 patients <=37 Cycle: 25-35 Normal FSH, LH BMI < 30 No PCO No Endometriosis	All patients: OCP GnRH agonist short (n=48): mg Gonapeptyl alternate days from cycle day 1. rFSH 225 x 3 days; rFSH: 150 from stim day 4 until foll=14 mm. Then rFSH 75 + rhCG 200 IU x 2days. Then rhCH alone GnRH antagonist (n=48): rFSH: 225 from CD3; rFSH 150 from foll=14 + Cetrotide 0.25. The day after: rFSH:75 + rhCG 200.	Clinical pregnancy rate	**GnRH agonist vs GnRH antagonist** CPR: 31.0% (13/48) vs. 52.1% (25/48)	we aimed to develop a protocol in which fewer GnRH injections and Gn amounts are required, thus reducing the total cost of IVF treatment. We reached our primary end point, demonstrated by a significant reduction in the pituitary suppression cost/cycle. However, our secondary end point was not achieved, because the GnRHa group had significantly lower pregnancy and higher miscarriage rates compared with the GnRHant group, resulting in a higher cost per pregnancy achievement. When subsequent embryo thawing cycles were included, the significant differences in pregnancy and miscarriage rates disappeared, but the cost per pregnancy was still significantly higher in the agonist group.	A very creative stimulation protocol with a short GnRH agonist regimen, did not show any benefit: lower outcome and higher costs per pregnancy, despite lower cost on medication

5.3 PROGESTIN

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Yu, S., Long, H., Chang, H. Y., Liu, Y., Gao, H., Zhu, J., Quan, X., Lyu, Q., Kuang, Y. and Ai, A. Hum Reprod. 2018; 33 (2): 229-237. (29300975)	RCT	516 Women under 36 years of age with normal ovarian reserve. BMI between 18 and 26 kg/m2.	Dydrogetserone + HMG (n=260) MPA + HMG (n=256)	Clinical pregnancy rate Number of oocytes retrieved, Number of metaphase II oocytes,	CPR: 125/217 (57.6) vs 132/212 (62.3) OR (95%CI): 0.82 (0.56–1.21) 0.33 No of oocytes: 10.8 (6.3) vs 11.1 (5.8) p=0.33 No of MII oocytes 9.4 (5.5) 9.7 (5.5) p=0.37	Our results showed that DYG can serve as an adjuvant to hMG during ovarian stimulation to achieve comparable oocyte retrieval and viable embryo numbers to MPA.	Good design and randomization method. Appropriate sample size.

Chen, Q., Wang, Y., Sun, L., Zhang, S., Chai, W., Hong, Q., Long, H., Wang, L., Lyu, Q. and Kuang, Y. Reprod Biol Endocrinol. 2017; 15 (1): 71. (28870217)	CS	Prospective cohort study 204 patients 25-45 y Cycle: 21-35 AFC < 5 FSH: 10-30 No real randomization. Patients assigned alternatively to each group. Comparable for age, BMI, basal FSH, E2. Type of infertility and indication, number of previous cycles	Jan 2014-Dec 2014 - Natural cycle (n=102). Trigger with 100ug Triptorelin at foliicle =18 - MPA (n=102). 10 mg/day from CD3. 75-150 hMG add back if FSH <8. Same triggering features All embryos were cryopreserved	 LBR/patient CPR/patient IR Miscarriage rate #oocytes #MII # fertilized # viable embryos Premature ovulation	Nat /MAP 3.92/8.33 (0.097) 5.88/11.77 15.4/21.4 33.3/8.33 0.76/1.09 (<0.001) 0.64/0.94 (<0.001) 0.48/0.76 (0.001) 0.89/1.10 (0.003) 10.8/2.0 (<0.05)	In poor responders undergoing P-priming minimal stimulation, the follicle continuously grows and appears more robust, and spontaneous LH surges and premature ovulation are inhibited. Oocyte quality is not adversely affected by continuous administration of P. This treatment provides a novel insight into the prevention of premature ovulation and improvement in the IVF programme for poor responders, although questions regarding possible effects on the embryo developmental potential remain to be investigated.	Novel approach to treat poor responders with a friendly and cheap protocol
Hamdi, K., Farzadi, L., Ghasemzadeh, A., Navali, N., Atashkhoei, S., Pia, H., Shahnazi, V., Fattahi, A., Bahrami-Asl, Z., Sepasi, F. and et al. International journal of women's health and reproduction sciences. 2018; 6 (2): 187-191. (CN-01602398)	CS	99 patients: age 20-40 years, AFC 4 or at least 4 on the third day of menstrual cycle, and FSH lower than 15 IU/L. Exclusion criteria included evidence of ovarian failure (FSH rate above 15 IU/L or lack of AFC in sonography, grade 3 or 4 endometriosis, contraindication for ovarian stimulation, and severe male factor.	MPA: 10 mg/day and 150-225 rFSH (n=50) GnRH antagonist and 150-225 FSH (n=49)	Nº oocytes Clinical preg	**MPA vs GnRH antagonist** Number of oocytes: 9.95 ± 0.91 vs 10.0 ± 0.88 (p=0.95) CPR: 23% vs 27% (p=0.21)	Results indicated that MPA could be prescribed as an alternative oral and easy access drug instead of GnRH antagonist in the patients that underwent OS in the case of IVF. In the patients undergoing OS for IVF, medroxyprogesterone could be used successfully as a treatment protocol	No randomization although prospective trial. Short sample size

Kuang, Y., Chen, Q., Fu, Y., Wang, Y., Hong, Q., Lyu, Q., Ai, A. and Shoham, Z. Fertil Steril. 2015; 104 (1): 62-70.e3. (25956370)	CS	300 patients <= 42 Cycles 25-35 AFC >3 FSH <=10 Excluison: Endometriosis III-IV PCOS Cyst or E2>100 Recnt horm ttments or counterindications	March-June 2014 Study group (n=150): MPA 10 mg/day from CD3; HMG: 150-225 according to AFC or FSH; GnRH agonist trigger (Triptorelin, 0.1 mg) Control group (n=150): Triptorelin 0.1 mg/day from CD2; HMG same dose; hCG trigger	 # oocytes # mature oocytes LH surge incidence Clinical PR from FET Cumulative PR/patient LBR/transfer	Control vs Study # oocytes 9.0 vs 9.9 MII oocytes 7.8 vs 8.8 Cumulative PR/patient 46.2 vs 50.5 LBR/transfer 35.5 vs 42.6	MPA is an effective oral alternative for the prevention of premature LH surge in woman undergoing COH for IVF. Compared with GnRH antagonists, MPA has advantages of being an oral administration route and providing easy access and more control over LH levels.	Pseudo-randomization First study showing the role of Progestins on pituitary suppression. Enough sample size .

6. Types of gonadotropins

KEY QUESTION: IS THE TYPE OF STIMULATION DRUG ASSOCIATED WITH EFFICACY AND SAFETY?

P	I	C	O
Women undergoing IVF/ICSI	- Recombinant – rFSH - Follitropin - corifollitropin - Purified urinary or p-FSH - Highly purified urinary FSH or hp-FSH - rec FSH+rec LH - HMG (uriFSH+uriLH/hCG enriched) - FSH substitution with aromatase inhibitors - FSH substitution with oestradiol receptor modulators (SERM) - Long-acting vs short acting rFSH	Compare against one another	Efficacy: - cumulative LBR/cycle - Cumulative ongoing pregnancy rate /started cycle (fresh + frozen) - Clinical pregnancy rate/started cycle - Nr of Oocytes/ nr of MII oocyte recovery rate (yield) - number of embryo's (fresh+frozen) Safety - incidence of different grades of OHSS - grade of OHSS - incidence of cycle cancellation for hyper-response (predefined) - Bleeding - Infection - Torsion - Long-term effect on maternal/child health - other adverse events (treatment related) Patient-related outcomes - Compliance - Drop-out rates - Patient burden - QoL - Patient preferences

Papers selected for this question that were already included in the evidence table of question 4	Type
Ebrahimi, M., Akbari-Asbagh, F. and Ghalandar-Attar, M. Int J Reprod Biomed (Yazd). 2017; 15 (2): 101-108. (28462402)	RCT
Verpoest, W. M., Kolibianakis, E., Papanikolaou, E., Smitz, J., Van Steirteghem, A. and Devroey, P. Reprod Biomed Online. 2006; 13 (2): 166-72. (16895628)	RCT

6.1 Recombinant FSH (rFSH)

6.1.1 recombinant FSH (rFSH) vs human menopausal gonadotropin (hMG)

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments

van Wely, M., Kwan, I., Burt, A. L., Thomas, J., Vail, A., Van der Veen, F. and Al-Inany, H. G. Cochrane Database Syst Rev. 2011; (2): Cd005354. (21328276)	SR	11 studies 3197 patients RCTs only (not quasi-randomized studies, no crossover studies	Ovarian stimulation with rFSH versus HMG/HP-HMG.	Primary: Live birth or, if not reported, ongoing pregnancy >20 weeks Secondary: Cumulative live birth/ongoing pregnancy per woman including the result of frozen-thawed embryo transfers[1]; Clinical pregnancy rate per woman (presence of foetal heart rate) Patient acceptability/satisfaction Number of oocytes produced per cycle COCs n=11 +1.287(+0.316 to +2.259) By analogue protocol Long agonist (n=9) 1.010 (-0.118 to +2.138) Antagonist n=1 +3.100 (+1.330 to +4.870) short agonist n=1 -0.300 (-4.065 to +3.465) no downregulation n=1 +2.900 (+0.160 to +5.640)	Live birth/ongoing pregnancy n=11 OR 0.843 (0.715 - 0.993) favors HMG long agonist (n=8) 0.825(0.691 - 0.985) short agonist (n=1) 0.722 (0.147 - 3.545) antagonist (n=1) 0.878 (0.533 - 1.447) no analogue (n=1) 1.714(0.546 - 5.380) CLB (n=2) long agonist 0.847 (0.664 - 1.080) OHSS n=9 0.997(0.582 - 1.709) Long agonist (n=8) 0.997(0.569 - 1.746) Antagonist n=1 1.000(0.139 - 7.200) Clinical pregnancy (n=12) 0.853 (0.738 - 0.985) Long agonist (n=9) 0.846 (0.725 - 0.987) Antagonist n=1 0.888 (0.551 - 1.431) short agonist n=1 0.800(0.215 - 2.972) no downregulation n=1 1.070 (0.391 - 2.926) Cumulative CP n=1 (long agonist) 0.947 (0.662 - 1.354)	Clinical choice of gonadotrophin should depend on availability, convenience and costs. Differences between urinary gonadotrophins were considered unlikely to be clinically significant. Further research on these comparisons is unlikely to identify substantive differences in effectiveness or safety.	GRADE evidence profile rFSH vs hMG significant difference in Live birth , clinical pregnancy with HMG as compared to rFSH in the long agonist protocol only. The difference in COCs in the antagonist and no downregulation in favor of rFSH refer to single studies

Devroey, P., Pellicer, A., Nyboe Andersen, A. and Arce, J. C. Fertil Steril. 2012; 97 (3): 561-71 (22244781)	RCT	749 patients 374 hphMG vs 375 rFSH Comparable groups Inclusion criteria women aged 21–34 years BMI of 18–25 kg/m2; primary diagnosis: unexplained infertility or mild male factor; eligible for ICSI according to the investigator; infertile for >12 months; regular menstrual cycles of 24–35 days, presumed to be ovulatory; hysterosalpingography, hysteroscopy, or transvaginal ultrasound documenting a uterus consistent with expected normal function; first or second OS cycle ever or the first or second OS cycle after having achieved ongoing pregnancy FSH of 1–12 IU/L; AFC>10 for both ovaries combined. Exclusion criteria PCO or endometriosis stage I-IV; poor response previous OHSS recurrent miscarriage; abuse of alcohol or drugs; smoking more than ten cigarettes per day within 3 months before randomization.	Hp-hMG or rFSH Menopur vs Puregon The gonadotropin starting dose was fixed at 150 IU for the first 5 days. in a GnRH antagonist cycle compulsory single-blastocyst transfer on day5 in one fresh or subsequent frozen blastocyst replacement in natural cycles initiated within 1 year of each patient's start of treatment.[SEP]	Primary end point: ongoing pregnancy rate, Secondary end points positive b-hCG rate and clinical pregnancy rate follicular development, endocrine profile, oocytes retrieved, fertilization rate, embryo quality, endometrial profile, safety assessments. OHSS, pregnancy loss, patient self-assessed local tolerability The percentage of patients with interventions associated with excessive response or to prevent early OHSS was significantly higher (P=.025) in the rFSH group	Ongoing pregnancy rate hphMG vs. rFSH, 29% versus 27% (ITT) Cumulative live birth rate for a single stimulation cycle (Considering frozen cycles initiated within 1 year) hphMG vs. rFSH, 40% and 38% OHSS 3% in each treatment group. moderate/severe grade for 1.6% in each treatment group. The percentage of patients with interventions associated with excessive response or to prevent early OHSS was significantly higher (p= 0.025) in the rFSH group than in the hphMG group. hphMG or rFSH COCs: 9.1±5.2 10.7±5.8 p<.001 Metaphase II oocytes/ oocytes retrieved 77±23% 78±19% p=0.798	Highly purified hMG is at least as effective as rFSH in GnRH antagonist cycles with compulsory single-blastocyst transfer.[SEP]	The interventions to prevent OHSS were not described in MM("measures to treat or prevent OHSS was according to local clinical practice.")

Figen Turkcapar, A., Seckin, B., Onalan, G., Ozdener, T. and Batioglu, S. Int J Fertil Steril. 2013; 6 (4): 238-43. (24520446)	RCT	38 patients HMG 42 Patients rFSH PCOS patients (PCOS Rotterdam criteria) Exclusion criteria were as follows: females older than 39 years or serum FSH levels >12mIU/mL, history of ovarian surgery and/or the presence of severe male infertility that required testicular sperm extraction. Patients' characteristics revealed no significant differences between the groups for age, body mass index and baseline hormone levels, which confirmed the appropriate randomization	HMG vs rFSH Long GnRH agonist protocol initial 150 IU daily dose January 2008-December 2008	Not clearly stated COCs, MII oocytes, OHSS	**rFSH vs hMG** COCs: (13.60 ± 5.56) vs. (9.54 ± 4.31, p=0.002). MII oocytes: (11.20 ± 5.06) vs. (7.65 ± 3.39, p=0.003). OHSS (mild) 11.9% (5 patients) vs. 0%, not significant (p=0.14). no severe OHSS in either group Clinical pregnancy rate per cycle (%) rFSH:40.5% HMG:23.1% p=0.14 Take home baby rate per cycle (%) rFSH: 35.7 % HMG:23.1% p=0.27	Ovarian stimulation with hMG and rFSH provides similar clinical pregnancy rates in PCOS patients treated with a long GnRH agonist protocol in IVF cycles. hMG stimulation appears to be associated with a lower rate of OHSS and decreased coasting requirements	There was no difference in any form of OHSS between the groups compared. No differences in take home baby rate and CP Less COCs in the HMG Less coasting requirement with HMG

Parsanezhad, Me, Jahromi, Bn, Rezaee, S, Kooshesh, L and Alaee, S. Iranian journal of medical sciences. 2017; 42 (1): 57-65. (28293051)	RCT	January 2014 to May 2014. 160 patients Inclusion criteria Patients with unexplained or male factor infertility were included in the study if they met the following criteria: 1) age between 20 and 38 years; 2) body mass index between 19 and 29 kg/m2; 3) history of regular menstrual cycles, ranging from 25–35 days; 4) no relevant systemic disease, severe endometriosis, or uterine or ovarian abnormalities; 5) no more than 3 previous IVF cycles; 6) no previous IVF cycle with a poor response or the ovarian hyperstimulation syndrome. Exclusion criteria Additionally, patients with FSH >10 IU/mL, with <5 follicles in antral follicle count, and anti-Müllerian hormone <1 ng/ mL were excluded from the study. age, body mass index, duration of infertility, and endometrial thickness at baseline were similar in all the groups.	40 patients hMG 40 patients FSH-HP 40 patients rFSH 40 patients who received hFSH for the first 6 days, followed by rFSH Long GnRH agonist	The primary end points were oocyte and embryo quality and pregnancy outcomes. The secondary endpoints were the total number of collected oocytes	LBR hMG 27.5% FSH-HP 22.5% rFSH 40% no significant differences CP hMG 45% FSH-HP 37.5% rFSH 50% no significant differences COCs retrieved hMG 9.5±4.83 FSH-HP 8.2±4.7 rFSH 11.2±6. 7 no significant differences	Our data revealed no statistically significant differences in the mean oocyte number, embryo quality, clinical pregnancy rate, or live birth rate between the hMG, hFSH, rFSH, and sequential hFSH/rFSH protocols. However, several differences in the duration of stimulation, serum estradiol levels, and number of large-sized follicles were detected between the groups.	No differences in LBR CP COCs Duration of stimulation longer with rFSH

Ye, H., Huang, G., Pei, L., Zeng, P. and Luo, X. Gynecol Endocrinol. 2012; 28 (7): 540-4. (22390186)	RCT	HP-hMG n = 63 rFSH n = 64 inclusion criteria were: (1) women age 35–39; (2) body mass index 18–25 kg/m2; (3) rst IVF/ICSI cycle; (4) normal ovulatory cycles with basal FSH concentration <10 IU/L measured on cycle day 2–3; (5) presence of both normal ovaries; (6) normal uterus; (7) no hormone therapy within past 3 months and (8) no current or past diseases a ecting the ovaries, gonadotropin, sex steroid secretion, clearance or excretion. Groups were comparable	rFSH vs. HP-hMG Long downregulation protocol An initial dose of 225 IU/day HP-hMG or rFSH for first 5 days, dosage on subsequent days was adjusted according to individual ovarian response. For both groups, 250 µg recombinant hCG was given when at least 3 follicles ≥18 mm were obtained, and oocytes retrieval was performed 36 h later. .	primary endpoint measure live birth rate per started cycle. Secondary endpoints ongoing/ clinical pregnancy rate, implantation rates, fertilization rate, number of oocytes retrieved, total gonadotropin dose, days of stimulation, and serum endocrine profile.	HP-hMG vs. rFSH COCs retrieved 7.2 ± 4.2 vs. 10.2 ± 5.2 p<0.001 MII oocytes 6.0 ± 3.7 vs. 8.9 ± 5. P<<0.001 2PN oocyte 4.7 ± 3.0 vs. 6.7 ± 3.8 p=0.002 clinical pregnancy/started cycle 57.1%) vs. 51.6%) ns OR 1.3 (0.6–2.5) Live birth per started cycle: (%) 44.4 vs. 29.7 ns OR 1.9 (0.9–3.9) OHSS/stimulation cycle 1.6) VS. 6.3 ns OR 0.2 (0.03–2.2)	following downregulated women of advanced reproductive age, more leading follicles and oocytes obtained from rFSH group than HP-hMG group, but the proportion of top-quality embryo and live birth rate were trended towards improvement with HP-hMG	Regarding the second part of authors conclusion no significant differences were shown No differences in LBR CP, OHSS More COCs, embryos, embryos cryopreserved with rFSH.

6.1.2 RECOMBINANT FSH (RFSH) VS PURIFIED FSH (P-FSH)

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
van Wely, M., Kwan, I., Burt, A. L., Thomas, J., Vail, A., Van der Veen, F. and Al-Inany, H. G. Cochrane Database Syst Rev. 2011; (2): Cd005354. (21328276)	SR	7 studies 1560 patients	rFSH versus FSH-P	Primary: Live birth or, if not reported, ongoing pregnancy >20 weeks Secondary: Cumulative live birth/ongoing pregnancy per woman including the result of frozen-thawed embryo transfers Clinical pregnancy rate per woman (as confirmed by the presence of foetal heart rate) Patient acceptability/satisfaction Number of oocytes produced per cycle COCs n=6 +0.691(-0.544 to +1.927) By analogue protocol Long agonist (n=4) +0.552(-1.058 to +2.163) no downregulation n=1 +1.000 (-0.629 to + 2.629)	Live birth/ongoing pregnancy (n=5) 1.261 (0.961 - 1.655) long agonist (n=4) 1.306(0.977 - 1.746) no analogue (n=1) 0.974(0.445 - 2.130) CLB (n=1) long agonist 1.333(0.979 - 1.815) OHSS n=4 Long agonist 1.819(0.851 - 3.886) Clinical pregnancy (n=7) 1.273 (1.007 - 1.610) Long agonist (n=6) 1.307 (1.021 - 1.672) no downregulation n=1 0.974 (0.445 - 2.130) Cumulative CP n=1 (long agonist) 1.304(0.987 - 1.722)	Clinical choice of gonadotrophin should depend on availability, convenience and costs. Differences between urinary gonadotrophins were considered unlikely to be clinically significant. Further research on these comparisons is unlikely to identify substantive differences in effectiveness or safety.	GRADE evidence profile rFSH vs p-FSH No differences in LBR Higher CP with rFSH when downregulation is achieved with GnRH agonists. No studies in GnRH antagonist cycles

6.1.3 RECOMBINANT FSH (RFSH) VS HIGHLY PURIFIED FSH (HP-FSH)

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
van Wely, M., Kwan, I., Burt, A. L., Thomas, J., Vail, A., Van der Veen, F. and Al-Inany, H. G. Cochrane Database Syst Rev. 2011; (2): Cd005354. (21328276)	SR	22 studies 4147 patients	rFSH versus FSH-HP	Primary: Live birth or, if not reported, ongoing pregnancy >20 weeks Secondary: Cumulative live birth/ongoing pregnancy per woman including the result of frozen-thawed embryo transfers Clinical pregnancy rate per woman (as confirmed by the presence of foetal heart rate) Patient acceptability/satisfaction Number of oocytes produced per cycle	Live birth/ongoing pregnancy n=13 OR 1.027(0.862 - 1.223) By analogue protocol long agonist (n=11) 1.059 (0.877 - 1.279) short agonist (n=2) 0.852(0.536 - 1.356) OHSS n= 13 long GnRH agonist OR: 1.250 (0.785 - 1.989) Clinical pregnancy (n=23) 1.049 (0.913 - 1.204) By analogue protocol Long agonist (n=18) 1.040 (0.897 - 1.207) short agonist (n=2) 0.958 (0.611 - 1.501) no downregulation (n=3) 1.606 (0.766 - 3.369) Cumulative CP n= (long agonist) COCs n=20 +0.241 (-0.473 to +0.955) By analogue protocol Long agonist (n=17) +0.327 (-0.519 to +1.173) Short agonist (n=2) -0.881(-2.417 to +0.654) no downregulation n=1 +0.400 (-0.379 to +1.179)	Clinical choice of gonadotrophin should depend on availability, convenience and costs. Differences between urinary gonadotrophins were considered unlikely to be clinically significant. Further research on these comparisons is unlikely to identify substantive differences in effectiveness or safety.	rFSH vs hp-FSH NO DIFFERENCES

Aboulghar, M., Saber, W., Amin, Y., Aboulghar, M., Mansour, R. and Serour, G. Fertil Steril. 2010; 94 (6): 2332-4. (20188364)	RCT	84 patients 42 rFSH 42 FSH-HP The study lasted from August 2008 to April 2009. PCOS according to Rotterdam criteria (2), with good physical health, age <39 years, normal basal FSH and prolactin levels. Exclusion criteria Patients with fibroids, endometriosis, general or medical disorders, body mass index (BMI) >35 kg/m2, participation in previous IVF trials There was no significant difference in patient characteristics between groups.	rFSH vs. FSH-HP Long GnRH agonist protocol. Starting dose of FSH was 2 to 3 ampoules, depending on age and weight of the patient. All patients received 500 mg metformin twice daily. In case of risk of ovarian hyperstimulation syndrome (OHSS), coasting was performed according to our coasting protocol	Primary endpoints: number and percentage of mature oocytes, Secondary endpoints: OHSS rate ongoing pregnancy rate.	COCs rFSH: 13.83±7.07 vs. FSH-HP: 17.1±8.66 NS Mature oocytes rFSH: 10.45±5.69 vs. FSH-HP:12.8±7.78 NS moderate OHSS 1 patient in FSH-HP Clinical pregnancy% rFSH: 50.23 vs. FSH-HP: 50 NS Ongoing pregnancy% rFSH: 47.6 vs. FSH-HP: 45.2 NS	For ovarian stimulation for IVF/ICSI in patients with PCOS, both highly purified urinary FSH and recombinant FSH produced excellent pregnancy rates; and if carefully managed, with precautions taken to prevent OHSS, the high risk of OHSS could be avoided to a great extent.	
Gholami, H., Vicari, E., Molis, M., La Vignera, S., Papaleo, E. and Cappiello, F. Eur Rev Med Pharmacol Sci. 2010; 14 (2): 97-102. (20329567)	RCT	115 patients hFSH (n=62) or rFSH (n=53) All patients undergoing a first attempt of in vitro fertilization (general population) Groups were comparable	rFSH vs FSH-HP Long protocol 150IU starting dose January 2008 and September 2008	Cancelled cycles retrieved oocytes Clinical PR	h-FSH Group B: r-FSH Cancelled cycles 1 vs 3 COCs 9.8 ± 4.vs. 12 10.9 ± 3.31 p=0.04 Clinical PR 38.7 vs. 39.6	This study did not demonstrate a difference between the use of h-FSH vs r-FSH for ovarian stimulation in terms of pregnancy outcome, in good prognosis patients undergoing their first IVF-ET procedure.	According to the Italian IVF law, a maximum of three oocytes per patient were fertilized.

Murber A, Fancsovits P, Ledó N, Szakács M, Rigó J, Urbancsek J. Acta Biol Hung. 2011; 62(3):255-64 (21840828)	RCT	indication of severe male factor Inclusion criteria : female, aged 18–39 years, body mass index (BMI) 19–30 kg/m2, <3 prior oocyte retrievals, basal FSH <10 IU/L within 3 months prior to the study, normal or clini- cally insignificant hematology and blood chemistry values. Exclusion criteria : oocyte donation, thawed embryo replacement, primary ovarian failure or women known to be poor responders, ovarian cyst (>20 mm), abnormal bleeding of undetermined origin, uncontrolled thyroid or adrenal dysfunction, neoplasia, severe impairment of renal or hepatic function. No significant differences were found between the HP-FSH and rFSH groups in patients' age, BMI and cause of infertility.	rFSH vs FSH-HP Long GnRH agonist protocol first 5 days of stimulation daily 225 IU of FSH	Not clearly defined	COCs FSH-HP 11.1±3.9 rFSH 11.9±4.1 P=0.46 Mature oocytes FSH-HP 9.9±4.1 rFSH 10.7±4.3 P=0.45 Clinical pregnancy rate/ET (%) FSH-HP 37.1 rFSH 34.4 p=0.68 Live birth rate% FSH-HP 31.4 rFSH 31.3 p=0.98	Our results showed a signi cantly higher proportion of embryos suitable for cryopreservation after HP-FSH stimulation, hence cumulative pregnancy rates are expected to be higher in this group.	A site from an RCT reporting results separately The conclusion about the cryopreservation is not valid since no difference was present in the number of cryopreserved embryos.

Parsanezhad, Me, Jahromi, Bn, Rezaee, S, Kooshesh, L and Alaee, S. Iranian journal of medical sciences. 2017; 42 (1): 57-65. (CN-01338801)	RCT	January 2014 to May 2014. 160 patients Inclusion criteria Patients with unexplained or male factor infertility were included in the study if they met the following criteria: 1) age 20 -38 years; 2) BMI 19 - 29 kg/m2; 3) history of regular menstrual cycles, ranging from 25–35 days; 4) no relevant systemic disease, severe endometriosis, or uterine or ovarian abnormalities; 5) no more than 3 previous IVF cycles; 6) no previous IVF cycle with a poor response or the ovarian hyperstimulation syndrome. Exclusion criteria Additionally, patients with FSH >10 IU/mL, with <5 follicles in AFC, and AMH<1 ng/ mL were excluded from the study. age, BMI, duration of infertility, and EMT at baseline were similar in all the groups.	40 patients hMG 40 patients FSH-HP 40 patients rFSH 40 patients who received hFSH for the first 6 days, followed by rFSH Long agonist	The primary end points were oocyte and embryo quality and pregnancy outcomes. The secondary endpoints were the total number of collected oocytes	LBR hMG 27.5% FSH-HP 22.5% rFSH 40% no significant differences CP hMG 45% FSH-HP 37.5% rFSH 50% no significant differences COCs retrieved hMG 9.5±4.83 FSH-HP 8.2±4.7 rFSH 11.2±6. 7 no significant differences	Our data revealed no statistically significant differences in the mean oocyte number, embryo quality, clinical pregnancy rate, or live birth rate between the hMG, hFSH, rFSH, and sequential hFSH/rFSH protocols. However, several differences in the duration of stimulation, serum estradiol levels, and number of large-sized follicles were detected between the groups.	No differences in LBR CP COCs Duration of stimulation longer with rFSH
Selman, H., Pacchiarotti, A. and El-Danasouri, I. Fertil Steril. 2010; 94 (5): 1782-6. (19939369)	RCT	60 patients HP-FSH 65 patients rFSH Women undergoing first IVF cycle (n=188) Age 27 to 38 years; BMI 20–26 kg/m2 infertility due to tubal factor, male factor or unexplained infertility January 2008 to February 2009. Groups were comparable	rFSH vs. FSH-HP Long down regulation with daily GnRH agonist 225 IU rFSH; 225 IU HP-hFSH; Triggering with 10 000 IU hCG	Primary: Number of COCs Oocytes Proportion of MII oocytes Pregnancy rate Secondary Cancellation rate Incidence of moderate or severe OHSS	rFSH vs. hFSH COCs 10.7±0.91 vs. 10.6±0.82 Proportion of mature oocytes 45.5 vs. 57.2 p<0.004 Pregnancy rate 21 vs 23 ns Incidence of moderate or severe OHSS Not reported	The conclusion is irrelevant to the pico question	Comparison for the MII proportion is incorrect (treated as binary outcome) The same is true for embryo grade and implantation rate The difference in pregnancy rates is not significant

Selman, H., Pacchiarotti, A., Rinaldi, L., Crescenzi, F., Lanzilotti, G., Lofino, S. and El-Danasouri, I. Eur Rev Med Pharmacol Sci. 2013; 17 (13): 1814-9. (23852909)	RCT	127 patients 65 rFSH 62 FSH-HP infertility attributable to tubal factor, male factor or idiopathic infertility serum hormonal profile (FSH and LH < 12 mIU/ml, E2 < 50 pg/ml and prolactin < 30 ng/ml) within the normal range regular ovulatory menstrual cycles; presence of normal uterine cavity; BMI ≥ 20 - ≤ 30 kg/m2. The patients were excluded if they had previous poor response to gonadotropins, history of severe OHSS, or current polycystic ovarian syndrome or the male partner had azoospermia. Groups were comparable	rFSH vs, FSH-HP January 2010 to December 2011 at two IVF Centers. Long GnRH agonist After 6 days of stimulation the FSH dose was adjusted as necessary according to follicular size and estradIol level. The patients with a poor response to gonadotropin treatment were withdrawn from the study. Patients with excessive response to gonadotropins were counseled about the risk for OHSS and were advised to interrupt the stimulation cycle or to undergo oocyte retrieval with cryopreservation of resultant embryos for re- placement in the subsequent cycle. Final oocyte maturation was triggered by the administration of 10.000 IU of hCG.	The primary end points were oocyte maturity, and clinical pregnancy and. The secondary end points were delivery rate, rate and incidence of moderate or severe OHSS.	rFSH vs. hFSH COCs 7.5 ± 1.5 vs. 7.1 ± 1.3 Proportion of mature oocytes 44.3 vs. 43.6 Pregnancy rate 18.5 vs 17.7 ns Incidence of moderate or severe OHSS Not reported	Our findings indicate that the combination be- tween acidic and less acidic FSH for ovarian stimulation may have a positive effect on follicu- lar development and oocytes by improving oocyte quality, embryo development, and ultimately clinical outcome in women with a history of previous IVF failures.	The conclusion is irrelevant to the pico question

Sohrabvand, F., Sheikhhassani, S., Bagheri, M., Haghollahi, F., Shabihkhani, M., Shariat, M. and Nasr Esfahani, M. Iran J Reprod Med. 2012; 10 (3): 229-36. (25242998)	RCT	PCOS according to Rotterdam criteria, aged 20-35 years. Exclusion criteria: BMI >30 kg/m2 Endometriosis, male factor infertility hypo and hyper-gonadotropic hypogonadism, hyperprolactinemia, thyroid disorders, ovarian or adrenal neoplasms, Cushing syndrome, a previous history of poor ovarian response Both groups had similar demographic and basic characteristics including age, BMI, type and duration of infertility and baseline hormonal profiles	Recombinant FSH vs. FSH-HP Long agonist each at a dose of 150 IU/d for 6 days	Primary outcome number of mature oocytes Secondary outcome number and top-quality embryos clinical pregnancy rate	Mature (MII) oocytes 9.55±4.37 (rFSH) 10.25±3.96(FSH-HP) p=0.29 Clinical pregnancy 33 (41.2%)(rFSH) 36 (45%)(FSH-HP) p=0.67 No severe OHSS in any group Live birth rate 17 (21.25%)%)(rFSH) 19 (23.75%) (FSH-HP) p=0.8	It seems that in PCOS patients, both pure FSH products used for controlled ovarian hyperstimulation have similar effects on ART outcome and can be used according to availability and patient acceptance without significant difference.	

6.1.4 RECOMBINANT (RFSH) VS RECOMBINANT FSH + RECOMBINANT LH (RFSH+RLH)

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Mochtar MH, Danhof NA, Ayeleke RO, Van der Veen F, van Wely M. Cochrane Database Syst Rev. 2017;5:CD005070. (28537052)	SR	36 RCTs - 8125 women	rLH combined with rFSH for ovarian stimulation compared to rFSH alone	Live birth rates OHSS Ongoing pregnancy rate Miscarriage rate Cancellation rate	LB: OR 1.32, 95% CI 0.85 - 2.06; n = 499; Agonist: 1.73 [0.95 - 3.16] Antagonist 0.94 [0.48 - 1.85] OHSS: OR 0.38, 95% CI 0.14 to 1.01; n = 2178 Agonist: 0.16 [0.03, 0.88) (favour rFSH) Antagonist 0.80 [0.21, 3.00] OPR: OR 1.20, 95% CI 1.01 to 1.42; participants = 3129; Agonist: 1.27 [1.02, 1.57] Antagonist 1.08 [0.82, 1.43] CP: OR 1.177 (1.034 - 1.340) Agonist: 1.215 (1.052 - 1.403) Antagonist: 1.029 (0.764 - 1.386) Cancellation due to imminent OHSS 0.821 (0.342 - 1.969) Agonist: 0.687(0.146 - 3.218) Antagonist 1.069 (0.541 - 2.113)	We found no clear evidence of a difference between rLH combined with rFSH and rFSH alone in rates of live birth or OHSS. We found moderate quality evidence that the use of rLH combined with rFSH may lead to more ongoing pregnancies than rFSH alone. There was no clear evidence of a difference between the groups in rates of cancellation due to low response or imminent OHSS, the evidence is insufficient to encourage or discourage stimulation regimens that include rLH combined with rFSH in IVF/ICSI cycles.	GRADE evidence profile quality of the evidence ranged from very low to moderate. A higher probability of OPR was observed in the agonist treated patients which was not accompanied by a significant difference in LB. In antagonist cycles no differences were observed in the review a fixed model was used despite significant heterogeneity (60.1 p=0.014)

Humaidan, P., Chin, W., Rogoff, D., D'Hooghe, T., Longobardi, S., Hubbard, J. and Schertz, J. Hum Reprod. 2017; 32 (3): 544-555. (28137754)	RCT	939 women were randomized (1:1) to receive either r-hFSH/r-hLH or r-hFSH ≥18–<41 years old, BMI between 18 and 31 kg/m2 diagnosis of POR (Bologna criteria) Baseline characteristics and demographics were similar for women in the two treatment groups	r-hFSH/r-hLH vs. r-hFSH r-hFSH 300 IU plus r-hLH 150 IU (follitropin alfa/ lutropin alfa; Pergoveris®) or r-hFSH 300 IU monotherapy (follitropin alfa; GONAL-f®), with the dose fixed for the first 4 days of OS. long GnRH agonist protocol January 2014 and February 2015.	The primary efficacy endpoint COCs retrieved Secondary endpoints biochemical pregnancy clinical pregnancy ongoing pregnancy live birth rate cycle cancellation rate; number of metaphase II (MII) oocytes in ICSI patients.	Rfsh+LH vs. rFSH COCs 3.6 (2.82) 3.3 (2.71) Cancelled cycles OR:1.12 (0.68, 1.85) Ongoing pregnancy OR:0.90 (0.60, 1.35) Live birth OR:0.91 (0.60, 1.38) MII oocytes in ICSI –0.24 (–0.64 to +0.15)	The study did not meet its primary endpoint of superiority of r-hFSH/r-hLH to r-hFSH in terms of number of oocytes retrieved following OS. Furthermore, the live birth rates per cycle were similar in both groups, but considerably higher than previously reported in retrospective studies that included Bologna POR patients, suggesting that recombinant gonadotropin stimulation protocols represent an effective treatment strategy in this challenging patient category.	

Lahoud, R, Ryan, J, Illingworth, P, Quinn, F and Costello, M. European journal of obstetrics gynecology and reproductive biology. 2017; 210 300-305. (28107729)	RCT	238 patients Inclusion criteria: Infertility, IVF/ICSI using long pituitary down regulation, no more than 3 previous stimulated IVF/ICSI treatment cycles, age 18 to 42, not an oocyte donor, not already taken part in the study, no current endocrine disorder A prospective RCT was performed from 2007 to 2009 at IVF Australia, a multi-center IVF organization based in Sydney, Australia. 2007 to 2009 mid-luteal long down-regulation protocol	Serum LH measurements were taken on day 0 and day 6 of FSH administration. A LH ratio was calculated by dividing the LH concentration on the day 6 of FSH injections by the LH concentration on LH day 0. LH ratio .LH day 6/ LH day 0 Where the ratio was less than or equal to 0.5 (LH ratio < = 0.5), the patient was randomised to one of two study groups Group 1: routine protocol of GnRH agonist and rFSH + rLH supplementation 75IU subcutaneously daily starting on days 7 or 8 of FSH injections and continuing daily until the day of rhCG trigger Group 2: no rLH supplementation. Where the LH ratio was greater than 0.5 (LH ratio > 0.5), the participant was not randomized but acted as a third study group.	The primary outcomes were live birth rate per embryo transfer and clinical pregnancy rate per embryo transfer. Secondary outcomes miscarriage rate, total amount of FSH days of FSH stimulation, peak estradiol level, progesterone concentration on day of HCG trigger, COCs retrieved, top grade embryos the number embryos for cryopreservation.	rLH+rFSH vs rFSH Number of oocytes retrieved 12 (6.3) vs. 11.6 (5.6) Clinical pregnancy rate/transfer RR 0.84, 95%CI 0.5–1.48, Live Birth rate/cycle started RR 0.78 95%CI 0.4–1.53,	In conclusion the addition of rLH in patients with a relative reduction in serum LH concentration during COH for IVF/ICSI did not improve live birth or clinical pregnancy rates. However the results were not conclusive and further large well-designed RCTs are required to confirm these findings.	

Rahman, A., Francomano, D., Sagnella, F., Lisi, F. and Manna, C. Eur Rev Med Pharmacol Sci. 2017; 21 (23): 5485-5490. (29243795)	RCT	prospective, open-label, parallel arm study. 33 women rFSH+LH (group A) 33 women Rfsh (group B) Four patients in group A and one patient in group B were protocol violators and were excluded. Inclusion criteria: RIF in at least two previous IVF cycles, regular spontaneous menstrual cycles (26-39 days), aged < 42years, FSH ≤ 10 IU/L, LH < 10 IU/L, estradiol < 60 pg/ml), BMI ≤ 30 kg/m2, presence of both ovaries and normal uterine cavity. Exclusion criteria: clinically significant system- ic disease, polycystic ovarian syndrome , history of OHSS, abnormal gynecological bleeding of unknown origin, history of intolerance to any agents used in the study. Groups were comparable	rFSH stimulation in both arms Downregulation with GnRH antagonists in both arms Addition of LH at the late follicular phase in one arm only. Duration: May 2014 and September 2015 Follow up until detection of FH (clinical pregnancy)	Positive regnancy test Clinical pregnancy	Group A vs group B Positive pregnancy test ITT 42.4 vs 24.3 (p=0.19) per protocol 48.3 vs 25.0 p=0.07 No data on clinical pregnancy rate or live birth rate COCs retrieved 7.2±4.8 vs. 7.3±5.3	These preliminary data demonstrate that adding r-LH during the late phase of ovarian stimulation improves the clinical outcome of patients with RIF.	Included No data on live birth rate Statistics on positive pregnancy rate incorrect (no statistically significant difference is present despite what the authors report) The same is true for an ITT analsysis Inapropriate analysis for implantation rate No power analysis Unclear intervention Quality of data analysis very low (Table II)

6.2 HIGHLY PURIFIED FSH (HP-FSH) VS HUMAN MENOPAUSAL GONADOTROPIN (HMG)

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Duijkers, I. J., Vemer, H. M., Hollanders, J. M., Willemsen, W. N., Bastiaans, L. A., Hamilton, C. J., Thomas, C. M. and Borm, G. F. Hum Reprod. 1993; 8 (9): 1387-91. (8253923)	RCT	20 patients 10: Org 31338 (containing 75 IU FSH and 25 IU LH per ampoule) 10: Metrodin (purified FSH) age between 20 and 40 years, a normal endocrine serum profile, no hormonal medication during the 3 months prior to the study, no endometriosis observed on laparoscopy, both ovaries present, normal semen analysis or >50% of the oocytes fertilized in a previous IVF treatment. Unclear whether patient characteristics were similar between groups compared	Org 31338 (FSH/LH 3:!) vs Metrodin	retrieved oocytes pregnancy	Org 31338 vs Metrodin retrieved oocytes: 13 (4-23) vs. 8 (4-11) 1 pregnancy in the Org 31338 group 2 pregnancies in the Metrodin group (1 miscarriage)	No significant differences were found in hormonal values. In women with normal endocrine profiles, lowering of the LH activity in gonadotrophic preparations during gonadotrophin-releasing hormone agonist treatment results in adequate ovarian stimulation. However, a preparation with some LH needed a shorter stimulation than a purified FSH preparation. Whether the other beneficial effects of Org 31338 also occur in a larger population needs further investigation.	Transferred from p-FSH search, Metrodin is hp-FSH

Parsanezhad, Me, Jahromi, Bn, Rezaee, S, Kooshesh, L and Alaee, S. Iranian journal of medical sciences. 2017; 42 (1): 57-65. (CN-01338801)	RCT	January 2014 to May 2014. 160 patients Inclusion criteria Patients with unexplained or male factor infertility were included in the study if they met the following criteria: 1) age 20 -38 years; 2) BMI 19 - 29 kg/m2; 3) history of regular menstrual cycles, ranging from 25–35 days; 4) no relevant systemic disease, severe endometriosis, or uterine or ovarian abnormalities; 5) no more than 3 previous IVF cycles; 6) no previous IVF cycle with a poor response or the ovarian hyperstimulation syndrome. Exclusion criteria Additionally, patients with FSH >10 IU/mL, with <5 follicles in AFC, and AMH<1 ng/ mL were excluded from the study. age, BMI, duration of infertility, and EMT at baseline were similar in all the groups.	40 patients hMG 40 patients FSH-HP 40 patients rFSH 40 patients who received hFSH for the first 6 days, followed by rFSH Long agonist	The primary end points were oocyte and embryo quality and pregnancy outcomes. The secondary endpoints were the total number of collected oocytes	LBR hMG 27.5% FSH-HP 22.5% rFSH 40% no significant differences CP hMG 45% FSH-HP 37.5% rFSH 50% no significant differences COCs retrieved hMG 9.5±4.83 FSH-HP 8.2±4.7 rFSH 11.2±6. 7 no significant differences	Our data revealed no statistically significant differences in the mean oocyte number, embryo quality, clinical pregnancy rate, or live birth rate between the hMG, hFSH, rFSH, and sequential hFSH/rFSH protocols. However, several differences in the duration of stimulation, serum estradiol levels, and number of large-sized follicles were detected between the groups.	No differences in LBR CP COCs Duration of stimulation longer with rFSH
Westergaard, L. G., Erb, K., Laursen, S., Rasmussen, P. E. and Rex, S. Hum Reprod. 1996; 11 (6): 1209-13. (8671425)	RCT	218 patients, 114 HMG 104 HP-FSH (i) age < 4 0 years; (ii) normal menstrual cycle ranging from 26 to 32 days and normal pretreatment scrum concentrations of FSH and LH; criteria were (i) infertility caused by endocrine abnormality and (ii) cases in which intracytoplasmic sperm injection (ICSI) or donor semen was used. Groups were comparable	FSH-HP vs.HMG October 1994 to April 1995 Long agonist	COCs Clinical pregnancy Ongoing pregnancy	HMG vs. HP-FSH COCs: 13.4 ± 0.6 vs. 13.7 ± 0.7 Clinical pregnancy: 36 vs 34% Ongoing pregnancy: 32 vs. 29%	No detrimental effect of the exogenous LH-like activity contained in HMG on the clinical outcome of FVF in GnRHa downregulated normogonadotrophic women Significantly more transferable pre-embryos in HMG compared to those treated with HP-FSH.	no clear primary outcome measure, no power analysis Fertilization rate is reported a significant although based on the numbers presented this is extremely unlikely

6.3 HUMAN MENOPAUSAL GONADOTROPIN (HMG) VS RECOMBINANT FSH + RECOMBINANT LH (RFSH+RLH)

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Pacchiarotti, A., Sbracia, M., Frega, A., Selman, H., Rinaldi, L. and Pacchiarotti, A. Fertil Steril. 2010; 94 (6): 2467-9. (20537626)	RCT	122 patients main causes of infertility attributable to tubal, idiopathic, or male factors; serum levels of FSH on day 3 of the ovarian cycle <12 IU/L regular menstrual cycle; [4] endogenous LH <1.2 IU/L; normal uterine cavity. Both groups were comparable to the main demographic charac teristics (mean age, body mass index, duration of sterility, primary infertility), as well as sterility factors (tubal, male, and idiophatic) and main cycle parameters	hMG vs. rFSH + rLH Meropur vs. Pergoveris Long agonist 225 starting dose fixed From July 2008 to September 2009 1	Not clearly stated Pregnancy rate per cycle Implantation rate, COCs, Cancelled patients for high risk of OHSS.	**HMG vs rFSH +LH** Pregnancy rate per cycle 17 vs. 15 COCs: 4.1±1.2 vs. 7.8±1.1 p=0.0021 Cancelled patients for high risk of OHSS 1.7 vs 11.1 p=0.042	The two groups proved to be comparable to the main IVF outcome (preg- nancy rate, implantation rate, oocytes, and embryos quality), with an increasing risk of ovarian hyperstimulation in the Pergoveris group.	The amount of FSH units required is not compatible with the duration of stimulation and the fixed dose used in both arms (Table 1)

6.3 AROMATASE INHIBITORS

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Ebrahimi, M., Akbari-Asbagh, F. and Ghalandar-Attar, M.. Int J Reprod Biomed (Yazd). 2017; 15 (2): 101-108. (28462402)	RCT	70 patients in two groups Inclusion criteria At least two of three features should be contemporaneously present in each patient: 1. At least one previous failed IVF/ICSI cycle with conventional long-agonist protocol and less than four mature oocytes 2- Decreased ovarian reserve: AFC < 5-7 or AMH < 1.1 ng/mL. 3- Age of participants' partner ≥40 years old The women with at least two episodes of poor ovarian response (≤3 oocytes with conventional stimulation protocol) after maximal stimulation were defined as POR in absence of advance age or diminished ovarian reserve. Exclusion criteria were as below: Metabolic or endocrine disorders including hyperprolactinoma and hypo/hyperthyroidism, Endometriosis History of previous surgery on ovaries Body mass index >30 Azoospermic male partner. There were no significant differences in demographic characteristics between groups	letrozole+GnRH-antagonist (LA) group VS placebo+GnRH-antagonist (PA) group The LA group involved at letrozole 2.5 mg daily over 5 days and recombinant human follicle stimulating hormone 225 IU/daily. The PA group received placebo over 5 days and recombinant human follicle stimulating hormone at the same starting day and dose, similar to LA group. GnRH-antagonist was introduced once one or more follicle reached ≥14 mm.	Main outcome measures COCs fertilization rate implantation rate cycle cancellation rate clinical pregnancy rate	**Ltz vs Placebo** COCs 2.80 ± 1.09 vs. 2.60±1.51 0.81, p=0.81 total cycle cancelation rate 20 vs. 22.9 (p=0.08) clinical pregnancy rate 14.3 vs. 11.4, p=0.12	In conclusion, there is insufficient evidence to establish recommendation on the use of low dose letrozole as an adjuvant in ART stimulation protocols of poor responder patients. General acceptances of a uniform definition for POR and performance of well- designed prospective randomize trials with large sample size are critical to drawing the precise conclusion on the role of letrozole in stimulation protocols of poor responder patients	

Verpoest, Wmja, Kolibianakis, E, Papanikolaou, E, Smitz, J, Steirteghem, A and Devroey, P. Reprod biomed online. 2006; 13 (2): 166-72. (16895628)	RCT	20 patients (10+10) (i) subfertility for more than 1 year requiring IVF/ICSI, (ii) age younger than 39 years, (iii) first or second IVF/ICSI trial and (iv) use of ejaculated spermatozoa only. Comparable groups	Letrozole 2.5 mg daily from day 2 until day 6 of the cycle and recombinant FSH starting on day 2 of the cycle. VS. rhFSH only, starting on day 2 of the cycle. In both groups, a constant daily dose of 150 IU rhFSH was used for stimulation and GnRH antagonist 0.25 mg/day was always started on day 6 of stimulation	Mean no. of oocytes Positive HCG rate per cycle Clinical pregnancy rate per cycle	Letrozole vs no letrozole COCs 13.8 (9.24) vs. 9.6 (7.73) Clinical pregnancy rate 50 vs.20	Pregnancies were achieved, supporting the idea that aromatase inhibitors can contribute to normal potential of implantation and follicular response, without having negative anti-oestrogenic effects. Larger randomized studies are needed to document the effect of aromatase inhibitors and their endocrine effects on ovarian stimulation for IVF/ICSI and reproductive outcome.	Due to the small numbers no conclusions can be drawn. The study describes some endocrine differences in LH that were statistically significant. No clear primary outcome measure
Yasa, C, Bastu, E, Dural, O, Celik, E and Ergun, B. Clin exp obstet gynecol. 2013; 40 (1): 98-100. (23724518)	RCT	50 patients (25+25) Patients who were clinically infertile for at least two years and who were attempting IVF for the first time were included in the study. Exclusion criteria were: age above 40 years, FSH levels of more than 15 IU/l, antral follicle count (AFC) less than 5, body mass index (BMI) greater than 30, any abnormal ultrasound results (i.e. cyst, endometrioma, endometrial polyp, etc.), and previous IVF attempt(s). Groups were comparable	gonadotropin treatment and letrozole along with gonadotropin-releasing hormone (GnRH) antagonist protocol, vs. gonadotropin treatment along with GnRH antagonist protocol without letrozole	retrieved oocytes ongoing pregnancy	Letrozole vs no letrozole COCs 10.44 ± 6.12 vs. 8.76 ± 7.35 p=0.38 ongoing pregnancy 20% vs. 20% NS	Addition of low-dose letrozole to gonadotropin treatment in GnRH antagonist protocols may result in a lower dose of gonadotropin administration. However, routine clinical practice remains questionable due to no evident positive effect on pregnancy rates.	No clear primary outcome measure The authors' conclusion about FSH dose is not based on their results

6.4 Clomiphene citrate

No relevant studies were identified

6.5 Long-acting vs daily rFSH

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Griesinger, G., Boostanfar, R., Gordon, K., Gates, D., McCrary Sisk, C. and Stegmann, B. J. Reprod Biomed Online. 2016; 33 (1): 56-60. (27178762)	SR	3292 patients 3 RCTs In Engage, women aged 18–36 years with a body weight >60 kg were randomized to 150 µg corifollitropin alfa (n = 756) or 200 IU rFSH (n = 750) (Devroey et al., 2009, In Ensure, women aged 18–36 years with lower body weight (≤60 kg) were randomized to 100 µg corifollitropin alfa (n = 268) or 150 IU rFSH (n = 128) (Corifollitropin alfa Ensure Study Group, 2010, In Pursue, older women (aged 35–42 years) with a body weight ≥50 kg were randomized to 150 µg corifollitropin alfa (n = 694) or 300 IU rFSH (n = 696) (Boostanfar et al., 2015, All three trials used a gonadotrophin-releasing hormone (GnRH) antagonist protocol.	corifollitropin alpha vs rFSH	COCs vital pregnancy rate, ongoing pregnancy rate, live-birth rate per started cycle, OHSS	Ca - FSH COCs +1.0 (95% CI, 0.5–1.5; Vital pregnancy OR: −2.2% (95% CI: −5.3% to 0.9%; Ongoing pregnancy OR:−1.7% (95% CI: −4.7% to 1.4%) OHSS any grade OR:1.15 (95% CI: 0.82–1.61, OHSS moderate/severe OR:1.29 (95% CI: 0.81–2.05,	A single dose of corifollitropin alfa for the first 7 days of ovarian stimulation is a generally well-tolerated and similarly effective treatment compared with daily rFSH[1]	IPD meta-analysis of three RCTs

Kolibianakis, E. M., Venetis, C. A., Bosdou, J. K., Zepiridis, L., Chatzimeletiou, K., Makedos, A., Masouridou, S., Triantafillidis, S., Mitsoli, A. and Tarlatzis, B. C. Hum Reprod. 2015; 30 (2): 432-40. (25492411)	RCT	Seventy-nine women with previous poor ovarian response undergoing ICSI treatment Inclusion criteria previous poor response to ovarian stimulation, <45 years, regular spontaneous menstrual cycle (24 – 35 days) BMI 18 – 32 kg/ basal FSH ≤20 IU/l. Only fresh ejaculated sperm was used no preimplantation genetic screening	single s.c dose of 150 mg corifollitropin alfa vs. seven fixed daily doses of 450 IU of follitropin beta In the corifollitropin alfa group, 450 IU of follitropin beta were administered from Day 8 of stimulation until the day of human chorionic gonadotrophin (hCG) administration, if necessary. LH suppression: a daily s.c dose of 0.25 mg of gonadotrophin releasing hormone (GnRH) antagonist ganirelix was administered Trigger: 250 mg of rhCG	Primary outcome measure: COCs Secondary outcome measures MII oocytes, 2pn zygotes, clinical pregnancy	CA vs Daily FSH COCs: [3.0 (4) versus 2.0 (3) P =0.26 MII oocytes 2.0(4, 1–3) vs.2.0 (3, 1–3) p=0.78 Live birth per patient reaching oocyte retrieval 7.9 (3) vs.2.6 (1)	Corifollitropin alfa for the first 7 days of ovarian stimulation, followed if necessary with 450 IU of follitropin beta/day, is not inferior to 450 IU of daily follitropin beta, considering the number of COCs retrieved, using a safety margin of 1.5 COCs (95% CI of the difference between medians in the number of COCs retrieved -1 to +1).	

7. Adjustment of gonadotropin dose

KEY QUESTION: IS ADJUSTMENT OF THE GONADOTROPIN DOSAGE DURING THE STIMULATION PHASE MEANINGFUL IN TERMS OF EFFICACY AND SAFETY?

P	I	C	O
Women undergoing IVF/ICSI (in case of **LOW** response)	- Adjustment of the stimulation dosage - Lower dose/ higher dose of gonadotropins / FSH?	Compare to: - No adjustment	Efficacy: - cumulative LBR/cycle - Cumulative ongoing pregnancy rate /started cycle (fresh + frozen) - Clinical pregnancy rate/started cycle - Nr of Oocytes/ nr of MII oocyte recovery rate (yield) - number of embryo's (fresh+frozen) Safety - incidence of different grades of OHSS - grade of OHSS - incidence of cycle cancellation for hyper-response (predefined) - Bleeding - Infection - Torsion - Long-term effect on maternal/child health - other adverse events (treatment related) Patient-related outcomes - Compliance - Drop-out rates - Patient burden - QoL - Patient preferences
Women undergoing IVF/ICSI (in case of **HIGH** response)	- Adjustment of the stimulation dosage - Lower dose/ higher dose of gonadotropins / FSH?	- No adjustment	

IS THE ADJUSTMENT OF THE STIMULATION DOSAGE DURING THE STIMULATION PHASE MEANINGFUL IN TERMS OF EFFICACY AND SAFETY?

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Aboulghar, M. A., Mansour, R. T., Serour, G. I., Al-Inany, H. G., Amin, Y. M. and Aboulghar, M. M. Reprod Biomed Online. 2004; 8 (5): 524-7. (15151713)	RCT	Total nr. of patients: 151. Group A : no dose increase n=72 Group B: dose increase n= 79 -inclusion cr.:age: lower 40y. -exclusion crit.: poor response previously, more than 3 failed IVF cycle in the past, clin. sign. syst. desease	A: no increase of HMG dose on day of antag. start B: increase of HMG with 1 amp. on day of antag.start Both groups start HMG on day3 with daily amp. No. 2- below age 30y 3- age 30-35y 4- age over 35 y +1 – if BMI above 30	Primary: cl. pregn. rate/cycle Secondary: N.of retr. oocytes,	No. oocytes: 10,1+/-3,8 vs. 9,2+/-2,1 NS Cl. preg. rate (%): 32,1 vs. 36,2 NS	There is no clinical evidence for increasing the dose of HMG on the day of antagonist administration.	No. of cases is too small to recognize small differences. This is specific to Antagonist starting DAY
Martin, J. R., Mahutte, N. G., Arici, A. and Sakkas, D. Reprod Biomed Online. 2006; 13 (5): 645-50. (17169173)	CS	Total No. of patients: 550 consecutive oocyte retrieval and fresh ET cycles. -No change in gonadotrophin dose: 427 -Increase dose: 39 -Decrease dose: 84	Starting dose(IU) of gonadotropin: -150-225: PCO patients -225: age below 35y -300-450: age 36-40y ->450: age over 40y	No. of retr. oocytes: cl. pregnancy rate: ongoing pregnancy rate	No. of retr. oocytes: 9,7+/-0,3 vs.9,1+/-0.8 vs.13,4+/-0,7 p<0,01 cl. pregnancy rate: 25,8 vs 28,2 vs 32,1 NS ongoing pregnancy rate 22,5 vs 23,1 vs 25,0 NS	Change (increase or decrease) of daily gonadotrophin dose during stimulation do not appear to have adverse effect on implantation or pregnancy rate.	

IS ADJUSTMENT OF THE GONADOTROPHIN DOSAGE DURING THE STIMULATION PHASE IN HIGH RESPONDER PATIENTS MEANINGFUL IN TERMS OF EFFICACY AND SAFETY?

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Aboulghar, M. A., Mansour, R. T., Serour, G. I., Rhodes, C. A. and Amin, Y. M.. J Assist Reprod Genet. 2000; 17 (5): 298-301. (10976419)	Clinical trial	No. of patients: 49 women at risk for OHSS (No. of foll. >20, E2> 3000 pg/ml, when leading foll. 13mm diam). during stimulation. A: (n=25) B: (n=24 C (n=32)	-HMG reduced to 75IU (from 150-225) or to 150IU (from 300) until coasting - HMG unchanged until coasting - HMG unchanged, no costing	No. of oocytes: Pregnancy rate %: No. of cancelled cycle: No. of severe OHSS: No. of moderate OHSS:	No of oocytes 15,5+/-4 vs 16+/-3,5 vs 21+/-5,5 p<0,001 Pregnancy rate %: 33,3 vs 35 vs 33,3 NS No. of cancelled cycle: 1 vs 4 vs 5 Severe OHSS 0 vs 0 vs 5 Moderate OHSS 1 vs 4 vs 8	When coasting is preceded by a decreased HMG dose, the duration of coasting and E2 level before coasting is reduced.	Fertilization rate and pregnancy rate is not influenced if gonadotrophin dose is reduced before coasting at patient with high risk for OHSS during stimulation. Pseudorandomisation!!

IS ADJUSTMENT OF THE GONADOTROPHIN DOSAGE DURING THE STIMULATION PHASE IN LOW RESPONDER PATIENTS MEANINGFUL IN TERMS OF EFFICACY AND SAFETY?

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
van Hooff, M. H., Alberda, A. T., Huisman, G. J., Zeilmaker, G. H. and Leerentveld, R. A. Hum Reprod. 1993; 8 (3): 369-73. (8473450)	RCT	No. of patients: 47 with low response during HMG stimulation (5days after stimulation <3 foll. <11mm diam. OR 1 foll.>11mm and 2 or less than 2 foll, with <11mm diam., AND E2 <500pmol/l.) Exclusion cr.: endocrine abnormality, severe endometriosis	A (n=22) no change in daily 225IU HMG B (n=25) doubling the HMG dose to 450IU Follow up was performed until oocyte pick-up.	-No. of cancelled cycles -No. of cycles with <=3 retrived oocytes - No. of cycles with >=4 retrived oocytes	10 vs. 9 NS 14 vs. 16 NS 8 vs 9 NS	Doubling the HMG dose in the course of an IVF treatment cycle is not effective in enhancing ovarian response in low responders.	Pregnancy rate is not given In the publication.
Cedrin-Durnerin, I., Bstandig, B., Herve, F., Wolf, J., Uzan, M. and Hugues, J. Fertil Steril. 2000; 73 (5): 1055-6. (10785239)	RCT	No. of randomized patients: 96 with poor ovarian response (<5 oocytes previously or elevated basal FSH / E2 on day 3) Short term, minidose GnRH-a protocol with 450IU/d FSH from day 3-5.	A (n=48) (-14 cancelled) step down of FSH to - 300 IU/d at 200 pg/ml - 150 IU/d at 2 foll. 12mm B (n=48) (-9 cancelled) continue of 450IU/day dose Follow up was performed until achievement of pr.	-No. of oocytes -Pregnancy rate/ET (%)	No. of oocytes 6,4+/-0,6 vs.6,3+/-0,6 NS Pregnancy rate/ET (%) 10,7 vs 12,9 NS	Reducing the amount of exogenous gonadotropins according to a step down regimen of administration is not detrimental for IVF outcome.	

8. Adjuvant therapies

KEY QUESTION: IS THE ADDITION OF ADJUVANTS IN OVARIAN STIMULATION MEANINGFUL IN TERMS OF EFFICACY AND SAFETY?

P	I	C	O
Women undergoing IVF/ICSI	- Metformin - GH - Testosterone - DHEA - Aspirin - Indometacin - Sildenafil	- No additional intervention	Efficacy: - cumulative LBR/cycle - Cumulative ongoing pregnancy rate /started cycle (fresh + frozen) - Clinical pregnancy rate/started cycle - Nr of Oocytes/ nr of MII oocyte recovery rate (yield) - number of embryo's (fresh+frozen) Safety - incidence of different grades of OHSS - grade of OHSS - incidence of cycle cancellation for hyper-response (predefined) - Bleeding - Infection - Torsion - Long-term effect on maternal/child health - other adverse events (treatment related) Patient-related outcomes - Compliance - Drop-out rates - Patient burden - QoL - Patient preferences

8.1 METFORMIN

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Tso, L. O., Costello, M. F., Albuquerque, L. E., Andriolo, R. B. and Macedo, C. R. Cochrane Database Syst Rev. 2014; (11): Cd006105. (25406011)	SR	Nine randomised controlled trials involving a total of 816 women with PCOS who were randomised to receive metformin (411) versus placebo or no treatment (405).	Metformin commencement varied from the start of ovarian stimulation with FSH or 16 weeks before (earliest) to the first day (latest) of GnRH-agonist administration in the studies reporting metformin use before FSH treatment and continued at least until the day of the hCG trigger. Metformin dose varied from 500 mg twice daily, 500 mg three times daily, 850 mg twice daily, 850 mg thrice daily, 1 gm twice daily, 500 mg twice daily gradually increased to 2 gm daily.	Number of oocytes retrieved Clinical pregnancy rate Live birth rate OHSS	No of oocytes retrieved (MD-0.76; 95% CI -2.02 to 0.50, eight RCTs, 635 women, I2 = 36%). Clinical pregnancy rates (OR 1.52; 95%CI 1.07 to 2.15, 8 studies, 775 women, I2 = 18%, moderate quality evidence). live birth rates (OR 1.39; 95% CI 0.81 to 2.40, five RCTs, 551 women, I2=52%, low quality evidence). The incidence of OHSS (OR 0.29; 95% CI 0.18 to 0.49, eight RCTs, 798 women, I2=11%, moderate quality evidence). GnRH agonist protocol: reduction in OHSS GnRH antagonist protocol: no reduction, 1 RCT	No conclusive evidence that metformin before or during ART cycles improves live birth rates in women with PCOS. However, use of metformin increased clinical pregnancy rates and decreased the risk of OHSS. The overall quality of the evidence was moderate for the outcomes of clinical pregnancy, OHSS and low for other outcomes. The main limitations in the evidence were imprecision and inconsistency.	GRADE evidence profile In the subgroup analysis OHSS was lower when used with the agonist regimen but no significant difference when used with the antagonist regimen.

Jacob, S. L., Brewer, C., Tang, T., Picton, H. M., Barth, J. H. and Balen, A. H. Hum Reprod. 2016; 31 (12): 2756-2764. (27816925)	RCT	153 patients were randomised, 77 received metformin and 76 placebo. All patients met the Rotterdam criteria for PCOS and were treated with a standard GnRH antagonist IVF/ICSI treatment cycle.	The study medication was started prior to stimulation and continued to oocyte retrieval.	Number of oocytes retrieved Clinical pregnancy rate Live birth rate OHSS	No of oocytes retrieved (placebo = 15, metformin = 14, 95% CI −2.37–4.37, P = 0.66). Clinical pregnancy rate (placebo = 48.7%, meformin = 28.6%, 95% CI 0.04–0.35, P = 0.02) live birth rate (placebo = 51.6%, metformin = 27.6%, 95% CI 0.05–0.40, P = 0.02). incidence of OHSS between the metformin and placebo groups (OR 1.376, 95% CI 0.542–3.491).	The first adequately powered RCT to assess the impact of metformin on OHSS in a high-risk group (women with PCOS) undergoing a GnRH antagonist cycle. It does not support the empirical prescribing of metformin as an adjunct to a GnRH antagonist treatment.	
Abdalmageed, O. S., Farghaly, T. A., Abdelaleem, A. A., Abdelmagied, A. E., Ali, M. K. and Abbas, A. M. Reprod Sci. 2018; 1933719118765985. (29576001)	RCT	Women with PCOS who were less than 39 years, overweight, and obese with body mass index (BMI) >24 kg/m2, having their first IVF. 102 women in total, 51 each in the study and placebo groups.	Eligible women were allocated to either group I (metformin group) received 2 tablets of metformin 500 mg or group II (placebo group) received 2 placebo tablets. Metformin or placebo were commenced from the start of controlled ovarian stimulation and continued until a negative pregnancy test or 12 weeks of pregnancy.	Number of oocytes retrieved Mature oocytes Clinical pregnanacy rate Miscarriage rate Llive birth rate	Metformin vs placebo: No of oocytes retrieved: (9.06+4.23 vs 16.86+8.3, P < .01). CPR 33% vs 27.5% .p = 0.52), LBR (25.5% vs 17.6%, P = 34).	Short-term administration of metformin to overweight or obese women with PCOS undergoing IVF decreased number of the retrieved oocytes but did not improve the LBR.	Authors state primary outcome is number of oocytes. However, sample size calculation was based on CPR increase 30% to 70% with metformin.

8.2 GROWTH HORMONE (GH)

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Duffy, J. M., Ahmad, G., Mohiyiddeen, L., Nardo, L. G. and Watson, A. Cochrane Database Syst Rev. 2010; (1): Cd000099. (20091500)	SR	Routine use of growth hormone as an adjuvant in IVF protocols – 2 trials. Non-routine use of growth hormone as an adjuvant in IVF protocols in women considered poor responders – 8 trials.	There was no consistency as to the dose or timing of growth hormone administration. The dose of growth hormone ranged from 8IU to 24IU.	Live birth rate per woman randomised Pregnancy rate per woman randomised Adverse events	Use of adjuvant growth hormone in women who are not poor responders live birth rate (OR 1.32; 95% CI 0.40 – 4.43) pregnancy rate (OR 1.78; 95% CI 0.49 – 6.50) adverse events with use of growth hormone (OR 0.62, 95% CI 0.18 to 2.15)	Results of the meta-analysis demonstrated no difference in outcome measures and adverse events in the routine use of adjuvant growth hormone in in-vitro fertilisation protocols. The result needs to be interpreted with caution, the included trials were few and small sample size.	GRADE evidence profile For GH in non-poor responder GRADE Evidence profile for GH in poor responders from Li 2017 (as is more recent to this review)
Li, X. L., Wang, L., Lv, F., Huang, X. M., Wang, L. P., Pan, Y. and Zhang, X. M. Medicine (Baltimore). 2017; 96 (12): e6443. (28328856)	SR	11 RCTs including women with POR undergoing IVF were included.		Number of oocytes retrieved Mature oocytes retrieved Clinical pregnancy rate Live birth rate	Number of oocytes (SMD 1.09, 95% CI 0.54–1.64). Number of MII oocytes (SMD 1.48, 0.84–2.13), Clinical pregnancy rate (RR 1.65, 95% CI 1.23–2.22). Live birth rate (RR1.73, 1.25–2.40).	The GH addition can significantly improve the clinical pregnancy rate and live birth rate.	GRADE evidence profile Poor responder Follicular – luteal administration

Choe, S. A., Kim, M. J., Lee, H. J., Kim, J., Chang, E. M., Kim, J. W., Park, H. M., Lyu, S. W., Lee, W. S., Yoon, T. K. and Kim, Y. S. Arch Gynecol Obstet. 2018; 297 (3): 791-796. (29264647)	RCT	RCT of sustained-release human GH inBologna criteria poor responders undergoing IVF, GH treatment group (N = 62) and controls (N = 65).	The treatment group received a sustained-release GH three times before and during OS (mid-luteal, late luteal, and menstrual cycle day 2).	Number of mature oocytes Clinical/ ongoing pregnanacy rate Miscarriage rate	Mature oocytes (67.5 vs. 52.3%, P = 0.030) were higher in the GH group than in controls. CPR 9.7% vs 16.9%, p = 0.348, OPR 8.1% vs 9.2%, p = 1.000.	Supplementation of sustained-release GH before and during OS improved ovarian response, with an increase in mature oocytes in poor responders. Further studies are needed to ensure this benefit in general infertility patients.	Primary outcomes of interest were the number of (mature) oocytes and serum level of estradiol on hCG triggering day. Secondary outcomes included serum level of IGF-1 and IGFBP-3, number of follicles with diameter ≥ 14 mm, level of progesterone on hCG triggering day, fertilization/ implantation rate, proportion of metaphase II (MII) oocytes, proportion of good quality embryos, clinical/ongoing pregnancy rate, and spontaneous abortion rate.
Owen, E. J., West, C., Mason, B. A. and Jacobs, H. S.. Hum Reprod. 1991; 6 (4): 524-8. (1918302)	RCT	Participation patients had to be <38 years, having undergone one or more IVF cycles in which the response was considered suboptimal, defined as a response in which fewer than six oocytes were collected and than four embryos developed. Twenty-five patients were recruited into this study of cotreatment with biosynthetic natural sequence human GH (n=13) compared with placebo (n=12).	GH (24 units per injection given 1M). The drug was given on alternate days for a maximum period of 2 weeks until the administration hCG.	Number of oocytes retrieved	No significant difference in the number of oocytes retrieved between the GH and placebo groups (6 (0-8) vs 3.5 (2-6).	There may be a place for GH treatment in selected IVF cycles after pituitary suppression.	

8.3 TESTOSTERONE

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Nagels, H. E., Rishworth, J. R., Siristatidis, C. S., Kroon, B. Cochrane Database Syst Rev 2015; 11: Cd009749 (26608695)	SR	Effect of transdermal testosterone preceding ovarian stimulation in women with poor ovarian response undergoing IVF. Four trials (Massin 2006; Fabregues 2009; Kim 2010; Kim 2011) were included (203 women in the testosterone group, 142 in the control group).	One study compared transdermal testosterone with placebo gel (Massin 2006). Three studies compared transdermal testosterone with no treatment (Fábregues 2009; Kim 2010; Kim 2011). The dose and length of pre-treatment varied: 2.5 mg/ day for 5 days (Fábregues 2009); 10 mg/ day for 15 to 20 days (Massin 2006); 12.5 mg/ day for 14, 21 or 28 days (Kim 2010) and 12.5 mg/ day for 21 days (Kim 2011)..	Ongoing pregnancy/ live birth rate Clinical pregnancy rate Adverse effects	Testosterone compared with controls higher live birth rates (OR 2.60, 95% CI 1.30 to 5.20; 4 RCTs, N = 345, moderate evidence). removal of studies at high risk of performance bias in a sensitivity analysis, the remaining study showed no evidence of a difference between the groups (OR 2.00, 95% CI 0.17 to 23.49; one RCT, N = 53)	In women identified as poor responders, testosterone may be associated with improved live birth rates. The overall quality of the evidence is moderate. There is insufficient evidence to draw any conclusions about the safety of testosterone. Definitive conclusions regarding the clinical role of testosterone awaits evidence from further well-designed studies.	

Gonzalez-Comadran, M., Duran, M., Sola, I., Fabregues, F., Carreras, R. and Checa, M. A. Reprod Biomed Online. 2012; 25 (5): 450-9. (22999555)	SR	Effect of transdermal testosterone preceding ovarian stimulation in women with poor ovarian response undergoing IVF. Three trials (Massin 2006; Fabregues 2009; Kim 2011) were included (113 women in the testosterone group, 112 in the control group). Type of intervention evaluated was administration of transdermal testosterone preceding gonadotrophin treatment compared with standard gonadotrophin ovarian stimulation protocols without administration of transdermal testosterone during the period of follicular stimulation.	Pretreatment with transdermal testosterone gel was applied in two studies (Massin et al., 2006; Kim et al., 2011), in a dose of 10 and 12.5 mg/day, respectively, for 15 to 21 days during pituitary desensitization. Testosterone patches of 2.5 mg daily for 5 days during pituitary desensitization (Fabregues 2009).	Number of oocytes retrieved Clinical pregnancy rate Live birth rate	number of oocytes retrieved (RR 1.28, 95% CI 0.77 to 1.78). clinical pregnancy rate (RR 2.07, 95% CI 1.13 to 3.78). live birth rate (RR 1.91, 95% CI 1.01 to 3.63).	Transdermal testosterone significantly increases live birth. The present data should be interpreted with caution because of the small number of trials and clinical heterogeneity. The identification of poor responders that could especially benefit from testosterone treatment should be addressed in further studies.	GRADE evidence profile Study included for outcome on number of oocytes as this outcome was not analysed in SR Nagels.
Bosdou, J. K., Venetis, C. A., Dafopoulos, K., Zepiridis, L., Chatzimeletiou, K., Anifandis, G., Mitsoli, A., Makedos, A., Messinis, I. E., Tarlatzis, B. C. and Kolibianakis, E. M. Hum Reprod. 2016; 31 (5): 977-85. (26956551)	RCT	50 poor responders fulfilling the Bologna criteria were randomized to either testosterone pretreatment for 21 days (n = 26) or no pretreatment (n = 24). No differences in baseline characteristics were observed between the two groups compared.	Daily dose of 10 mg of testosterone gel was applied transdermally for 21 days starting from GnRHa initiation.	Number of oocytes retrieved Clinical pregnancy rate Live birth rate	COCs retrieved 3.5 (2.0-5.0) vs 3.0 (2.7-4.3) P=0.76. number of MII oocytes 3.0 (2.0-3.5) vs 3.0 (1.7-3.0) P=0.66. clinical pregnancy (7.7% vs 8.3%; p=1.0) live birth rate (7.7% vs 8.3%; p=1.0)	Testosterone pretreatment failed to increase the number of COCs by more than 1.5 as compared with no pretreatment in poor responders undergoing ICSI.	

Kim, C. H., Ahn, J. W., Moon, J. W., Kim, S. H., Chae, H. D. and Kang, B. M. Dev Reprod. 2014; 18 (3): 145-52. (25949183)	RCT	Poor responders undergoing IVF were randomized into control, 2 weeks, 3 weeks or 4 weeks transdermal testosterone gel (TTG) treatment groups. 120 women (30 in each group) were enrolled who failed to produce over 3 follicles with a mean diameter of ≥ 16 mm, and then less than 3 follicles were retrieved even a high total dose of recombinant human follicle stimulating hormone > 2,500 IU.	For three TTG treatment groups, 12.5 mg TTG was applied daily for 2 weeks, 3 weeks or 4 weeks in preceding period of study stimulation cycle. Before starting OS cycle, all of the patients had taken estrogen and progesterone pretreatment for 25 days using E2 valerate 1 mg/d and norethindrone 5 mg/d. In all subgroups, GnRH antagonist multiple dose protocol was used for ovarian stimulation.	Number of oocytes retrieved Number of mature oocytes Clinical pregnancy rate Live birth rate	Number of oocytes retrieved 3 wks (5.3±2.0) and 4 wks (5.8±1.9) TTG groups vs. control (3.9±1.3, P< 0.001). 2 wks TTG (4.3±1.6) vs control group, NS. Number of MII oocytes 3 (4.5±1.8) and 4 wks (4.9±1.6) TTG groups vs. control group (3 3.1±1.1, P< 0.001). 2 wks (3.6±1.3) TTG vs control group. Clinical pregnancy rate 4 weeks TTG (36.7%) vs control group (10%, P=0.030). 2 (16.7%) and 3 (30%) weeks TTG vs control group, NS Live birth rate 4 wks TTG (30%) vs control group (6.7%, P=0.042). 2 (13.4%) and 3 (20%) wks TTG vs control.	TTG pretreatment for 3 to 4 weeks increases AFC and ovarian stromal blood flow, thereby potentially improving the ovarian response to OS and IVF outcome in poor responders undergoing IVF/ICSI.	4 ARM RCT, PILOT STUDY WITH CONTROL 2 WEEK TESTOSTERONE 3 WEEK TESTOSTERONE WEEK TESTOSTERONE

8.4 DEHYDROEPIANDROSTERONE (DHEA)

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Nagels, H. E., Rishworth, J. R., Siristatidis, C. S., Kroon, B. Cochrane Database Syst Rev 2015; 11: Cd009749 (26608695)	SR	Of the 12 included studies, majority (10) of the studies were in women identified as poor responders. Two studies included women with normal ovarian reserve (Yeung et al., 2013; Tartagni et al., 2016).	6 studies compared DHEA with placebo (Divita 2003; Evans 2013; Tartagni 2015a; Tartagni 2015b; Yeung 2013a; Yeung 2014). and six studies (Artini 2012; Jindal 2014; Kara 2014; Moawad 2012; Wiser 2010; Zhang 2014) compared DHEA with no treatment. Studies varied in the dose and duration of the intervention, but most studies used 75 mg of DHEA daily before and during stimulation, The long GNRH agonist protocol was most commonly used in majority of the studies.	Ongoing pregnancy/ live birth rate Clinical pregnancy rate Adverse effects	live birth or ongoing pregnancy (OR 1.88, 95% CI 1.30 to 2.71; 8 RCTs, N = 878, moderate quality evidence). However, in a sensitivity analysis removing trials at high risk of performance bias, the effect size was reduced and no longer reached significance (OR 1.50, 95% CI 0.88 to 2.56; 5 RCTs, N = 306).	In women identified as poor responders undergoing ART, pre-treatment with DHEA may be associated with improved live birth rates. The overall quality of the evidence is moderate. There is insufficient evidence to draw any conclusions about safety. Definitive conclusions regarding the clinical role of DHEA awaits evidence from further well-designed studies	Studies involving poor responders and normal responders were pooled together in the meta-analysis.
Kotb, M. M., Hassan, A. M. and AwadAllah, A. M. Eur J Obstet Gynecol Reprod Biol. 2016; 200 11-5. (26963897)	RCT	140 women undergoing IVF/ICSI with POR according to the Bologna criteria were randomly divided into 2 equal groups.	The study group received DHEA 75 mg daily for 12 weeks before the IVF/ICSI cycles and the control group did not receive DHEA.	Number of oocytes retrieved Mature oocytes Clinical pregnancy rate Ongoing pregnancy rate	**DHEA vs control** Number of oocytes retrieved (6.9±3 vs 5.8±3.1; p=0.03). Clinical pregnancy rate (32.8% vs 15.7%; p=0.029). Ongoing pregnancy (28.5% vs 12.8%; p=0.036).	DHEA increases the number of oocytes, fertilization rate, fertilized oocytes, and clinical pregnancy rate and ongoing pregnancy rate in women with POR according to the Bologna criteria. DHEA was well tolerated by the patients and was associated with less COH days and gonadotropins doses.	Number of oocytes and clinical outcomes inconsistent with what would be expected for Bologna criteria poor responders.

Narkwichean, A., Maalouf, W., Baumgarten, M., Polanski, L., Raine-Fenning, N., Campbell, B. and Jayaprakasan, K. Eur J Obstet Gynecol Reprod Biol. 2017; 218 39-48. (28934714)	RCT	60 women with POR based on antral follicle count or anti- Mullerian hormone thresholds undergoing IVF/ ICSI were randomised to receive DHEA or placebo. Following exclusion of 8 women, 25 women received DHEA and 27 women received placebo. AFC less than 10 and/or AMH less than 5 pmol/L.	The study group received 75 mg DHEA and the control group received placebo capsule. Both groups were advised to take intervention for at least 12 weeks before the egg collection procedure (prior to and during controlled ovarian stimulation).	Number of oocytes retrieved Clinical pregnancy rate Live birth rate	**DHEA vs control** number of oocytes retrieved (median 4, 0-18 vs 4, 0-15, p=0.54) clinical pregnancy rate (30% vs 36%, P=0.63) live birth rate (26% vs 32%, P=0.63)	Pre-treatment DHEA supplementation, albeit statistical power in this study is low, did not improve the response to controlled ovarian hyperstimulation or oocyte quality or live birth rates during IVF treatment with long protocol in women predicted to have POR.	
Yeung, T., Chai, J., Li, R., Lee, V., Ho, P. C. and Ng, E. Bjog. 2016; 123 (7): 1097-105. (26663817)	RCT	72 subfertile women with AFC of 5–15 undergoing IVF (anticipated normal responders), 36 in the DHEA and 36 in the placebo group. Both groups (study and control) were comparable.	Twelve weeks before scheduled IVF women in study group received 75 mg of DHEA daily and women in control group received placebo.	Number of oocytes retrieved	**DHEA vs control** number of oocytes retrieved (6 (4-9) vs 7 (3-10), NS	No significant differences in AFC, ovarian response to a standard low dose of gonadotrophin stimulation and number of oocytes obtained were detected in anticipated normal responders receiving 12 weeks of DHEA prior to IVF treatment relative to placebo.	

8.5 Aspirin

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Siristatidis, C. S., Basios, G., Pergialiotis, V. and Vogiatzi, P. Cochrane Database Syst Rev. 2016; 11 Cd004832. (27807847)	SR	ONLY ANALYSIS FOR LIVE BIRTH AND ONGOING PREGNANACY RATES INCLUDED FROM THIS SR (ANALYSES EXCLUDED ARE - CLINICAL PREGNANCY RATE WHICH POOLED STUDIES THAT STARTED ASPIRIN AT THE TIME OF EMBRYO TRANSFER AND MISCARRIAGE RATE WHICH INCLUDED STUDY THAT HAD CO-INTERVENTIONS COMMENECED BEFORE THE MISCARRIAGE OUTCOME – URMAN 2000) Patient characteristics varied between the included studies. Likely to be comparable between study and control groups as all studies included in the meta-analysis are RCTs	Aspirin was commenced before stimulation or during stimulation and continued until hCG administration, fetal heart noted on ultrasound or until delivery. Dose of aspirin was 100 mg/ day in all studies pooled in the meta-analysis for outcome of live birth and ongoing pregnancy.	Live birth rate per woman or couple Ongoing pregnancy rate per woman or couple Safety – vaginal bleeding	**Aspirin vs placebo** live birth rate; pooled risk ratio (RR) 0.91, 95% CI 0.72 to 1.15. ongoing pregnancy rate; pooled risk ratio (RR) 0.94, 95% CI 0.69 to 1.27. adverse events (vaginal bleeding) (RR) 1.01, 95% CI 0.14 to 7.13.	Currently there is no evidence in favour of routine use of aspirin to improve pregnancy rates for a general IVF population.	GRADE evidence profile.
Dirckx, K., Cabri, P., Merien, A., Galajdova, L., Gerris, J., Dhont, M. and De Sutter, P. Hum Reprod. 2009; 24 (4): 856-60. (19131401)	RCT	97 women received aspirin and 96 women received placebo.		Number of oocytes Clinical pregnancy rate/cycle Live birth rate/cycle	**Aspirin vs placebo** number of oocytes retrieved (12.6±7.6 vs 12.9±7.9; p=0.788). Clinical pregnancy rate (OR 1.033; 95% CI 0.565–1.890).		This study is included in the live birth rate meta-analysis in Siristatidis (2016). Hence evidence not formulated separately in detail.

Lambers, M. J., Hoozemans, D. A., Schats, R., Homburg, R., Lambalk, C. B. and Hompes, P. G. Fertil Steril. 2009; 92 (3): 923-9. (18973893)	RCT	169 patients, 84 assigned to aspirin treatment and 85 to placebo treatment.			**Aspirin vs placebo** number of oocytes retrieved (13.7 vs 13.5; NS). clinical pregnancy rate (41.8% vs 36.9%, p=0.525).		This study is included in the ongoing pregnancy rate meta-analysis in Siristatidis (2016). Hence evidence not formulated separately in detail.
Lok, I. H., Yip, S. K., Cheung, L. P., Yin Leung, P. H. and Haines, C. J. Fertil Steril. 2004; 81 (3): 556-61. (15037402)	RCT	Patients included were poor responders defined as previous IVF cycles cancelled because of recruitment of fewer than three mature follicles (≥17 mm) or patients with repeated high basal levels of FSH (>10 IU/L). Patients older than 40 years of age were excluded. Patients with polycystic ovarian syndrome or those with an ovarian cyst or endometrioma at baseline were also excluded. Heavy smokers, patients with cardiovascular disorders, and those taking medications that could affect the circulation were also excluded.	Patients were randomly allocated to receive either low-dose aspirin (80 mg daily) or placebo beginning at the time of commencement of GnRH agonist in the preceding cycle and continuing until the day of hCG administration or cancellation Total of 60 women (30 in each group) completed treatment and were analysed. 62 women were randomised initially but 1 women in each group dropped out.	1. Cycle cancellation rate 2. Number of oocytes retrieved 3. Clinical pregnancy	**Aspirin vs placebo** cycle cancellation rate (26.7% vs 33.3%) . median number of oocytes retrieved (3; IQR 2 – 7.25 vs 4; IQR 2 – 7.25) clinical pregnancy rate (1 in vs 2)	Supplementation with low dose aspirin failed to improve ovarian response in poor responders.	Evidence formulated as this study was not included in the outcomes of the included SR detailed in this evidence table.
Moini, A., Zafarani, F., Haddadian, S., Ahmadi, J., Honar, H. and Riazi, K. Saudi Med J. 2007; 28 (5): 732-6. (17457441)	RCT	145 women undergoing IVF (72 in the study and 73 in the control group) were randomised and analysed. Mean age was similar in both groups.	Aspirin (100 mg) or placebo was started on the 21st day of the preceding menstrual cycle and continued until a negative pregnancy test or 12 weeks of pregnancy.	Number of oocytes retrieved Pregnancy rate OHSS STUDY DID NOT PROVIDE DEFITION/ CRITERIA FOR OHSS.	**Aspirin vs placebo** number of oocytes retrieved (6.9±5.6 vs 8.6±6.8). clinical pregnancy rate (45.5% vs. 33.3%) OHSS rate (5.6%) vs. (23.3%).	The addition of aspirin did not improve pregnancy and implantation rates in unselected women undergoing IVF cycles.	Evidence formulated as this study was not included in the outcomes of the SR Siristatidis (2016) that are detailed in this evidence table. Note: No actual numbers were provided for outcome clinical pregnancy, results only given as %

Pakkila, M., Rasanen, J., Heinonen, S., Tinkanen, H., Tuomivaara, L., Makikallio, K., Hippelainen, M., Tapanainen, J. S. and Martikainen, H. Hum Reprod. 2005; 20 (8): 2211-4. (15817582)	RCT	374 women who were to undergo IVF/ICSI were randomized to receive 100mg of aspirin (n = 186) or placebo (n = 188) daily.		Number of oocytes Clinical pregnancy rate	**Aspirin vs placebo** number of oocytes retrieved (12.0±7.0 vs 12.7±7.2; NS). clinical pregnancy/ embryo transferred (25.3% vs 27.4%).		This study is included in the live birth rate meta-analysis in Siristatidis (2016). Hence evidence not formulated separately in detail.
Rubinstein, M., Marazzi, A. and Polak de Fried, E. Fertil Steril. 1999; 71 (5): 825-9. (10231040)	RCT	298 patients were randomly divided into treatment and control groups. The treatment group (149 patients; mean [± SD] age, 35.9 ± 4.2 years) received a daily oral dose of 100 mg aspirin, and the control group (149 patients; mean age, 35.4 ± 3.9 years) received placebo. No significant difference in age between the two groups.	Both groups started aspirin or placebo cotreatment on the 21st day of their preceding menstrual cycle. Pregnant patients continued the medication, which included aspirin or placebo cotreatment, through 12 weeks' gestation.	Number of oocytes retrieved Cycle cancellation rate Clinical pregnancy rate Safety	**Aspirin vs control** Mean (± SD) number of oocytes retrieved 16.2 ± 6.7, vs 8.6 ± 4.6 (P<05). cancellation rate (4% vs 9%; P<05). Clinical pregnancy rate was 45% vs 28% (P<05). No side effects were observed in patients treated with aspirin, and bleeding was similar for both groups.	Low-dose aspirin treatment significantly improves ovarian responsiveness, implantation and pregnancy rates in IVF patients.	Evidence formulated as this study was not included in the outcomes of the SR Siristatidis (2016) that are detailed in this evidence table. Note: No actual numbers were provided for outcome clinical pregnancy, results only given as %

8.6 INDOMETACIN

No relevant studies were identified

8.7 SILDENAFIL

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Ataalla, Wm, Elhamid, Ta and Elhalwagy, Ae. Middle east fertility society journal. 2017; 21 (3): 175-179. (CN-01308022)	RCT	Sixty patients were classified as low responders undergoing IVF, 30 in the study and 30 in the placebo group. Low responders were defined as those who had <3 dominant follicles on the day of hCG administration or <3 retrieved oocytes or those who had previous cycle cancelation due to poor follicular development. There were no significant differences in the patient characteristics in the two groups.	Supplementation with sildenafil (50 mg daily) or Placebo.	Number of oocytes retrieved	The difference between the number of oocytes retrieved was not statistically significant in the two groups. MEAN OR MEDIAN NUMBER OF OOCYTES NOT STATED IN THE PAPER.	Adjuvant sildenafil does not enhance ovarian responsiveness in cases of previous low ovarian response to controlled ovarian hyperstimulation.	Pseudorandomisation.

9. Non-conventional start of ovarian stimulation

KEY QUESTION: WHAT IS THE SAFETY AND EFFICACY OF NON-CONVENTIONAL START STIMULATION COMPARED TO STANDARD EARLY FOLLICULAR PHASE STIMULATION?

P	I	C	O
Women undergoing IVF/ICSI	Non-conventional start Luteal phase stimulation Double stimulation		Efficacy: - cumulative LBR/cycle - Cumulative ongoing pregnancy rate /started cycle (fresh + frozen) - Clinical pregnancy rate/started cycle - Nr of Oocytes/ nr of MII oocyte recovery rate (yield) - number of embryo's (fresh+frozen) Safety - incidence of different grades of OHSS - grade of OHSS - incidence of cycle cancellation for hyper-response (predefined) - Bleeding - Infection - Torsion - Long-term effect on maternal/child health - other adverse events (treatment related) Patient-related outcomes - Compliance - Drop-out rates - Patient burden - QoL - Patient preferences

9.1 NON-CONVENTIONAL START

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments

Pereira, N., Voskuilen-Gonzalez, A., Hancock, K., Lekovich, J. P., Schattman, G. L. and Rosenwaks, Z. Reprod Biomed Online. 2017; 35 (4): 400-406. (28647355)	CS	retrospective Not randomized (women choice) N=1302 women desiring non-medical egg freezing excluded medical pb and cancer	Control (N=852): D2/3 start (+/- OCP prettt) rFSH + flexible antagonist protocol (with switch to HMG) or short agonist (12.5%) Study(N=443): random start + rFSH flexible antagonist protocol -group early FP D4-7 (N=342) -group late FP > D7 (start antagonist same day FSH) (N=42) -group luteal Prog >3 (N=59) trigger: rHCG or uHCG or agonist or dual trigger	1/ number of oocytes	1/ number of oocytes control: 13.1(2.3) early FP: 12.7(2.7) late FP: 13(3.1) luteal: 13.2(2.9) NS	the number of total and MII oocytes derived from random-start ovarian stimula- tion protocols initiated during any phase of the menstrual cycle are similar to conventional CD 2/3 ovarian stimulation start protocols	Retrospective but large Increased ovarian stimulation duration and increased gonadotrophin utilization in late FP and luteal phase
Qin, N., Chen, Q., Hong, Q., Cai, R., Gao, H., Wang, Y., Sun, L., Zhang, S., Guo, H., Fu, Y., Ai, A., Tian, H., Lyu, Q., Daya, S. and Kuang, Y. Fertil Steril. 2016; 106 (2): 334-341.e1. (27114329)	CS	Retrospective N=150 Age<42, AFC>3, FSH <12	Control (N=50): D2-5 HMG 150-225 + MPA +CC Late FP (N=50): D6-14 triptorelin 0.1 + HMG +MPA +CC Luteal (N=50): >D14 (prog>6.5) HMG+CC Trigger triptorelin 0.1 +HCG 1000 Freeze all FET: natural or artificial cycle	1/ ongoing PR 2/ number of oocytes	1/ ongoing PR control: 39% (16/41) lateFP: 39.4% (13/33) luteal: 33.3% (12/36) NS 2/ number of oocytes control: 6.6(3.8) lateFP: 5.9(4.3) luteal: 5.9(4.2) NS	All three ovarian stimulation protocols were observed to be equally effective. These results demonstrate that ovarian stimulation can be commenced on any day of the menstrual cycle	Retrospective but large Higher duration and FSH dose in Late FP and Luteal

9.2 LUTEAL PHASE STIMULATION

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Kansal Kalra, S., Ratcliffe, S., Gracia, C. R., Martino, L., Coutifaris, C. and Barnhart, K. T. Reprod Biomed Online. 2008; 17 (6): 745-50. (19079956)	RCT	N=18 (9+9) History of POR = <5 foll or 5 oo or cancel for POR And FSH <12	Study group: rFSH start at LH peak + 9 (D23) 150 IU x2/d and after menses 300 IUx2/d Control: rFSH start at D1-2 300 IUx2/d flexible antagonist 0.25 (foll>12) HCG 10000 Fresh transfer	1/ live birth rate 2/clinical pregnancy rate 3/ number of oocytes (primary endpoint)	1/live birth rate luteal 0% 0/9 foll 22% (2/9) 2/ clinical preg rate luteal 11% foll 33% 3/ number oo luteal 5 (3-8) foll 5.5 (1-14)	luteal phase initiation of FSH with GnRH antagonist appears to be a safe alternative in patients with poor ovarian response. Although no clear bene t of this protocol was discerned in comparison with a standard GnRH antagonist protocol initiating FSH in the follicular phase	Very small number of patients, pilot study. POR patients Antagonist protocol Prettt with FSH more than luteal stimulation (fresh transfer)
Kucuk, T., Goktolga, U. and Sozen, E. J Obstet Gynaecol Res. 2008; 34 (4): 574-7. (18946938)	RCT	N=42 (21+21) POR patients: FSH<15 and < 4 oo in previous ICSI	Study group: long agonist luteal start D21 tripto 0.1 + rFSH 150IU until D2 and then tripto 0.05 + 450 IU Control group: long agonist luteal start D21 tripto 0.1 until D2 and then tripto 0.05 + 450 IU rHCG Fresh transfer	1/ clinical PR 2/ number of M2 oo	1/ clinical PR luteal 38% foll 10.5% p<0.005 2/ number of M2 oo luteal 6.8 foll 3.2 p<0.05	commencement of recFSH during the luteal phase improves outcomes in poor responder women compared with the conventional COH proto-col. Although the total cost of the treatment is high. More studies are needed to reach more reliable conclusions	Small number of patients. POR patients Long agonist protocol Prettt with FSH more than luteal stimulation (fresh transfer)

Rombauts, L., Suikkari, A. M., MacLachlan, V., Trounson, A. O. and Healy, D. L. Fertil Steril. 1998; 69 (4): 665-9. (9548155)	RCT	N= 40 < 38y 3-6 oocytes previous IVF	Study group: D25 rFSH 150IU Control group: D3 rFSH 150 Short agonist (start D2) HCG 5000	1/ number of oocytes	1/ number of oocytes luteal 4.5 (2-12) foll 6 (1-10) NS	compared with the typical short or ‘‘flare-up’’ protocol, poor responders did not benefit from com-mencing recombinant human FSH administration in the luteal phase. The cumulative dose of recombinant human FSH was higher and, more important, the total number of oocytes retrieved at pick-up was not different	Small number of patients. POR patients Short agonist protocol Prettt with FSH more than luteal stimulation (fresh transfer)
Kuang, Y., Chen, Q., Hong, Q., Lyu, Q., Ai, A., Fu, Y. and Shoham, Z. Reprod Biomed Online. 2014; 29 (6): 684-91. (25444501)	CS	Pilot (prospective?) POR (Bologna) N=38 (1 cycle) include 30 with duostim	1st cycle: start D3 CC (until trigger) +letrozole (4d) + HMG 150 1d/2 starting D6 trigger triptoreline 0.1 freeze all embryos 2nd cycle if at least to AFC 2 the day of OPU or the day after: HMG 225 + letrozole and MPA at the end (prevent menstruation) trigger triptoreline 0.1 No analog used. FET: natural or artificial cycle	1/ongoing pregnancy/tranfer 2/number of oocytes	1/ongoing pregnancy/transfer Foll: 53.8% (7/13) LPS: 57.1% (4/7) Mixed: 2/number of oocytes Foll: 1.7(1) LPS: 3.5(3.2) p 0.001	double stimulation during the follicular and luteal phases in the same menstrual cycle provided more opportunities to retrieve oocytes in poor responders, with the resulting embryos having similar devel- opment potential	Not all the women had FET at the end of research (21 of 26)

Liu, C., Jiang, H., Zhang, W. and Yin, H. Reprod Biomed Online. 2017; 35(6):678-684. (29030068)	CS	Retrospective case-control (case own control) N=116 enrolled after OPU Age> 38 and at least AFC 1 after 1st OPU	1st cycle: group 1: short agonist (27) group 2: antagonist (32) group 3: mild (21) group 4: MPA (23) long agonist (13) excluded from subgroup analysis trigger rHCG 2nd cycle (luteal) day 1-3 after OPU HMG 225 trigger rHCG freeze all FET: artificial cycle	1/clinical preg rate 2/ Number of oocytes	1/ clinical preg rate Foll: 25% (4/1) LPS: 20.6% (7/34) NS 2/number of oocytes Foll: 2.3(2) LPS: 3.5(3.6) p 0.002	double ovarian stimulation could increase the chances of achieving pregnancy by accumulating more oocytes/embryos in a short time	Design similar to UBaldi/Vaiarelli
Vaiarelli, A., Cimadomo, D., Trabucco, E., Vallefuoco, R., Buffo, L., Dusi, L., Fiorini, F., Barnocchi, N., Bulletti, F. M., Rienzi, L. and Ubaldi, F. M. Front Endocrinol (Lausanne). 2018; 9 317. (29963011)	CS	Prospective, continuation of Ubaldi 2016 and Vaiarelli 2017 N= 310 “poor prognosis” (group 4 of Poseidon with PGD-A	Cf Ubaldi 2016	1/ ongoing pregnancy 2/ number of M2 oocytes	1/ ongoing pregnancy/transfer of euploid blastocyst (not all embryo used) LPS: 49.4% Foll: 39.5% NS 2/number of M2 oocytes Higher in LPS: 4.7(3) Foll: 4.0(2.5) P<0.01 Same euploid rate	Duostim instead can maximize the number of oocytes obtained per menstrual cycle, in turn increasing the chance to obtain reproductively competent embryos in the shortest possible time, a crucial perspective for patients with a short-term fertility because of AMA and/or with reduced ovarian reserve	Narrative review reporting continuous practice

Wu, Y., Zhao, F. C., Sun, Y. and Liu, P. S. J Int Med Res. 2017; 300060516669898. (28661216)	CS	Retrospective N=274 patients (337 cycles) LPS 108 (113) Control 166(224) POR patients (Bologna)	LPS: start after ovulation or oocyte pick up HMG 225 (no analog) Control: flexible antagonist protocol HMG 225 D2 Fresh or frozen (no precision for control group)	1/pregnancy rate/tr 2/ number of oocytes 3/ number of embryos	1/pregnancy rate/tr LPS: 26.2% Foll: 25% NS 2/ number of oocytes LPS:3.5(2.5) Foll: 3.5(2.9) NS 3/ number of embryos LPS: 1.7(1.2) Foll: 1.7(1.5) NS	The luteal phase ovarian stimulation protocol can be applied in women with poor ovarian response and attain comparable clinical pregnancy and implantation rates to those of the GnRH antagonist protocol	Retrospective BIAS++ more cycles than patients LPS in spontaneous cycle mixed with LPS after oocyte retrieval (duostim)
Zhang, Q., Guo, X. M. and Li, Y. Reprod Fertil Dev. 2016; (27166216)	CS	Retrospective N= 153 POR Bologna	1st cycle CC+ uFSH 150 trigger triptorelin 0.2 2nd cycle D1 after OPU uFSH 150-225 trigger HCG 10000 freeze all embryo no analog used FET: artificial cycle	1/clinical preg rate 2/ Number of oocytes	1/ clinical preg rate Foll: 10.7% LPS: 38.9% p 0.04 Mixed: 31.25% 2/number of oocytes Foll: 2.2(1.6) LPS: 3.3(2.6) p <0.001	Embryo produced in the luteal phase resulted in higher implantation rates	Retrospective but large group

9.3 DOUBLE STIMULATION

No relevant studies were identified

10. Ovarian stimulation for fertility preservation

KEY QUESTION: WHAT IS THE PREFERRED STIMULATION PROTOCOL FOR FERTILITY PRESERVATION AND FREEZING FOR SOCIAL REASONS

P	I	C	O
Women undergoing fertility preservation	-Which is the preferred stimulation protocol (drugs, trigger and timing) -Duostim/Random start -Indication of letrozole/tamoxifen		Efficacy: - cumulative LBR/cycle - Cumulative ongoing pregnancy rate /started cycle (fresh + frozen) - Clinical pregnancy rate/started cycle - Nr of Oocytes/ nr of MII oocyte recovery rate (yield) - number of embryo's (fresh+frozen) Safety - incidence of different grades of OHSS - grade of OHSS - incidence of cycle cancellation for hyper-response (predefined) - Bleeding - Infection - Torsion - Long-term effect on maternal/child health - other adverse events (treatment related) Patient-related outcomes - Compliance - Drop-out rates - Patient burden - QoL - Patient preferences

10.1 PREFERRED PROTOCOL

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Boots, C. E., Meister, M., Cooper, A. R., Hardi, A. and Jungheim, E. S. J Assist Reprod Genet. 2016; 33 (8): 971-80. (27146151)	SR	8 non-randomized studies, 251 women	Follicular phase stimulation Vs. Luteal phase stimulation	Duration of stimulation Total Gn dose Peak serum oestradiol Number of oocytes retrieved	Duration of stimulation WMD 1.3 days, 95 % CI 0.37–2.1 Total Gn dose WMD 683 IU, 95 % CI 369–997 Peak serum oestradiol WMD −337 pg/mL, 95% CI −849–175 No of oocytes retrieved WMD 0.16, 95 % CI 0.13 to 0.19		GRADE evidence profile Luteal vs follicular phase No separate meta-analysis for pregnancy outcomes for fertility preservation.
Rodgers, R. J., Reid, G. D., Koch, J., Deans, R., Ledger, W. L., Friedlander, M., Gilchrist, R. B., Walters, K. A. and Abbott, J. A. Hum Reprod. 2017; 32 (5): 1033-1045. (28333356)	SR						No meta-analysis, only Number of oocytes per stimulation protocol

Alvarez RM, Ramanathan P. Hum Reprod. 2016; Jul 1. pii: dew158 (27370358)	CS	306 cancer patients underwent OS Breast Cancer (n=145), Haematological cancer (n=79), gynecological malignancies (n=42), Gastrointestinal cancer (n=20), others (n=20) Baseline characteristics Significant differences for age (age superior in Breast cancer group), no significantly differences for BMI and AFC	Stimulation protocol: GnRH antagonist, Short flare, Luteal phase GnRH agonist with or without letrozole, all started in early follicular phase Recombinant or urinary FSH	Ovarian response to OS and especially mature oocytes (MII)	Mature oocytes: - Gynecological cancer 7.73 ± 6.33 MII significantly decrease vs non-gynecological - Hematological malignancies 13.33 ± 9.01 MII significantly higher than non haematological and BC (9.64 ± 6.31) Significantly more embryo in hematological malignancies	The main difference between cancer group is the number of mature oocyte retrieved, being lower in patients with gynecological cancer	Although not significant, gynecologic cancer patients showed reduced number of AFC as compared to breast and hematological cancer which might explained the final results
Ben-Haroush, A., Farhi, J., Ben-Aharon, I., Sapir, O., Pinkas, H., Fisch, B. Isr Med Assoc J 2011; 13(12):753-6 (22332446)	CS	Prospective cohort study including 24 breast cancer patients Groups comparable at baseline	long GnRH agonist (n=7) + letrozole GnRH antagonist protocols (n=17) + letrozole	No of oocytes OHSS	GnRH antagonist vs GnRH agonist No of oocytes 24.8±24.6 vs. 12.0±8.8, NS No cases of OHSS	FSH can be used in IVF cycles for fertility preservation in patients with breast cancer when the potent aromatase inhibitor letrozole is added. This combination yields a high number of oocytes with low peak estradiol levels in both the long GnRH agonist and GnRH antagonist protocol, while sparing patients' exposure to high E2 levels.	

Cardozo, E. R., Thomson, A. P., Karmon, A. E., Dickinson, K. A., Wright, D. L. and Sabatini, M. E. J Assist Reprod Genet. 2015; 32 (4): 587-96. (25595540)	CS	Retrospective cohort study 63 Cancer patients (Breast, Lymphoma and cervix cancer) prior CT (65 cycles IVF with Embryo or oocyte cryopreservation) 122 aged matched controls (122 IVF cycle) Date 3 FSH: Cancer 6.4 vs 7.3, p=0.01	Various OS protocol, various gonadotropins No random start protocol	OS outcomes	Cancer patients vs. controls - Oocyte recovered 12 vs 10.9 - Embryo 6.6 vs 7.2 - No significant difference 21 patients underwent FET: 13/21 pregnancies, 9/21 live birth No difference for Live birth rate per IVF cycle between both group	Most IVF outcomes appears comparable between cancer and controls patients	Various OS protocol No ovarian reserve baseline characteristics
Chan JL, Johnson LN, Efymow BL, Sammel MD, Gracia CR. J Assist Reprod Genet. 2015; 32(10):1537-45. (26400507)	CS	130 patients with cancer or auto-immune disease: 95 before chemotherapy (BCT), 35 post chemotherapy (PCT) PCT (27.7 years) significantly younger than BCT (32 years) p<0.001 AMH and basal FSH were no significantly different between groups AFC were significantly decrease in PCT (9 vs 17, p<0.001)	GnRH antagonist and GnRH agonist, with or without letrozole	To evaluate the response to OS in patients with history of cancer or benign disease treated with gonadotoxic chemotherapy	PCT versus BCT Significantly differences for - total Gn dose 4612 vs 3075 UI, p= 0.0208 - total follicles > 14 mm 5 vs 11, p= 0.01 - cancellation rate 23% vs 4%, p=0.003 Number of MII: 8 vs 8 (median)	Patients post chemotherapy have lower AFC compared with chemotherapy naïve and higher cancellation rate among those who underwent oocytes retrieval, oocyte yield were similar in both groups	

Das M, Shehata F, Moria A, Holzer H, Son WY, Tulandi T. Fertil Steril. 2011; 96(1):122-5 (21575940)	CS	Retrospective cohort study 41 K (19 hemato / 10 Gyneco and Gastro / 5 Brain / 5 Bone) 48 age matched IVF male factor Np difference: age / AFC / baseline FSH	Same protocol GnRHa protocol	Ovarian response Oocyte maturity	No difference in any parameter between K and controls No of oocyte retrieved: 13 hemato 11 Gyn Gastro 18 Brain 14 Bone 12 controls	Ovarian reserve, response to GF, oocyte recovered and maturity were unaltered by neoplastic process	Limited population in each group
Devesa M, Martínez F, Coroleu B, Rodríguez I, González C, Barri PN. J Assist Reprod Genet. 2014; 31(5):583-8. (24493387)	CS	Retrospective cohort study 48 K (26 BC / 7 hemato) Early foll or random COSTLES in hormone sensitive diseases	GnRH Antago Z score for comparing with an age specific nomogram of oocyte recovered	No of oocytes recovered Z score to compare with an age specific nomogram	No of oocytes recovered 14 No of mature oocytes 11.38	Ovarian response as apected by age. More oocytes recovered In COSTLES or when GnRHa trigger	Low number of patients
Druckenmiller, S., Goldman, K. N., Labella, P. A., Fino, M. E., Bazzocchi, A. and Noyes, N. Obstet Gynecol. 2016; 127 (3): 474-80. (26855092)	CS	Retrospective cohort study 176 K (75 BC / 51 Gyneco / 35 Hemato / 18 others) 182 cycles No comparative group	GnRHa and GnRH antago protocols hCG or GnRHa trigger COSTLES in estrogen sensitive diseases Random start	No of oocytes cryopreserved PR after thawing	No of oocytes recovered: 15 No of mature oocytes frozen: 10 11 frozen thaw cycles in 10 patients: 5 live births	Oocytes cryopresevation is feasible for female FP	
Garcia-Velasco, J. A., Domingo, J., Cobo, A., Martinez, M., Carmona, L. and Pellicer, A. Fertil Steril. 2013; 99 (7): 1994-9. (23465707)	CS	Retrospective cohort study 560 cycles in non-oncologic patients 355 cycles in K patients	GnRH antagonist only COSTLES Random stat	No of mature oocytes Total dose of FSH Duration of stim Outcomes after thawing	Non-K were older: 36.7 vs 31.9 y Duration of stim longer in non-K: 190.1 vs 9.5 days Total dose of FSH > in non-K: 3038 vs 1851 No of mature oocytes similar: 9.5 vs 8.5, NS After thawing: CPR: 7/26 (46%) in non-K CPR: in K: 4 patients!!!	Oocyte cryopreservation feasible in oncologic and non onco patients with similar results. Almost no data after thawing in K patients	

Johnson LN, Dillon KE, Sammel MD, Efymow BL, Mainigi MA, Dokras A, Gracia CR. Reprod Biomed Online. 2013; 26(4):337-44. (23415997)	CS	Retrospective cohort study 50 K (29 breast) or medical condition requiring gonadotoxic therapy 50 matched-controls: age, race, date of stimulation, fertilization method. Tubal or male factors or egg donors. 22 COSTLES among 50	GnRH antagonists or luteal phase GnRHa Early follicular phase 2 random start 22 letro		Baseline E2 lower in controls 39 vs 48 (p:0.04). FSH, AMH, AFC were comparable No of mature oocytes: 9 vs 8.9, NS Fertilization rate: 51.6 vs 69.5 p: 0.02 Letro vs controls: E2 lower, Higher total FG dose (3077 vs 2259) bu after higher starintng ddose (317 vs 203) Non letro vs controls: E2 1664 vs 2705, p0.01 Fertilization rate 55 vs 72	Chemo naive FP patients have similar ovarian reserve, ovarian stimulation characteristics and similar oocyte and embryo yield Patients with COSTLES require more GF dose and produce more immature oocytes	Limited population

Lawrenz, B., Jauckus, J., Kupka, M., Strowitzki, T. and von Wolff, M. Fertil Steril. 2010; 94 (7): 2871-3. (20678763)	CS	Retrospective cohort study 205 stimulation treatment BC (42.1%), lymphoma (33%), other gynecologic malignancies (9.1%), other non oncologic malignancies (14.4%), benign disease (1.4%) 125 (60.9%) patients attempted to fertilize all their oocytes	Short agonist protocol, antagonist protocol, hMG or FSH Categorization on age (18-25/ 26-30/ 31-35/36-40 years)		Mean number of removed oocyte: 11 Mean duration of stimulation: 10.9 days Mean total dose of Gn: 2465 IU No OHSS, no postponed chemotherapy Complication (no response, no puncture, failure to retrieve, unsuccessfull fertilization): 2.9% (6 patients) Fertilization rate per removed oocyte: 61.3% Significant relationship between the patient's age and Gn dose, total number of oocytes and number of cryopreserved PN stages	OS with cryopreservation of oocyte or PN stage embryo before the start of CT can be effectively performed with a low risk of complications for the patient. However, it needs to be stated that the chance to become pregnant is still limited	
Lee, S., Ozkavukcu, S., Heytens, E., Moy, F. and Oktay, K. J Clin Oncol. 2010; 28 (31): 4683-6. (20876425)	CS	93 breast cancer patients: 35 addressed before Breast surgery and 58 addressed after Breast surgery No difference for baseline or cancer characteristic	COSLES (controlled ovarian stimulation with letrozole supplementation)	FP outcomes	No difference for the first cycle outcomes between the two groups (embryos, oocytes) Time between initial diagnosis and ovarian stimulation reduced in the "before" group. 2 OS cycles: Before group: 9/35 After group 1/58	A significantly larger proportion of patient in the before group were able to undergo an additional cycle which resulted an 18.2 vs 0.6% increase in the total oocyte yield and the number of Embryo cryopreserved increase 17.2 vs 0.6%	

Muteshi, C., Child, T., Ohuma, E. and Fatum, M.. Eur J Obstet Gynecol Reprod Biol. 2018; 230 10-14. (30227359)	CS	Retrospective cohort study 127 cancer patients GnRH antagonist protocol Groups comparable at baseline	Group 1: Early follicular stimulation N=103 Group 2: Random-start stimulation N=24	Number of oocytes retrieved Total Gn dose Duration of stimulation Peak serum oestradiol	Group 1 vs 2 **Number of oocytes retrieved** 11.9 (95% CI 10.3–13.5) and 12.9 (95% CI 9.6–16.2), NS **Total Gn dose** 2543.4 (2328.3–2758.5) 2811.9 (2090.8–3533.1), NS **Duration of stimulation** 11.5 (11.2–12.0) 12.2 (10.7–13.7), NS **Peak serum oestradiol** 5426.3 (4682.9–6169.7) 4423.1 (2866.9–5979.3), NS	Our study demonstrates that ovarian stimulation using the antagonist protocol in a simplified random start protocol is comparable to the early follicular phase start.	

Pereira, N., Hancock, K., Cordeiro, C. N., Lekovich, J. P., Schattman, G. L. and Rosenwaks, Z. Gynecol Endocrinol. 2016; 32(10):823-826. (27114051)	CS	220 Breast Cancer patients 220 cycles: 91 oocyte cryopreservation, 129 2PN cryopreservation) 439 patients for Elective cryopreservation (451 cycles) No significant difference for Baseline characteristics between groups (age, gravidity, BMI and AMH)	Most ofter OS began in early follicular phase but some random start in BC group. GnRH antagonist protocol Letrozole for all BC hCG for ovulatory trigger	OS parameters	BC vs elective Number of oocyte retrieved 12.3 vs 10.9, p<0.01 Mature oocyte 87.9% vs 72.8%, p0.01 E2 on day of trigger and after the day of trigger significantly reduced in BC group Comparison luteal start vs day2 start: No statistical difference in BC group 56 FET in BC group: CP/FET:39.7% LBR/FET: 32.3% LBR in the study cohort comparable to age matched counterpart undergoing FET in the same institution	OS with letrozole and Gn yield more mature oocytes at lower estradiol levels compared to OS with Gn alone BC undergoing FET after oncologic treatment have live bith rates comparable to age matched counterparts	Number of MII vitrified? Pregnancy from cryopreservec Embryo or OoCytes?
Shapira M, Raanani H, Feldman B, Srebnik N, Dereck-Haim S, Manela D, Brenghausen M, Geva-Lerner L, Friedman E, Levi-Lahad E, Goldberg D, Perri T, Eldar-Geva T, Meirow D. Fertil Steril. 2015; 104(5):1162-7. (26335130)	CS	Retrospective cohort study 62 BRCA + 62 Non-carriers	Long GNnRH a GnRH antag Tam in estrogen sensitive tumors	Ovarian response	Comparable age Comparable FSH and E2 on baseline No significant difference in OS outcome Similar poor response rate No oocyte recovered in BRCA + vs BRCA -: 13.7 vs 14.7, NS	Normal ovarian response in BRCA mutated patients	

10.2 RANDOM-START PROTOCOL

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Boots, C. E., Meister, M., Cooper, A. R., Hardi, A. and Jungheim, E. S. J Assist Reprod Genet. 2016; 33 (8): 971-80. (27146151)	SR	8 non-randomized studies, 251 women	Follicular phase stimulation Vs. Luteal phase stimulation	Duration of stimulation Total Gn dose Peak serum oestradiol Number of oocytes retrieved	**Duration of stimulation** WMD 1.3 days, 95 % CI 0.37–2.1 **Total Gn dose** WMD 683 IU, 95 % CI 369–997 **Peak serum oestradiol** WMD −337 pg/mL, 95% CI −849–175 **No of oocytes retrieved** WMD 0.16, 95 % CI 0.13 to 0.19		GRADE evidence profile Luteal vs follicular phase No separate meta-analysis for pregnancy outcomes for fertility preservation.
Muteshi, C., Child, T., Ohuma, E. and Fatum, M.. Eur J Obstet Gynecol Reprod Biol. 2018; 230 10-14. (30227359)	CS	Retrospective cohort study 127 cancer patients GnRH antagonist protocol Groups comparable at baseline	Group 1: Early follicular stimulation N=103 Group 2: Random-start stimulation N=24	Number of oocytes retrieved Total Gn dose Duration of stimulation Peak serum oestradiol	Group 1 vs 2 **Number of oocytes retrieved** 11.9 (95% CI 10.3–13.5) vs. 12.9 (95% CI 9.6–16.2), NS **Total Gn dose** 2543.4 (2328.3–2758.5) vs. 2811.9 (2090.8–3533.1) IU, NS **Duration of stimulation** 11.5 (11.2–12.0) vs. 12.2 (10.7–13.7) days, NS **Peak serum oestradiol** 5426.3 (4682.9–6169.7) 4423.1 (2866.9–5979.3) pmol/L, NS	Our study demonstrates that ovarian stimulation using the antagonist protocol in a simplified random start protocol is comparable to the early follicular phase start.	

Pereira, N., Hancock, K., Cordeiro, C. N., Lekovich, J. P., Schattman, G. L. and Rosenwaks, Z. Gynecol Endocrinol. 2016; 32(10):823-826. (27114051)	CS	Retrospective cohort study? 220 Breast Cancer patients 220 cycles: 91 oocyte cryopreservation, 129 2PN cryopreservation) No significant difference for Baseline characteristics between groups (age, gravidity, BMI and AMH)	Group 1: BC, luteal start N=36 Group 2: BC, follicular start N=184	No of oocytes retrieved Total stimulation days Total Gn dose Peak serum oestradiol	Group 1 vs 2 **No of oocytes retrieved** 12.6 (±6.23) vs. 12.1 (±5.78), NS OR 1.05, 95% CI 0.45–2.45 **Total stimulation days** 11.8 (±2.41) vs. 10.7 (±2.71), p<0.05 **Total Gn dose** 3527.4 (±1668.9) vs. 3498.3 (±1563.1), NS **Peak serum oestradiol** 443.8 (285.2-603.5) vs. 473.3 (262.4-615.7), NS	OS with letrozole and Gn yield more mature oocytes at lower estradiol levels compared to OS with Gn alone BC undergoing FET after oncologic treatment have live bith rates comparable to age matched counterparts	

10.3 ANTI-OESTROGEN THERAPIES

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Rodgers, R. J., Reid, G. D., Koch, J., Deans, R., Ledger, W. L., Friedlander, M., Gilchrist, R. B., Walters, K. A. and Abbott, J. A. Hum Reprod. 2017; 32 (5): 1033-1045. (28333356)	SR						No meta-analysis, only Number of oocytes per stimulation protocol

Pereira, N., Hancock, K., Cordeiro, C. N., Lekovich, J. P., Schattman, G. L. and Rosenwaks, Z. Gynecol Endocrinol. 2016; 32(10):823-826. (27114051)	CS	220 Breast Cancer patients 220 cycles: 91 oocyte cryopreservation, 129 2PN cryopreservation) 439 patients for Elective cryopreservation (451 cycles) No significant difference for Baseline characteristics between groups (age, gravidity, BMI and AMH)	Most ofter OS began in early follicular phase but some random start in BC group. GnRH antagonist protocol Letrozole for all BC hCG for ovulatory trigger	OS parameters	BC vs elective Number of oocyte retrieved 12.3 vs 10.9, p<0.01 Mature oocyte 87.9% vs 72.8%, p0.01 E2 on day of trigger and after the day of trigger significantly reduced in BC group Comparison luteal start vs day2 start: No statistical difference in BC group 56 FET in BC group: CP/FET:39.7% LBR/FET: 32.3% LBR in the study cohort comparable to age matched counterpart undergoing FET in the same institution	OS with letrozole and Gn yield more mature oocytes at lower estradiol levels compared to OS with Gn alone BC undergoing FET after oncologic treatment have live bith rates comparable to age matched counterparts	Number of MII vitrified? Pregnancy from cryopreservec Embryo or OoCytes?

PART C: Monitoring

11. Hormonal assessment during ovarian stimulation

KEY QUESTION: IS THE ADDITION OF HORMONAL ASSESSMENT (OESTRADIOL/PROGESTERONE/LH) TO ULTRASOUND MONITORING IMPROVING EFFICACY AND SAFETY?

P	I	C	O
Women undergoing IVF/ICSI	Ultrasound + E2 Ultrasound + progesterone Ultrasound + LH Ultrasound + E2 AND/OR LH AND/OR progesterone	Ultrasound only Blind IVF	Efficacy: - cumulative LBR/cycle - Cumulative ongoing pregnancy rate /started cycle (fresh + frozen) - Clinical pregnancy rate/started cycle - Nr of Oocytes/ nr of MII oocyte recovery rate (yield) - number of embryo's (fresh+frozen) Safety - incidence of different grades of OHSS - grade of OHSS - incidence of cycle cancellation for hyper-response (predefined) - Bleeding - Infection - Torsion - Long-term effect on maternal/child health - other adverse events (treatment related) Patient-related outcomes - Compliance - Drop-out rates - Patient burden - QoL - Patient preferences

11.1 ULTRASOUND AND OESTRADIOL MEASUREMENTS

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Kwan I, Bhattacharya S, Kang A, Woolner A 2014 Cochrane Library	SR Cochrane	six trials including 781 women	In 4 out of the six studies The comparison was between USS and USS+E2 In the remaining studies the comparison was between USS and USS+E2+P(Wiser) and between USS and USS+E2+P+LH (Golan)	Clinical pregnancy, OHSS, COCs, cancellation	Clinical pregnancy per woman: OR 1.05 (0.79 to 1.54) 617 (4 studies) COCs per woman: +0.32 higher in the USS only group (-0.6 to +1.24), N= 595(5 studies) Cycle cancellation rate per woman: OR 0.57 (0.07 to 4.39) N=115, (2 studies) OHSS rate (mild, moderate or severe) per woman: OR 1.03 (0.48 to 2.20) N=781, (6 studies) RECALCULATED OUTCOMES without Wiser (2012) and Golan (1994): OR for clinical pregnancy: 1.02 (0.71-1.45) OR for OHSS: 0.94(0.39-2.26) OR for cancellation(1 study) 0.5 (0.04 – 5.89) WMD for COCs: 0.03(-0.99 to 1.04)	This review update found no evidence from RCTs to suggest that combined monitoring by TVUS and serum estradiol is more efficacious than monitoring by TVUS alone with regard to clinical pregnancy rates and the incidence of OHSS. The number of oocytes retrieved appeared similar for both monitoring protocols. The data suggest that both these monitoring methods are safe and reliable. However, these results should be interpreted with caution because the overall quality of the evidence was low. Results were compromised by imprecision and poor reporting of study methodology. A combined monitoring protocol including both TVUS and serum estradiol may need to be retained as precautionary good clinical practice and as a confirmatory test in a subset of women to identify those at high risk of OHSS. An economic evaluation of the costs involved with the two methods and the views of the women undergoing cycle monitoring would be welcome.	Quality of the evidence (GRADE) Low for all evaluated outcomes The objective is relevant and clear: “To assess the effect of monitoring controlled ovarian hyperstimulation (COH) in IVF and ICSI cycles in subfertile couples with TVUS only versus TVUS plus serum estradiol concentration, with respect to rates of live birth, pregnancy and OHSS.” However, the studies by Wiser and Golan assess besides E2 progesterone (Wiser, Golan) and LH(Golan).

11.2 Ultrasound and progesterone measurements or ultrasound and LH measurements

No relevant studies were identified

11.3 Ultrasound and combination of hormonal measurements

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Golan, A., Herman, A., Soffer, Y., Bukovsky, I. and Ron-El, R.. Hum Reprod. 1994; 9 (9): 1631-3. (7836512)	RCT	114 comparable groups	Monitoring by USS alone vs. USS+E2+P+LH (The concentrations of serum oestradiol were determined in Group B as well, and only became known to the clinicians after oocyte retrieval)	Outcome measures not defined Outcome measures used: duration of stimulation, FSH required, E2 patterns, COCs, pregnancy rate, OHSS	**Hormonal panel +USS vs USS** Pregnancy rate: 22% vs 25% Difference 1.8% 95%CI:-17.2 to +13.8 severe OHSS: 1.7% vs 1.7% difference: 0 (95%CI of the difference: -7.6 to+7.6)	We conclude that 'ultrasound-only' monitoring of ovulation induction in IVF cycles treated by GnRHa-HMG in the long protocol is as effective and safe as the conventional ultrasound and hormone determination, but far simpler, swifter and more cost-effective.	
Wiser, A., Gonen, O., Ghetler, Y., Shavit, T., Berkovitz, A. and Shulman, A. Gynecol Endocrinol. 2012; 28 (6): 429-31. (22456062)	RCT	65 patients Inclusion criteria were patients before first IVF treatment (to avoid bias from determining doses according to the previous treatment) and women younger than 40 years of age. Groups were comparable at baseline	Study group: USS only for follicle size and endometrial thickness without blood tests. In this group, only one blood test was taken before hCG injection, to ensure safe estradiol level regarding OHSS risk. N=34 The control group: USS+ serum estradiol + P at each visit. N=31	CPR OHSS	**USS alone vs USS+E2** clinical pregnancy rate (57.5%) vs (40.0%), P = 0.25. No cases of OHSS were found in either group.		

12. Endometrial thickness

KEY QUESTION: DOES MONITORING OF ENDOMETRIAL THICKNESS AFFECT THE EFFICACY AND SAFETY?

P	I	C	O
Women undergoing IVF/ICSI	Ultrasound of the endometrium On day of triggering Any day of stimulation phase	- No monitoring	Efficacy: - cumulative LBR/cycle - Cumulative ongoing pregnancy rate /started cycle (fresh + frozen) - Clinical pregnancy rate/started cycle - Nr of Oocytes/ nr of MII oocyte recovery rate (yield) - number of embryo's (fresh+frozen) Safety - incidence of different grades of OHSS - grade of OHSS - incidence of cycle cancellation for hyper-response (predefined) - Bleeding - Infection - Torsion - Long-term effect on maternal/child health - other adverse events (treatment related) Patient-related outcomes - Compliance - Drop-out rates - Patient burden - QoL - Patient preferences

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Diagnostic test evaluated Reference standard test Include: Time interval and treatment	Prevalence	Accuracy (Se, Sp, PPV, NPV, LR+, LR-)	Reproducibility	Authors conclusion	Comments
Kasius A, Smit JG, Torrance HL, Eijkemans MJ, Mol BW, Opmeer BC, Broekmans FJ. Hum Reprod Update. 2014 Jul-Aug;20(4):530-41. (24664156)	SR	22 studies 10 724 Exclusion criteria: - donor oocyte cycles; - intra uterine pathology [e.g. uterine polyps, submucosal or intramural myoma's and adhesions (Asherman syndrome)].	EMT had to be measured by TVU on the day of ovulation triggering as the maximal echogenic distance between the junction of the endometrium and myometrium in the mid-sagittal plane.	A thin endometrium (≤7 mm) was observed in 2.4% (260/10724)	STROBE checklist sROC ORs with 95% CIs were calculated using a Mantel–Haenszel random effect model Meta-regression Analyses for the different cut-off values show that sensitivity increases from near zero at a cut-off of ≤7 mm [0.05 (95% CI 0.03–0.09)] to a sensitivity of 0.21 (95%CI 0.18–0.26) at a cut-off of≤9 mm. The specificity decreases at the same rate from close to 1 at ≤ 7 mm [0.98 (95%CI 0.97–0.99)] to a minimum level of 0.85 at ≤9m 5%CI0.81–0.87)	Positive and negative predictive values for the outcome of pregnancy 77 and 48%, respectively The predictive accuracy of EMT for non-pregnancy was low, AUC=0.56	Current data indicate that EMT has a limited capacity to identify women who have a low chance to conceive after IVF. The frequently reported cut-off of 7 mm is related to a lower chance of pregnancy but occurs infrequently. The use of EMT as a tool to decide on cycle cancellation, freezing of all embryos or refraining from further IVF treatment seems not to be justified based on the current meta-analysis. Further research is needed to investigate the real independent significance of EMT in IVF.	This lack of consensus can possibly be explained by the fact that no exact definition of thin endometrium as assessed by ultrasound exists. EMT cannot be used to predict IVF outcome in terms of the occurrence of pregnancy (pregnant versus not pregnant), it does seem to be a factor for the assessment of the probability of conceiving after IVF. For clinical pregnancy rates, the probability of pregnancy was significantly lower in the group with thin EMT [EMT≤7 mm: OR 0.42 (95% CI 0.27–0.67] P=0.0003)

Aydin, T., Kara, M. and Nurettin, T. Int J Fertil Steril. 2013; 7 (1): 29-34. (24520460)	CS	593 women Age /20-39/ The groups were homogeneous: basal hormonal levels, duration of infertility, BMI, AFC and age. Exclusion: TESE, BMI>30 Agonist /n=135/ Antagonist /n=458/ N=14 EMT<7 mm (group 1), N=177 EMT 7-10 mm (group 2), N=366 EMT 10-14 mm(group 3), N=36 EMT>14 mm (group 4). Retrieved oocyte number, transferred embryo number, and the fertilization, cleavage, and IR were similar in groups.	EMT on the hCG day was measured by TV-USG.	Thin endometrium 2.4% 14/593		Group 1 vs 2 vs 3 vs 4 CPR, and OPR were significantly lower in group 1 than the other three groups ($p<0.05$). However, there was no significant difference among groups 2, 3, 4. CPR: 14.3 (2/14)* vs. 45.7 (81/177)* vs. 8.6 (178/366)* vs. 47.2 (17/36)* OPR: 7.1 (1/14)* vs. 35.5 (63/177)* vs. 43.9 (161/366)* vs. 41.7(15/36)*		
Coelho Neto, M. A., Martins, W. P., Lima, M. L., Barbosa, M. A., Nastri, C. O., Ferriani, R. A. and Navarro, P. A. Ultrasound Obstet Gynecol. 2015; 46 (4): 501-5. (25914103)	CS	517 women with ET long protocol flexible antagonist protocol CC+antagonist protocol	Thin endometrium < 7mm on day of hCG	11% thin endom 19% POR		CPR were good in women with a thin endometrium who had ≥7 oocytes retrieved (44%) or ≥4 embryos available at cleavage stage (41%). thinnest endometrial thickness at which pregnancy occurred was 5.6 mm	Ovarian response is better predictor of pregnancy than thin endometrium. The proportion of women with POR was higher in women with a thin endometrium compared to those with a normal endometrium	The aim of the study is to determine the best predictor of pregnancy while endometrial assessment is secondary.

Gallos ID, Khairy M, Chu J, Rajkhowa M, Tobias A, Campbell A, Dowell K, Fishel S, Coomarasamy A. Reprod Biomed Online. 2018 Oct 6. pii: S1472-6483(18)30466-8. doi: 10.1016/j.rbmo.2018.08.025. (30366837)	CS	25,767 IVF cycles excluding cycles using donated oocytes, frozen embryo cycles and cycles that were cancelled before ET	Measurements were conducted in the mid-sagittal plane, from the outer edge of the endometrial–myometrial interface to the outer edge of the widest part of the endometrium. The ultrasound scans were carried out by sonographers, trained nurse sonographers or reproductive medicine specialists.		The rates of reproductive outcomes were plotted graphically using mean proportions and 95% CI. Logistic regression model. Non-parametric receiver operating characteristic analyses	LBR 15.6% with 5 mm or less EMT and gradually increased to 33.1% with an EMT of 10 mm. The pregnancy loss rate was 41.7% with 5 mm or less EMT and gradually decreased to 26.5% with an EMT of 10 mm	This is the first study to independently associate early pregnancy loss with decreased EMT	INCLUDED This study confirms the clinical usefulness of EMT as a surrogate marker of endometrial receptivity and a favourable reproductive outcome in IVF–ICSI cycles.

Griesinger, G., Trevisan, S.,Cometti, B. Hum Reprod Open 2018(1):hox031-hox031	CS	n = 1401 aged between 18 and 42 years, BMI <30 kg/m2, <3 prior ART cycles ≥ 3 oocytes after COH with GnRH-agonist or GnRH antagonist. EMT≤8 mm n=117 (8.35%) EMT 8-15 mm n=1200(85.65%) EMT >15 mm n=84 (6%)	EMT was assessed on day of embryo transfer	EMT≤8 mm n=117 (8.35%) On-going PR in patients with EMT ≤8mm was 29.1% (95% CI: 21.60–37.8%).	univariate analysis: ongoing PR correlate to EMT. cut-off of ≥9 mm EMT, the chance of pregnancy was higher as compared to patients with an EMT of 3–8 mm (OR = 1.69, 95% CI: 1.23–2.35, P = 0.001; sensitivity 88.89%, specificity 17.52%, PPV 39.02%, NPV 72.64% and likelihood ratio 1.08). In multivariate regression analysis, after controlling for trial, female age and oocyte numbers, EMT was a statistically significant predictor of live birth (OR = 1.05, 95% CI: 1.00–1.10; P = 0.0351). poor performance of the EMT to predict ongoing PR (AUC: 0.53; 95% CI: 0.50–0.56).	An increase of the on-going PR with increasing EMT was observed (Mantel–Haenszel chi-square P = 0.042). Spearman's and Pearson's correlation coefficients indicated a positive, yet weak linear trend (r = 0.0537 and r = 0.0543, respectively).	The independent contribution of EMT to live birth likelihood is small and may result from (undetermined) confounding. EMT can be ignored during cycle monitoring, only the extremes of EMT deserve further diagnostic work-up. Oocyte number is significantly related to EMT, e.g. the more oocytes collected, the higher the EMT. EMT assessed on day of embryo transfer, a cut-off of 9 mm could predict ongoing pregnancy, but the predictive performance was poor overall and also highly similar to the poor test characteristics reported by Kasius et al. (2014). Interventions to correct thin EMT have little rational basis and should be abandoned until contrary evidence arises.	The predictive capacity of EMT was tested for each millimeter cut off. The on-going PR was compared below and above each millimeter threshold to determine the optimal cut-off of EMT. At present it appears as if for the clinical utility of endometrial pattern assessment, no clear message can be derived from conflicting study results.

Holden, E. C. Dodge, L. E. Sneeringer, R. Moragianni, V. A. Penzias, A. S. Hacker, M. R. Hum Fertil (Camb) 2017; 1-6. (28627314)	CS	6331 women undergoing their first, fresh autologous IVF cycle 347 (5.5%) EMT≤7mm 2943 (46.5%) EMT >7/<11mm 3041 (48.0%) EMT ≥11mm. The three groups were similar with regards to age, BMI, gravidity and the median number of embryos transferred and embryos frozen (all p>0.07).	EMT was measured by professional sonographers for all patients on the day of ovulation trigger using TV ultrasound. The lining was measured in the sagittal plane at the point of the largest anterior to posterior thickness.	347 (5.5%) EMT≤7mm 151 (2.4%) cycles were cancelled on or after the day of trigger. Among women with EMT ≤7mm, 32 cycles (9.2%) were cancelled, which was significantly more than among the >7 to<11mm group (3.1%) and the ≥11 group (1.0%; p<0.001).	SAS 9.3 risk ratio (RR) and 95% confidence interval (CI) Poisson regression with robust variance estimates post hoc analysis	Likelihood of a live birth was significantly lower for the ≤7mm group (adjusted RR: 0.64; 95% CI: 0.45–0.90). For each additional millimetre of EMT, a statistically significant increased risk of positive b-hCG (adjusted RR: 1.14; 95% CI: 1.09–1.18) and live birth (RR: 1.08; 95% CI: 1.05–1.11).	Women in the ≥11mm group had a significantly higher likelihood of delivering a live infant (32.2%) compared with women in the >7 to<11mm group (27.1%), which yielded a statistically significant age-adjusted RR of 1.23 (95% CI: 1.11–1.37). In conclusion, thicker endometrial linings were associated with increased pregnancy and live birth rates.	Interesting The thinnest EMT at which pregnancy occurred was 3.7mm, and this pregnancy resulted in a live birth. The thickest EMT at which pregnancy occurred was 27mm, and this pregnancy also resulted in a live birth. There does not appear to be an upper limit at which pregnancy is guaranteed or a lower limit of endometrial thickness at which pregnancy cannot be achieved. This suggests that there are likely to be other uterine and endometrial factors that influence the likelihood of live birth.

Lamanna, G., Scioscia, M., Lorusso, F., Serrati, G., Selvaggi, L. E. and Depalo, R. Fertil Steril. 2008; 90 (4): 1272-4. (17953948)	CS	N=685 n=31 women were excluded after office HS with evidence of endometrial anomalies (polypus, hyperplasia, endometritis, synechia, or septum, or submucosus/intramural fibroids n=48 other exclusion criteria: - age≥41; - FSH≥10 mUI/mL; - poor response; N=606 patients Long protocol Mean age 34.7±4.9 Duration of infertility 4.6±2.8 EMT < 8 mm EMT 8-14 mm EMT >14 mm	EMT was measured at: Day 0 - baseline; Day 7 - of stimulation; Day hCG Day of egg retrieval; Day of ET	8.4% (EMT < 8 mm) 85.3% (EMT 8-14 mm) 6.3% (EMT >14 mm)	two-tailed Chi-square test Mann–Whitney test ROC analysis	Age was negatively associated with EMT at ET (r=-0.14; p<0.001) ROC anlysis for CPR was not able to identify any endometrial value with good discrimina-tory ability AUC ≥ 0.70	EMT < 8 mm CPR 20.0% EMT 8-14 mm CPR 26.3% EMT >14 mm CPR 17.7% Thick endometrium on the day of ET may not represent a favorable sign or predictor for positive outcome.	Detrimental effect of "overgrown" endometrium on implantation rates in IVF cycles.
Rehman, R., Fatima, S. S., Hussain, M., Khan, R. and Khan, T. A. J Pak Med Assoc. 2015; 65 (5): 448-51. (26028374)	CS	282 patients Age 20-40, BMI 18-30, Duration of infertility>2 years Regular 28±7 cycle, FSH>10 COH - Long protocol Only ICSI/ET day 5 116 group A EMT<8mm 166 group B EMT>8mm Compared parameters: Oocyte maturity rate, FR, Cleavage rate, IR	EMT was measured on 12±2 days /rFSH/ of ovarian induction by sonographers in the midsagittal plane by two dimensional ultrasound with a 7.5 MHz vaginal probe	41% EMT<8mm 59% EMT>8mm Better response to COH shown in gr. B compare to gr. A 6(5%) in gr. A, and 95(57.2%) in gr. B, had a positive preg. test (p<0.0001)	EMT correlated with ROC curve with AUC 87.5% Se 94.1 Sp 60.8	Patients with oocyte maturity >50% became pregnant by acquiring EMT >8 mm (OR:12.2; 95% CI: 2.7-54.4). EMT was 8.7 times higher in females with cleav. rate >50% (OR:8.7; 95% CI:2.5-30.6).	EMT of 8mm was associated with a positive pregnancy outcome after ICSI. Implantation of embryo was facilitated by better oocyte parameters, oocyte maturity, fertilisation and its cleavage in females who exhibited EMT above the cut-off value.	Estimation of EMT is important in the sense that if it is not ideal, some remedial action can be taken, such as postponing hCG administration and continuing ovarian stimulation, or freezing the embryos obtained for future transfer under better endometrial conditions.

Ribeiro, V. C., Santos-Ribeiro, S., De Munck, N., Drakopoulos, P., Polyzos, N. P., Schutyser, V., Verheyen, G., Tournaye, H., Blockeel, C. Reprod Biomed Online 2018; 10.1016/j.rbmo.2017.12.016 (29361452)	CS	n=3350 IVF cycles (2827 women) GnRH antagonist protocol Excluded cycles: - women aged 40 years or older - known uterine abnormalities - surgically retrieved sperm, - donor oocytes, - in-vitro maturation, - preimplantation genetic diagnosis Only singleton live births were evaluated	On the day of, or day before, ovulation triggering, EMT was measured in millimeters as the maximal anterior–posterior distance between both endometrial layers about 1 cm from the uterine fundus. EMT was also assigned to the following regular 2-mm-intervalled categories: less than 7.0 mm, 7.0–8.9 mm, 9.0–10.9 mm, 11.0–12.9 mm and 13.0 mm or over.	<7mm 8.48% 284/3350	multivariable regression models	The duration of OS and late-follicular E2 were independently and non-linearly associated with an increase in EMT (P = 0.001 and P < 0.001, respectively) probability of pregnancy with EMT <8:21.8%, >8: 35.2%	A thinned or absent functional layer may subject the embryo to higher vascularity from the basal endometrium, which might explain the reduction of implantation caused by elevated oxygen tension and the production of detrimental reactive oxygen species. Specifically, each 1 kg/m2 increase in BMI was linearly associated with a 0.07 mm increase in EMT, and each ng/ml increase in progesterone was linearly associated with a 0.25 mm decrease in EMT. Specifically, the mean EMT seemed to stabilize once a minimum of 7 days of OS and concentration of 1000 pg/ml of oestradiol were reached.	
Wu, Y., Gao, X., Lu, X., Xi, J., Jiang, S., Sun, Y. and Xi, X. Reprod Biol Endocrinol. 2014; 1296. (25296555)	CS	2106 embryotransfer cycles - normal responders; - GnRH antagonist; - age 21-39; - PR 44.87% N=29 group 1: <7 mm N=162 group 2: =7>8 mm N=1852 group 3: =8<14 mm N=64 group 4: >=14 mm	US assessment of EMT Day of HCG	Thin endometrium 1.4% 29/2106	SPSS χ2 test t-test ANOVA	CPR, On-going PR, IR are significantly lower (17.28%, 13.79%, 10.17%) in group 1 compared to the other three groups (p<0.05). No pregnancy was observed in the patients with EMT less than 6 mm.	Multiple IVF attempts (two or more) were found in the group 1. Threshold of EMT<7 mm with a significant reduction in IR, CPR	

Yuan, X., Saravelos, S. H., Wang, Q., Xu, Y., Li, T. C., Zhou, C. Reprod Biomed Online 2016; 33(2): 197-205 (27238372)	CS	n = 10.787 fresh IVF and ICSI cycles /8690/ woman Gr 1: < 8 mm; Gr 2: ≥ 8 ≤11 mm; Gr 3: > 11 ≤15 mm; Gr 4: > 15 mm	EMT on HCG administration day	EMT< 8 mm 4.83% (521/10787) .	Logistic regression analyses showed EMT as one of the independent variables predictive of clinical pregnancy (OR = 1.097; P < 0.001), live birth (OR = 1.078; P < 0.001), spont. abortion (OR = 0.948; P < 0.001), and ectopic pregnancy (OR = 0.851; P < 0.001).	EMT on HCG day (OR=1.097; P<0.001), № of oocytes (OR=1.011; P=0.012), Are positively correlated with improved CPR The lowest SA rate of 17.5% in thickest EMT (>15 mm), and the highest SA rate of 26.7% in the thinnest EMT (<8 mm) CPR 23.0%, 37.2%, 46.2%, 53.3% LBR/CPR 63.3%, 72.0%, 78.1%, 80.3%	This study indicated that EMT is a significant and independent predictor of intrauterine pregnancy, ectopic pregnancy, spontaneous abortion and live birth after IVF–ICSI treatment.	Meanwhile, the thin endometrium (<8 mm) is a relatively uncommon phenomenon (5th centile, 521/10787), and the conception rate in this group (23.0%, 120/521) is still reasonable. Women with thin endometrium should be properly counselled about the lower chance of conception, and, should conception occur, an increased risk of spontaneous abortion and ectopic pregnancy.
Zhang, T., He, Y., Wang, Y., Zhu, Q., Yang, J., Zhao, X. and Sun, Y.. Eur J Obstet Gynecol Reprod Biol. 2016; 203 66-71. (27254812)	CS	435 patients First IVF cycle Long protocol aGnRH+rFSH /150-225E/ Cryopreservation if E2>6000pg/ml - 285 positive preg test - 253 /58.2%/ clinical preg - 49 /17.2%/ miscarriage (11.2% biochemical 6% clinical miscarriage)	3D sonographic measurements were performed on hCG day Color Doppler /S,D,RI,PI/ 3D PDUS histogram analysis used to calculate the endometrial volume and vascularity indices /VI, FI, VFI/	10.1% (44/435) Thin endometrium group EMT≤8.5 mm	Kolmogorov-Smirnov test Mann-Whitney, Chi-square analysis, Fisher's exact test,	Mean ICC with 95%CI 0.968 EMT 0.978 PI 0.961 RI 0.960 endometrial volume, VI,FI, VFI	There were no significant difference in EMT, endometrial volume and pattern, ratio of PSV and EDV, uterine PI, uterine RI, endometrial and subendometrial VI,FI,VFI between pregnant and non-pregnant patients, also for miscarriage group.	Expansion of the arsenal from endometrial investigations is also related to the contemporary capabilities of ultrasound technique that should be used optimally.

Zhao, J., Zhang, Q., Wang, Y. and Li, Y. Reprod Biomed Online. 2014; 29 (3): 291-8. (25070912)	CS	3319 women Long protocol /HMG 150-450E/ Exclusion criteria: endometrial polyp, uterine anomaly, and insemination method other than IVF, cycles using donor oocytes or cryopreserved embryos. Pregnant - 1010 Non-pregnant - 923	EMT, growth and pattern /A,B,C/ were assessed at: - day 3 of Gn-stimulation; - day of HCG administration EMT was measured in a median longitudinal plane of the uterus as the maximum distance between the endometrial–myometrial interface of the anterior to the posterior wall of the uterus. Pattern A (triple-line central hyperechoic line surrounded by two hypoechoic layers), Pattern B (an intermediate isoechogenic with the same reflectivity as the surrounding myometrium and a poorly defined central echogenic line) Pattern C (homogenous, hyperechogenic endom		mean ± SD values Student's t-test Chi-square test Binary logistic regression analysis and ROC	Assessing predictive value of EMT on day 3, day of HCG and the change during stimulation AUC=0.528 EMT day 3/pr AUC= 0.428(1–0.472) (95% CI, 0.503–0.554) EMT d HCG/pr AUC=0.596 (95% CI, 0.571 to 0.621) changeEMT/pr AUC= 0.606 (95% CI, 0.580–0.630)	Receiver operator characteristic curves showed that endometrial pattern, thickness and changes were not good predictors of clinical pregnancy. Pregnant women had significantly thinner endometrial linings on day 3 of Gn-stimulation (P = 0.008), significantly thicker endometrial linings on the day of HCG administration (P < 0.001), and a greater change with EMT (P < 0.001). Age(R =−0.047, P < 0.001), EMT on day 3 (R =−0.097,P < 0.05), endometrial pattern on the day of HCG(R =−0.228, P < 0.05) were negatively correlated with CPR. Increasing EMT on the day of HCG (R = 0.150, P < 0.001), and the № of embryos (R = 0.046, P < 0.05) were associated with improved CPR.	The evaluation the change in EMT occurring during IVF stimulation. But the combined endometrial characteristics cannot predict the clinical outcome correctly.

13. Criteria for triggering

KEY QUESTION: IS THE OUTCOME OF OVARIAN STIMULATION DEPENDENT ON THE CRITERIA FOR TRIGGERING?

P	I	C	O
Women undergoing IVF/ICSI	Follicle size + Number Oestradiol Oestradiol/Follicle Ratio	Ultrasound only Blind IVF	Efficacy: - cumulative LBR/cycle - Cumulative ongoing pregnancy rate /started cycle (fresh + frozen) - Clinical pregnancy rate/started cycle - Nr of Oocytes/ nr of MII oocyte recovery rate (yield) - number of embryo's (fresh+frozen) Safety - incidence of different grades of OHSS - grade of OHSS - incidence of cycle cancellation for hyper-response (predefined) - Bleeding - Infection - Torsion - Long-term effect on maternal/child health - other adverse events (treatment related) Patient-related outcomes - Compliance - Drop-out rates - Patient burden - QoL - Patient preferences

13.1 FOLLICLE SIZE

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Chen Y, Zhang Y, Hu M, Liu X, Qi H. Gynecol Endocrinol. 2014 Jun;30(6):431-7 (24731070)	SR	N=1295	5 of 6 RCTs: Control group intervention: hCG administration by the criterion "number and size of follicles growing in response to ovarian stimulation for IVF assessed by transvaginal sonography" Timing of hCG administration in early hCG group At least three follicles reached a diameter of ≥17 mm The leading follicle reached a diameter of 18 mm (±1 mm) Three or more follicles of ≥16 mm At least three follicles reached a diameter of ≥17 mm The largest follicle reached 18 mm, at least two other follicles reached a diameter of ≥14 mm The leading two follicle reached a diameter of ≥17 mm Three largest follicles reached a diameter of ≥17 mm and eatrsdiol consistent with the number of follicles Study group interventions: As control group +24h As control group +48h As control group +24h or +48h 1 of 6 RCTs: hCG administration when the leading follicle was 18 mm vs. 22mm	Estradiol levels on day of hCG (pg/ml) Progesterone levels on day of hCG (ng/ml) Oocyte numbers Fertilitzation rate oPR (per cycle) LBR (per cycle) Miscarriage rate	Oocyte numbers increased in late hCG groups (MD= +1.2, P<0.00001) [comment: homogenous effect in 2 GnRH agonist and 2 GnRH antagonist studies] No homogenous and/or statistically significant effets on OPR (per cycle) more women reached an ongoing pregnancy (38% (37/97)) compared with the 18-mm group (24% (22/93)) (RR 1.6, 95% CI: 1.03–2.5) LBR (per cycle) 22 mm (35% (34/97)) compared to 18 mm (23% (21/93)) (RR 1.6 (0.98–2.47))	The prolongation of follicular phase by delaying hCG administration could increase estradiol, progesterone levels and oocyte retrieval, which will not influence ongoing pregnancy rate per oocyte pick-up, miscarriage rate and live birth rate.	Non-randomized study included (Dimitry et al. 1991) All studies, but one, measure effect of delay of hCG administration instead of effect of giving hCG at different follicular size criteria Studies heterogenous in methodology (most importantly triggering criteria in the control group, quality, protocols and time intervals) Studies significantly heterogenous for most outcomes except estradiol and progesterone levels and oocyte numbers Fertilization rate: authors conclude that a significant difference exists in favor of late group, but the combined effect is 0.7% and 99.7% of weight comes for one study with implausible SDs and fertilization rate is only a surrogate outcome

13.2 Oestradiol level

No relevant studies were identified

13.3 Oestradiol/follicle ratio

No relevant studies were identified

14. Criteria for cycle cancellation

KEY QUESTION: WHICH CRITERIA FOR CYCLE CANCELLATION ARE MEANINGFULL REGARDING PREDICTED LOW/HIGH OOCYTE YIELD?

P	I	C	O
Women undergoing IVF/ICSI with predicted **LOW** ovarian response	Cancellation criterium: Number of follicles		Efficacy: - cumulative LBR/cycle - Cumulative ongoing pregnancy rate /started cycle (fresh + frozen) - Clinical pregnancy rate/started cycle - Nr of Oocytes/ nr of MII oocyte recovery rate (yield) - number of embryo's (fresh+frozen) Safety - incidence of different grades of OHSS - grade of OHSS - incidence of cycle cancellation for hyper-response (predefined) - Bleeding - Infection - Torsion - Long-term effect on maternal/child health - other adverse events (treatment related) Patient-related outcomes - Compliance - Drop-out rates - Patient burden - QoL - Patient preferences
Women undergoing IVF/ICSI with predicted **HIGH** ovarian response	Cancellation criterium: Number of follicles		

LOW OOCYTE YIELD

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Diagnostic test evaluated Reference standard test Include: Time interval and treatment	Prevalence	Accuracy (Se, Sp, PPV, NPV, LR+, LR-)	Reproducibility	Authors conclusion	Comments
Oudendijk JF, Yarde F, Eijkemans MJ, Broekmans FJ, Broer SL. Hum Reprod Update. 2012 Jan-Feb;18(1):1-11 (21987525)	SR	14.338 patients, with poor response (different definition) from ≤3 follicles (oocytes) to < ≤5 oocytes No information regarding type of stimulation in the study but included studies use both ago and antagonist cycles	Pregnancy rate (%) in poor responders vs normal responders Female age and pregnancy rate (%) per started cycle Number of oocytes retrieved and pregnancy rate per first cycle started Poor responder and pregnancy rate in subsequent cycles.		CPR 1 oocyte 0–7% 2 ooctes 4.3-11.5% 3 oocytes 8.7-15.6% 4 oocytes11.5–18.6%		Poor responders are not a homogeneous group of women with regards to pregnancy prospects. Female age and number of oocytes retrieved in particular will modulate the chances for pregnancy in current and subsequent cycles. Applying these criteria will allow the identification of couples with a reasonable	The decision should be individually making taking into account history of the couple, burden of therapy, quality of life, preferences. The pregnancy could occur even with one follicle/oocyte retrieved
Jayaprakasan, K., Chan, Y., Islam, R., Haoula, Z., Hopkisson, J., Coomarasamy, A. and Raine-Fenning, N. Fertil Steril. 2012; 98 (3): 657-63. (22749225)	CS	1012 women Subjects were excluded if they were found to have an ovarian cyst or follicle measuring 20 mm or more in diameter on their pretreatment ultrasound scan long GnRH agonist protocol hCG trigger 10000uhCG or 6000rhCG	Live birth rate, poor ovarian response, and ovarian hyperstimulation syndrome (OHSS) in relation to different AFC At AFC quartiles of 3–10, 11–15, 16–22, and>23, the mean live birth rates were 23%, 34%, 39%, and 44%, respectively. No live birth was observed in women with AFC <4.		AFC was the best predictor of poor ovarian response (odds ratio [95% CI]: 0.86 [0.82–0.90])		AFC is a significant predictor of ovarian response and live birth after IVF/ICSI treatment. There are limitations with the use of AFC cutoff levels, particularly if they are used to deny couples ART: the live birth rate was still 5% at an AFC cutoff of four and only fell to zero for women with three or fewer follicles,	The decision making is always difficult although it this study no LBR was reported when AFC was <4 The limitations was the small number of women with such low no AFC Additionally I agree AFC predicts quantitative aspects of ovarian reserve (e.g. response to gonadotropins) than the qualitative as LBR .The pregnancy and LBR could bewhen one follicle is present

Nicopoullos, J. D. and Abdalla, H.. Fertil Steril. 2011; 95 (1): 68-71. (20646690)	CS	1350 women ICSI Long GnRH agonist/GnRH antagonist protocol hCG trigger 39.6 + 3.9 one or two follicles>12 mm	Live birth rate, clinical pregnancy rate, and biochemical pregnancy rate BPR of 13.1%, CPR of 8.1%, OPR- 6.8%,		One follicle: BPR-8.5%, CPR 5.4%, OPR-4.5% Two follicles: BPR-14.9%, CPR 9.2%, OPR-7.6%		1.for poor responders, proceeding to VEC may represent their best chanceof successful outcome. 2.Conversion to IUI offers the poorest outcome, 3.Abandoning and a further attempt does not improve outcome	The presence of one or two follicles in poor responders still could lead to obtain pregnancy. Thus the strategy should be discussed with couples as the IVF even with one or two follicles could be the best choice.
Sunkara, S. K., Rittenberg, V., Raine-Fenning, N., Bhattacharya, S., Zamora, J. and Coomarasamy, A.. Hum Reprod. 2011; 26 (7): 1768-74. (21558332)	CS	400 135 IVF cycles no of eggs in respect to LBR (not directly related to cycle cancellation) cycles involving gamete or zygote intra-fallopian transfer (GIFT, ZIFT), egg donation, egg sharing, embryo donation or where the source of embryos was not specified, preimplantation genetic diagnosis, surrogacy, oocyte cryopreservation, frozen embryo replacement, and cycles where no eggs were retrieved or all embryos were frozen were excluded from the analysis no info on LH suppression regimes	LBR in relation to age category		the predicted LBR for women with 15 eggs retrieved in age groups 18–34, 35–37, 38–39 and 40 years and over was 40, 36, 27 and 16%,		There was a strong association between the number of eggs and LBR; LBR rose with an increasing number of eggs up to 15, plateaued between 15 and 20 eggs and steadily declined beyond 20 eggs	No data regarding cancellation both with small and excessive no of egss. If we look on the results: in women >40 years with only one egg the predicted LBR is 2 % thus decision regarding cancellation evan with one follicle should be discussed with patients

Steward, R. G., Lan, L., Shah, A. A., Yeh, J. S., Price, T. M., Goldfarb, J. M. and Muasher, S. J. Fertil Steril. 2014; 101 (4): 967-73. (24462057)	CS	256,381 cycles SART registry all fresh nondonor IVF cycles performed in the U.S. from 2008 to 2010 five groups based on retrieved oocyte number no info on LH suppression regimes	0–5, 6–10, 11–15, 16–20, 21–25, and >25. LBR, OHSS (moderate and severe) The LB rate increased up to 15 oocytes, then plateaued (0–5: 17%, 6–10: 31.7%; 11–15: 39.3%; 16–20: 42.7%; 21–25: 43.8%; and >25 oocytes: 41.8%). However, the rate of OHSS became much more clinically significant after 15 oocytes (0–5: 0.09%; 6–10: 0.37%; 11–15: 0.93%; 16–20: 1.67%; 21–25: 3.03%; and >25 oocytes: 6.34%).	.	ROC curve for retrieved oocyte number asa predictor of OHSS. Oocyte number thresholds: A: 5; B: 10; C: 15; D: 20; E: 25		Retrieval of >15 oocytes significantly increases OHSS risk without improving LB rate in fresh autologous IVF cycles.	As we discussed during the meeting no hard data on cycle cancellation rather prediction of OHSS From the other side the number of 0-5 oocytes lead to the pregnancy (with71% of cycles in this group had at least two extra embryos available for cryopreservation.

HIGH OOCYTE YIELD

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Diagnostic test evaluated Reference standard test Include: Time interval and treatment	Prevalence	Accuracy (Se, Sp, PPV, NPV, LR+, LR-)	Reproducibility	Authors conclusion	Comments
Mathur, R. S., Akande, A. V., Keay, S. D., Hunt, L. P. and Jenkins, J. M. Fertil Steril. 2000; 73 (5): 901-7. (10785214)	CS	2,362 consecutive cycles of IVF, ICSI, or GIFT in 1,565 patients long GnRH agonist protocol hCG trigger 5000IU	If the E2 concentration exceeded 15,000 pmol/L or the number of follicles>12 mm in mean diameter exceeded 30, the cycle was cancelled		Diagnostic analysis of optimum cutoff oocyte numbers in predicting the risk of OHSS . All OHSS: (10oocytes) Se75%, Sp 61%,PLR 1.98 (1.68–2.22) NLR 0.39 (0.26–0.56) Moderate or severe OHSS (9) Se 80%, SP 55%,PLR 1.80 (1.51–2.01),NLR 0.35 (0.20–0.57) Early OHSS (10) Se81% Sp 61% PLR 2.10 (1.75–2.36) NLR 0.30 (0.16–0.51)	Cycles with either early or late OHSS had significantly more oocytes collected than those without OHSS	Early OHSS relates to “excessive” preovulatory response to stimulation, whereas late OHSS depends on the occurrence of pregnancy, is likelier to be severe, and is only poorly related to preovulatory events	Prediction of OHSS based on no of oocytes and serum E2 levels Maybe > 12 mm>30 cancellation of the cycle
Papanikolaou, E. G., Pozzobon, C., Kolibianakis, E. M., Camus, M., Tournaye, H., Fatemi, H. M., Van Steirteghem, A. and Devroey, P. Fertil Steril. 2006; 85 (1): 112-20. (16412740)	CS	1801 patients (2524 cycles) GnRH antagonist cycles hCG trigger 10.000IU	Prediction of OHSS		the combination of a threshold of > or =18 follicles and/or E2 of > or =5,000 ng/L yields a 83% sensitivity rate with a specificity as high as 84% for the severe OHSS cases Fifty-three patients were hospitalized because of OHSS (2.1%; 95% confidence interval [CI]:1.6-2.8		The number of follicles can discriminate the patients who are at risk for developing OHSS, whereas E2 concentrations are less reliable for the purpose of prediction	Prediction of OHSS

Steward, R. G., Lan, L., Shah, A. A., Yeh, J. S., Price, T. M., Goldfarb, J. M. and Muasher, S. J. Fertil Steril. 2014; 101 (4): 967-73. (24462057)	CS	256,381 cycles SART registry They did not analyze data on stimulation protocol type or medication dosing five groups based on retrieved oocyte number	0–5, 6–10, 11–15, 16–20, 21–25, and >25. LBR, OHSS (moderate and severe) The LB rate increased up to 15 oocytes, then plateaued (0–5: 17%, 6–10: 31.7%; 11–15: 39.3%; 16–20: 42.7%; 21–25: 43.8%; and >25 oocytes: 41.8%). However, the rate of OHSS became much more clinically significant after 15 oocytes (0–5: 0.09%; 6–10: 0.37%; 11–15: 0.93%; 16–20: 1.67%; 21–25: 3.03%; and >25 oocytes: 6.34%).	.	ROC curve for retrieved oocyte number asa predictor of OHSS. Oocyte number thresholds: A: 5; B: 10; C: 15; D: 20; E: 25		Retrieval of >15 oocytes significantly increases OHSS risk without improving LB rate in fresh autologous IVF cycles.	As we discussed during the meeting no hard data on cycle cancellation rather prediction of OHSS From the other side the number of 0-5 oocytes lead to the pregnancy (with71% of cycles in this group had at least two extra embryos available for cryopreservation.

Sunkara, S. K., Rittenberg, V., Raine-Fenning, N., Bhattacharya, S., Zamora, J. and Coomarasamy, A.. Hum Reprod. 2011; 26 (7): 1768-74. (21558332)	CS	400 135 IVF cycles no of eggs in respect to LBR (not directly related to cycle cancellation) cycles involving gamete or zygote intra-fallopian transfer (GIFT, ZIFT), egg donation, egg sharing, embryo donation or where the source of embryos was not specified, preimplantation genetic diagnosis, surrogacy, oocyte cryopreservation, frozen embryo replacement, and cycles where no eggs were retrieved or all embryos were frozen were excluded from the analysis no info on LH suppression regimes	LBR in relation to age category		the predicted LBR for women with 15 eggs retrieved in age groups 18–34, 35–37, 38–39 and 40 years and over was 40, 36, 27 and 16%,		There was a strong association between the number of eggs and LBR; LBR rose with an increasing number of eggs up to 15, plateaued between 15 and 20 eggs and steadily declined beyond 20 eggs	No data regarding cancellation both with small and excessive no of egss. If we look on the results: in women >40 years with only one egg the predicted LBR is 2 % thus decision regarding cancellation evan with one follicle should be discussed with patients
Griesinger, G,. Verweij P ,Gates D, Devroey P, Gordon K.,Stegmann B.J,. Tarlatzis B.C. PLOS ONE 2016; 11(3):e0149615 (26950065)	CS	2433 women from the Engage, Ensure and Trust trials, retrospective analysis of combined data from three trials following ovarian stimulation with two different gonadotropins GnRH antagonist protocol hCG trigger 5000-10.000IU	the threshold for the prediction of moderate to severe or severe ovarian hyperstimulation syndrome (OHSS) based on the number of growing follicles 11 mm and/or estradiol (E2) levels?		Severe OHSS Follicles >11 mm OR 1.105 95% CI (1.064, -1.148) p<0.0001 AUC 0.769 Severe OHSS Follicles >11 mm Sensitivity74.3% Specificity 75.3% PPV4.2% NPV 99.5% >19 follicles Moderate to severe:62,3%,75,6% PPV 6.9%, NPV 98,6%,>19 fol		The optimal threshold of follicles 11 mm on the day of hCG to identify those at risk was 19 for both moderate to severe OHSS and for severe OHSS.	Prediction of moderate and severe OHSS in ant cycle

PART D: Triggering ovulation and luteal support

15. Triggering of final oocyte maturation

KEY QUESTION: WHAT IS THE PREFERRED DRUG FOR TRIGGERING OF FINAL OOCYTE MATURATION IN TERMS OF EFFICACY AND SAFETY IN THE OVERALL IVF/ICSI POPULATION?

P	I	C	O
Women undergoing IVF/ICSI	- rhCG - rLH - rLH GNRH agonist - Triptorelin 0.1 mg - Buserelin 0.2 mg - Leuprolide 0.15 mg	uhCG (5000 or. 10000) uhCG (5000 or. 10000) rhCG (5000 or. 10000) hCG (5000 or. 10000) Triptorelin (0.2, 0.3, 0.4 mg) Buserelin (0.5, 1, 2 mg) Leuprolide (0.5, 1, 2, 4 mg)	Efficacy: - cumulative LBR/cycle - Cumulative ongoing pregnancy rate /started cycle (fresh + frozen) - Clinical pregnancy rate/started cycle - Nr of Oocytes/ nr of MII oocyte recovery rate (yield) - number of embryo's (fresh+frozen) Safety - incidence of different grades of OHSS - grade of OHSS - incidence of cycle cancellation for hyper-response (predefined) - Bleeding - Infection - Torsion - Long-term effect on maternal/child health - other adverse events (treatment related) Patient-related outcomes - Compliance - Drop-out rates - Patient burden - QoL - Patient preferences

Papers selected for this question that were already included in the evidence table of question 16	Type
Papanikolaou, E. G., Verpoest, W., Fatemi, H., Tarlatzis, B., Devroey, P., Tournaye, H. Fertil Steril 2011; 95(3): 1174-7. (20979997)	RCT

Papers selected for this question that were already included in the evidence table of question 17	Type
Youssef, M. A., Van der Veen, F., Al-Inany, H. G., Mochtar, M. H., Griesinger, G., Nagi Mohesen, M., Aboulfoutouh, I. and van Wely, M. Cochrane Database Syst Rev. 2014; (10): Cd008046. (25358904)	SR
Humaidan, P., Polyzos, N. P., Alsbjerg, B., Erb, K., Mikkelsen, A. L., Elbaek, H. O., Papanikolaou, E. G. and Andersen, C. Y Hum Reprod. 2013; 28 (9): 2511-21. (23753114)	RCT

15.1 Urinary (uhCG) vs Recombinant Human chorionic gonadotrophin (rhCG)

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments

Youssef, M. A., Abou-Setta, A. M. and Lam, W. S. Cochrane Database Syst Rev. 2016; 4 Cd003719. (27106604)	SR	18 RCTs involving 2952 participants; Fifteen trials in 2473 women compared rhCG with uhCG, (and three trials in 479 women compared rLH with uhCG.) rhCG Vs uhCG -LBR was reported in 3 trials (n=452, rhCG n=228 uhCG n=224) -Ongoing PR was reported in 4 trials (n=684, rhCG n=293 uhCG n=391)	Women were randomised to receive either 1. 250 µg rhCG or 10,000IU uhCG n= 1993 2. 250 µg rhCG or 7500IU uhCG n= 180 (Kovacs 2008) 3. 250 µg rhCG or 5000IU uhCG n= 578 All trials performed pituitary down regulation using a long GnRH agonist protocol, except Papanikolaou 2010, which used a GnRH antagonist protocol.	-primary outcomes: 1. ongoing pregnancy/live birth 2.incidence of OHSS -secondary outcomes 3.Clinical pregnancy, 5.number of oocytes retrieved 6.adverse events	1. live birth rate/ongoing pregnancy rate (OR 1.15, 95% CI 0.89 to 1.49; 7 RCTs, N = 1136, I2 = 0%, MQ (Papanikolaou 2010 was the only study to use GnaRH antagonist protocol, There was a higher live birth rate in the rhCG group (OR 2.17, 95% CI 1.00 to 4.68, 1 RCT, N = 119; LQ) 2a. Moderate to severe OHSS (OR 1.76, 95%CI 0.37-8.45; 3 RCTs, N = 417) (LQ) 2b. Moderate OHSS (OR 0.78, 95% CI 0.27-2.27, 1 RCT, N = 243) 2c. Mild to moderate OHSS (OR 1.00, 95%CI 0.42-2.38; 2 RCTs, N = 320) (LQ) 3. Clinical pregnancy rates (OR 1.06, 95% CI 0.87-1.29, 13 RCTs, N= 1806 (MQ) (Long GnRH agonist protocol (OR 1.01, 95% CI 0.82-1.24, 12 RCTs, N= 1687) GnRH antagonist protocol (OR 1.97, 95% CI 0.93-4.18, 1 RCT, N = 119) 5. Number of oocytes (MD−0.11, 95% CI −0.70-0.47, 12 RCTs, N = 1744). Long GnRH agonist protocol (MD −0.14, 95% CI −0.73-0.45, 11 RCTs; N = 1625) GnRH antagonist protocol (MD 1.20, 95% CI −3.14-5.54, 1 RCT, N = 119)	There is no evidence of a difference between rhCG or rhLH and uhCG in live birth/ongoing pregnancy rates or rates of OHSS.	GRADE evidence profile

					6.Adverse events (OR 0.52, 95% CI 0.35 to 0.76; 5 RCTS, N = 561) (MQ) Analysis 1.6. The most commonly reported event was injection site reaction. However, when we used a random-effects model due to substantial statistical heterogeneity, there was no evidence of a difference between the groups (OR 0.56, 95% CI 0.27-1.13; 5 RCTs, N= 561)		

HCG DOSING

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Kolibianakis, E. M., Papanikolaou, E. G., Tournaye, H., Camus, M., Van Steirteghem, A. C., Devroey, P. Fertil Steril 2007; 88(5):1382-8 (17445806)	RCT	Eighty PCOS patients	Patients were randomized to receive 10,000 IU (n: 28), 5000 IU (n: 26), or 2500 IU (n: 26) of hCG for triggering final oocyte maturation as soon asR3 or more follicles of 17 mm or larger were present at ultrasound. Patients were stimulated with recombinant follicle stimulating hormone (FSH) and daily gonadotropinreleasing hormone (GnRH) antagonist, starting on day 6 of stimulation.	Ongoing pregnancy, MII oocytes OHSS.	Ongoing pregnancy per patient randomized % (95% CI) (n) 25.0 (12.7–43.4) (7/28) 30.8 (16.5–49.9) (8/26) 30.8 (16.5–49.9) (8/26) p=0.64 MII (%) 84.5 (30.2) 92.1 (18.9) 74.3 (52.6) .17 OHSS 1 case of early moderate OHSS in 10000 group and 1 moderate early OHSS in 5000 group	A decrease in the dose of hCG used to trigger final oocyte maturation does not appear to affect adversely the probability of pregnancy in PCOS patients treated by IVF using GnRH antagonists and recombinant FSH, and further testing in future larger-scale trials is recommended	

Madani, T., Mohammadi Yeganeh, L., Ezabadi, Z. Hasani, F., Chehrazi, M. J Assist Reprod Genet 2013; 30(2): 239-45 (23274511)	RCT	180 primary infertile women who were eligible for the ICSI program treated with Long down regulation	Group A (60 patients): received intramuscularly 10,000 IU urinary hCG Group B (60 patients): received subcutaneous injection of 250 µg recombinant hCG Group C (60 patients): received a subcutaneous injection of 500 µg recombinant hCG	Primary outcome measure number of oocytes retrieved per number of aspirated follicles. Secondary outcome number of oocytes retrieved, number of mature oocytes, chemical and clinical pregnancy rates OHSS occurrence rate.	Number of retrieved oocytes per aspirated follicles 71.82±15.09 69.84±17.44 77.16±17.61 a 0.04 Number of metaphase II oocytes (MII) 9.62±4.50 10.67±5.88 10.75±5.07 0.41 .58 Chemical pregnancy rate (%) 43.4(23/53) 46.7(21/45) 43.6(24/55) 0.93 Clinical pregnancy rate (%) 43.4(23/53) 42.2(19/45) 34.5(19/55) 0.60 Occurrence of OHSS (%) 3(5) 4(6.7) 6(10) 0.56	recombinant hCG shows equivalent efficacy to urinary hCG in terms of the number of oocytes per aspirated follicles in selected patients undergoing ICSI; however, 500 µg rhCG seems to be more advantageous than the lower dose in this indication.	
Shaltout, Aam, Eid, Ms and Shohayeb, Aa. Middle East Fertility Society Journal. 2006; 11 (2): 99-103. (CN-00613393)	RCT	One hundred patients scheduled for ICSI Inclusion criteria included: age<35 years, BMI<30 kg/mÇ and basal FSH<10 IU/l. patients Long down-regulation using GnRHa	group I (n=50) received 5000 IU and group II (n=48) received 10000 IU uhCG via intramuscular route	total number of oocytes retrieved, oocyte recovery rate, number of mature oocytes, fertilization and pregnancy rates , serum progesterone (P) on day 6-7 post hCG and incidence of OHSS.	Total number of oocytes 7±3.5 7.4±3 0.54 Oocyte recovery rate 87% 90% 0.5 Number of mature oocytes 5.6 ±3 5.9±2.6 0.6 Pregnancy rate 33.3% 35.4% 0.75 Incidence of OHSS % 2% 8.3% 0.17	5000 IU of uhCG is as effective as 10000 IU for triggering of ovulation, with the added advantage of lesser incidence of OHSS which is the most serious complication of ovulation induction. We therefore recommend optimizing the triggering dose of uhCG at 5000 IU, especially in young lean patients undergoing ovulation induction for infertility treatment.	No power analysis

15.2 Recombinant LH (rLH) vs urinary hCG (uhCG)

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments

Youssef, M. A., Abou-Setta, A. M. and Lam, W. S. Cochrane Database Syst Rev. 2016; 4 Cd003719. (27106604)	SR	Three trials in 479 women compared rLH with uhCG	ERLH groupr Patients in treatment arms 1, 2, 3 received an im injection of uhCG (5000 IU or placebo) in the buttock and a sc injection of rhLH (either 5000 IU, 15,000 IU, 30,000 IU, or placebo) in the abdomen. Patients in arm 4 received a single im injection of uhCG (5,000 IU or placebo) and 2sc injections of rhLH. The first rhLH injection (15,000 IU or placebo) was given on the same d as hCG; the second (10,000 IU or placebo) was administered 3 days later." Manau et al Group 1: hCG 5000 IU im Group 2: rhLH 5000 IU sc Participants started LPS no later than the day after embryo transfer, as per the clinic's routine practice. Physicians performed a pregnancy test 15 to 21 days after hCG if no menstruation had occurred All trials performed oocyte pick-up 30 to 38 hours after triggering, followed by IVF or ICSI, with no more than three embryos being replaced two to five days thereafter.	primary outcomes: 1. ongoing pregnancy/live birth 2. incidence of OHSS -secondary outcomes 3. Clinical pregnancy, 4. number of oocytes retrieved 6.adverse events	Ongoing pregnancy/live birth rate no evidence of a difference between the groups (OR 0.95, 95% CI 0.51-1.78; 2 RCTs, N= 289, (VLQ) Clinical pregnancy rate (OR 0.94, 95% CI 0.54-1.64; 2 RCTs, N = 2890, (VLQ) Number of oocytes retrieved. The number of retrieved oocytes was 10.23 ± 4.70 versus 11.74 ± 6.27 in participants receiving 5000 IU of rLH versus uhCG; 11.84 ± 7.53 versus 11.78 ± 6.75 in participants receiving 15,000 IU of rLH versus uhCG; and 12.62 ± 6.22 versus 10.82 ± 5.70 in participants receiving 30,000 IU of rLH versus uhCG (ERLH Group 2001). The mean number of oocytes retrieved was 11.56 in the rhCG group and 11.44 in the uhCG group. The number of oocytes was 10.2 ± 4.64 in the uhCG group versus 9.1± 3.4 in the rLH group (Manau 2002). Pooling the results of the arm using 5000 IU of rLH in ERLH Group 2001 withManau 2002 showed no evidence of a difference between the groups (MD−1.33, 95%CI −3.26 to 0.60; 2 RCTs, N = 103 (VLQ) Adverse events There was no evidence of a difference between the groups: over the trial, 158 events occurred in 71 women treated with rhLH (55%) and 171 events in 77 women treated with uhCG (63.6%) (OR 0.73, 95% CI 0.44-1.19	There is no evidence of a difference between rhLH and uhCG in live birth/ongoing pregnancy rates or rates of OHSS	GRADE evidence profile

15.3 GnRH AGONIST TRIGGER VERSUS hCG

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Griesinger, G., Diedrich, K., Devroey, P. and Kolibianakis, E. M. Hum Reprod Update. 2006; 12 (2): 159-68. (16254001)	SR	3 RCT's n=275 (139 GnRH agonist, 136 HCG) Two of the studies (Humaidan et al., 2005; Kolibianakis et al., 2005) were prematurely stopped due to significant differences between study groups in clinical pregnancy rates	triggering of final oocyte maturation with GnRH agonist; control group randomized to receive HCG for final oocyte maturation Luteal phase support: any means of luteal phase support other than HCG.	-clinical pregnancy per randomized patient; -number of oocytes retrieved; -proportion of metaphase II -fertilization rate; -embryo quality score; -first trimester abortion rate; -(OHSS) incidence	-Clinical pregnancy rate: Combined point estimate calculation was performed on the number of patients randomized 0.21, 95% CI = 0.05–0.84, P = 0.03, in favour of HCG -Number of oocytes –0.94, –0.33–0.14, P = 0.43. -Proportion of metaphase II oocytes –0.03, –0.58–0.52, P = 0.90 -OHSS incidence No cases of OHSS occurred in two of the trials (Humaidan et al., 2005; Kolibianakis et al., 2005), irrespective of the type of drug employed for triggering final oocyte maturation. In the third trial, (Fauser et al., 2002) OHSS incidence was not reported. Thus, no estimate on OHSS incidence can be inferred from the literature	GnRH agonist administration in) GnRH antagonist protocols to triggering final oocyte maturation yields a number of oocytes capable of undergoing fertilization and subsequent embryonic cleavage, which is comparable to that achieved with HCG. However, GnRH agonist usage for this purpose as assessed by the available studies is associated with decreased pregnancy likelihood.	

Youssef, M. A., Van der Veen, F., Al-Inany, H. G., Mochtar, M. H., Griesinger, G., Nagi Mohesen, M., Aboulfoutouh, I. and van Wely, M. Cochrane Database Syst Rev. 2014; (10): Cd008046. (25358904)	SR	17 RCTs (n = 1847 Subfertile women undergoing IVF/ICSI treatment cycles. At high or low risk to develop OHSS), of which 13 studies assessed fresh autologous cycles and four studies assessed donor-recipient cycles. High risk for OHSS was defined as studies including women with PCOS or women witH high numbers of ovarian follicles (≥ 14 follicles) ≥ 11 mm in diameter.	GnRH agonists in comparison with HCG for final oocyte maturation triggering in GnRH antagonist-controlled hyperstimulation cycles, IVF or ICSI followed by embryo transfer (ET) with or without luteal phase support,(Type of luteal phase support (• Luteal phase support with LH activity (single or two doses of HCG, recLH and repeated GnRH doses) • Luteal phase support without LH activity (progesterone only or progesterone plus oestradiol).) in autologous or donor cycle	• Live birth rate (LBR) per woman randomised: • Incidence of OHSS per woman randomised (mild, moderate or severe) . Secondary outcomes • Ongoing pregnancy rate (OPR) per woman randomised: • Clinical pregnancy rate (CPR) per woman randomised	LBR (OR 0.47, 95% CI 0.31-0.70; 5 RCTs, 532 women (MQ) studies with LPS with LH activity: OR 0.63, 95% CI 0.40-0.98; 3 RCTs, 382 women; studies with LPS without LH activity: OR 0.13, 95% CI 0.04-0.39; 2 RCTS, 150 women, OHSS (OR 0.15, 95% CI 0.05-0.47; 8 RCTs, 989 women (MQ) No evidence was found of a difference between GnRHa and HCG groups among women who had LPS with LH activity (OR 0.47, 95%CI 0.11-2.09; 5 RCTs), but the OHSS rate was lower in the GnRHa group among women who had LPS without LH activity (OR 0.04, 95% CI 0.01-0.34) Ongoing PR (OR 0.70, 95% CI 0.54-0.91; 11 RCTs, 1198 women (MQ) No evidence was found of differences between groups among women who had LPS with LH activity (OR 0.89, 95% CI 0.65-1.21; 5 RCTs), but the ongoing PR in the HCG group was higher among women who had LPS without LH activity (OR 0.36, 95% CI 0.21-0.62; 5 RCTs, 370 women) Clinical pregnancy rate per woman randomised (OR 0.81, 95% CI 0.61-1.04; 11 RCTs, 1198 women)	Final oocyte maturation triggering with GnRHa instead of HCG in fresh autologous GnRH antagonist IVF/ICSI treatment cycles prevents OHSS to the detriment of the live birth rate. In donor-recipient cycles, use of GnRH agonists instead of HCG resulted in a lower incidence of OHSS, with no evidence of a difference in live birth rate. Evidence suggests that GnRH agonist as a final oocyte maturation trigger in fresh autologous cycles is associated with a lower live birth rate, a lower ongoing pregnancy rate (pregnancy beyond 12 weeks and a higher rate of early miscarriage (less than 12 weeks). GnRH agonist as an oocyte maturation trigger could be useful for women who choose to avoid fresh transfers (for whatever reason), women who donate oocytes to recipients or women who wish to freeze their eggs for later use in the context of fertility preservation.	GRADE evidence profile

Humaidan, P., Bungum, L., Bungum, M., Yding Andersen, C. Reprod Biomed Online 2006; 13(2):173-8 (16895629)	RCT	45 normogonadotrophic women inclusion criteria: (i) female age >25 and <40 years; (ii) baseline FSH and LH <12 IU/l; (iii) menstrual cycles between 25 and 34 days; (iv) body mass index (BMI) >18 and <30; (v) both ovaries present; (v) absence of uterine abnormalities.	rFSH 150-200IU D2-6, afterwards adjusted to OR leading follicle =15 mm, GnRH antagonist ganirelix 0.25 mg was initiated and continued up to and including the day of ovulation induction. Group 2,3: bolus of 0.5 mg buserelin s.c. Group 1: 10,000 IU of HCG (group 1) s.c. followed by oocyte retrieval 34 h later	No of oocytes Clinical pregnancy rate/cycle	**Group 1 vs 2 vs 3** No of oocytes 7.0 ± 3.5 vs 10.8 ± 7.7 vs 12.5 ± 4.0, (p<0.05 2 vs 1 and 3) Clinical pregnancy rate / cycle 53% (8/15) vs 12% (2/17) vs 46% (6/13) (p< 0.05 2 vs 1 and 3)	The study demonstrates that the administration of a bolus of 1500 IU HCG 35 h after triggering of ovulation with GnRHa rescues the corpora lutea, resulting in luteal phase characteristics similar to those of HCG.	
Humaidan, P., Ejdrup Bredkjaer, H., Westergaard, L. G., Yding Andersen, C. Fertil Steril 2010; 93(3): 847-54. (19200959)	RCT	302 normogonadotrophic women inclusion criteria: [1] female age >25 years and <40 years; [2] baseline FSH and LH levels <12 IU/L; [3] menstrual cycles between 25 and 34 days; [4] body mass index>18 kg/m2 and<30 kg/m2; [5] both ovaries present; and [6] absence of uterine abnormalities.	rFSH 150-200IU D2-6, afterwards adjusted to OR leading follicle =15 mm, GnRH antagonist ganirelix 0.25 mg was initiated and continued up to and including the day of ovulation induction GnRHa group: a single SC bolus of 0.5 mg buserelin a small bolus of 1,500 IU hCG administered IM on the day of OPU hCG group: hCG (10,000 IU SC) OPU 34 hours later	No of oocytes Clinical pregnancy rate Ongoing pregnancy rate Live birth rate OHSS	**GnRHa vs hCG** No of oocytes 8.9±5.4 vs 9.3±5.0, NS Clinical PR: 33% (50/152) vs. 37% (55/150), NS Ongoing PR: 26% (40/152) vs. 33% (49/150), NS LBR: 24% (36/152) vs. 31% (47/150), NS OHSS Three cases of OHSS, one severe and two moderate (2%) were reported in the hCG group, whereas no OHSS case was seen in the GnRHa group.	a small bolus of 1,500 IU hCG administered at the time of oocyte retrieval seems to rescue the luteal function without increasing the OHSS rate when GnRHa is used to induce final oocyte maturation.	

Humaidan, P., Polyzos, N. P., Alsbjerg, B., Erb, K., Mikkelsen, A. L., Elbaek, H. O., Papanikolaou, E. G. and Andersen, C. Y Hum Reprod. 2013; 28 (9): 2511-21. (23753114)	RCT	118 patients at risk of OHSS Group C: 125 women Group D: 141 women	Group C: 0.5 mg Buserelin with 1.500 hCG on day FA Group D: 5.000 hCG. Study duration 2 years, one cycle.	Outcome OHSS (moderate and severe, Navot) Ongoing pregnancy rate	Ongoing pregnancy rate Ago: 29.6% (37/125) hCG: 25.5% (36/141) RR: 1.15 [0.78-1.71] OHSS Ago: 2/125 hCG: 1/41	GnRHa triggering followed by supplementation with one bolus of 1.500 IU hCG appears to reduce the OHSS incidence in the group at risk of OHSS when an upper limit of 25 follicles is used as a cut-off. Above this limit, to completely eliminate OHSS we recommend either an intensive luteal phase support strategy with E2 and progesterone	Fulfills meaning of Q12 GROUPS SIZES may limit final conclusion on equivalence of efficacy, as well as difference in Safety.
Papanikolaou, E. G., Verpoest, W., Fatemi, H., Tarlatzis, B., Devroey, P., Tournaye, H. Fertil Steril 2011; 95(3): 1174-7. (20979997)	RCT	39 patients Inclusion criteria were: [1] age less than 36 years, [2] elective single embryo transfer on day 5, and [3] basal FSH less than 12 mIU/mL. Exclusion criteria were: [1] polycystic ovary syndrome (PCOS); [2] use of testicular sperm; and [3] endometriosis stages III and IV.	fixed dose 187.5 IU rFSH starting on day 2 of the cycle with co-administration of GnRH-antagonist, 0.25 mg cetrorelix on cycle day 7 and continued daily until the day of trigger. Group 1: n=17 250 µg rhCG And P for LPS Group 2: n=18 0.2 mg of triptorelin P+300IU LH for LPS	No of COCs retrieved OHSS Clinical pregnancy rate Live birth rate	**Group 1 vs 2** No of COCs: 13.8±1.8 vs 11.7±1.9, NS OHSS 0 vs 0 Clinical PR: 26.7% (4/15) vs. 25.0% (4/16) LBR: 23.5% (4/17) vs. 22.2% (4/18), NS	Luteal supplementation with recombinant LH in conjunction with the standard regimen of vaginal micronized P seems efficient in terms of the establishment of a clinical pregnancy in IVF cycles when a GnRH-a is used for final oocyte maturation	

15.3.1 Triptorelin 0.1 mg versus higher dosages

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Vuong, T. N., Ho, M. T., Ha, T. D., Phung, H. T., Huynh, G. B. and Humaidan, P Fertil Steril. 2016; 105 (2): 356-63. (26523330)	RCT	RCT n=165 Asian egg donors	Ovulation trigger with 0.2, OR 0.3, OR 0.4 mg triptorelin in a GnRH antagonist cycle. Stimulation was performed with corifollitropin alfa (100 or 150 mg) for stimulation on cycle day 2 + ganirelix (starting on day 5 after stimulation) and follitropin-b (dose was depending on body weight 150 or 200 IU/d, starting from day 8 of simulation until the day of triggering). Triggering of final oocyte maturation:As soon as two follicles reached a size of 17 mm, (OPU) was performed 35 hours later.	-number of metaphase II oocytes.	**triptorelin 0.2 vs 0.3 vs 0.4 mg trigger groups** No of oocytes retrieved 18.4±8.8 vs. 18.7±8.9 vs. 17.8±10.7, NS No of M II oocytes (16.0±8.5 vs., 15.9±7.8 vs. 14.7±8.4), NS One case of OHSS in the 0.3mg group	No significant differences between triptorelin doses of 0.2, 0.3, and 0.4 mg used for ovulation trigger in oocyte donors were seen with regard to the number of mature oocytes and top-quality embryos.	Study in oocyte donors RCT well designed , original. Throwback the population (only Asian egg donors)

15.3.2 Buserelin 0.2 mg vs 0.5 – 1 – 2 mg

No relevant studies were identified

15.3.3 Leuprolide 0.15 mg vs 0.5 – 1 – 2 - 4 mg

No relevant studies were identified

15.4 DUAL TRIGGER

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Ding, N., Liu, X., Jian, Q., Liang, Z. and Wang, F. Eur J Obstet Gynecol Reprod Biol. 2017; 218 92-98. (28957685)	SR	-4 RCT's -527 patients Inclusion criteria (i) RCTs and (ii) studies that included patients with mild male factor infertility, unexplained infertility, or tubal factor infertility that require IVF/ICSI Exclusion Criteria: (i) had high or poor ovarian response to OS (ii) were aged 40 years; (iii) had a severe underweight or overweight status (body mass index <18 or >30 kg/m2); (iv) had an occult ovarian failure (day-3 FSH concentration of >10 IU/L or serum anti-Müllerian hormone level of 1.0 ng/mL); and (v) had endocrine disorders or uterine abnormalities confirmed by either hysterosalpingography or hysteroscopy.	hCG-triggering, 5000 or 10,000 IU was administered in 3 trials and 250 µg of rhCG; was used in 1 trial For dual triggering, triptorelin 0.1 or 0.2 mg In 2 studies, leuprolide acetate 1 mg [12] in 1 study concomitantly with hCG 5000 in 3 studies and 250µg rhCG in one study. Fresh ET was performed in 3 studies, 1 study did not report pregnancy outcome. LPS was administered in 3 different dosages of PRG.	Number of oocytes retrieved: Number of mature oocytes retrieved Number of fertilized oocytes Number of good-quality embryos Implantation rate Pregnancy rate	Number of oocytes retrieved: 4 studies WMD, 0.47; 95% CI, _0.42 to 1.37 Number of mature oocytes retrieved (3 studies) (WMD, 0.47; 95% CI, _0.32 to 1.26 Ongoing/clinical Pregnancy rate 2 studies (RR, 1.55; 95% CI, 1.17–2.06),	GnRH-a and hCG as dual trigger was equivalent to hCG in triggering oocyte maturation and may be beneficial in improving reproductive outcomes. Further intensive randomized-controlled studies should be conducted to investigate the efficacy of the dual trigger.	Include DUAL trigger vs hCG trigger Contains the same included RCTs as Chen 2018 No OHSS rate is reported No LBR is reported

Eftekhar, M., Mojtahedi, M. F., Miraj, S. and Omid, M. Int J Reprod Biomed (Yazd). 2017; 15 (7): 429-434. (29177244)]	RCT	192 normal responders (Group 1 n=93) (Group 2 n=99) inclusion criteria were BMI 18-30 age ≤42 yr history of infertility for at least 1 yr exclusion criteria : presence of endocrine disorders Azoospermia D3 FSH >10, AMH<1,0 POR : (E2) level less than 500 pg/mL on the day of triggering or the number of retrieved oocytes less than three High ovarian response was defined as E2 level higher than 3,000 pg/mL on the day of triggering or the number of retrieved oocytes more than 15.	Group I triggered by 6500 IU human chorionic gonadotropin (hCG) alone, Group II by 6500 IU hCG plus 0.2 mg of triptorelin.	Chemical pregnancy clinical pregancy ongoing pregnancy, No of oocytes MII oocytes	Chemical pregnancy rate 30.3 vs 25.8 p 0.5 Clinical pregnancy rate 26.3 vs 22.6 p 0.3 Ongoing pregnnacy rate 24.2 vs 22.9 p 0,77 Oocytes retrieved 10.85± 4.71 vs 9.35 ±4.35 p= 0.009 MII 8.80 ± 3.99 vs 7.98 ± 3.85 p=0.12	Our results indicate that mean number of retrieved oocytes, mature metaphase II oocytes and formed embryos were higher in the dual-trigger group compared with the hCG	Include single-blind randomized controlled trial. randomization was performed on the day of triggering final oocyte maturation No OHSS rate in outcomes No LBR rate DUAL TRIGGERING

16. Luteal phase support (LPS)

KEY QUESTION: WHAT IS THE EFFICACY AND SAFETY OF LUTEAL SUPPORT PROTOCOLS?

P	I	C	O
Women undergoing IVF/ICSI	Progesterone - Oral - Intramuscular - Vaginal Dydrogesterone estradiol plus prog hCG GnRH agonists (+progesterone) repeated agonist LH Timing of initiation OPU, OPU +1 etc)	- LPS vs no LPS - Different routes of administration - versus other approaches	Efficacy: - cumulative LBR/cycle - Cumulative ongoing pregnancy rate /started cycle (fresh + frozen) - Clinical pregnancy rate/started cycle - Nr of Oocytes/ nr of MII oocyte recovery rate (yield) - number of embryo's (fresh+frozen) Safety - incidence of different grades of OHSS - grade of OHSS - incidence of cycle cancellation for hyper-response (predefined) - Bleeding - Infection - Torsion - Long-term effect on maternal/child health - other adverse events (treatment related) Patient-related outcomes - Compliance - Drop-out rates - Patient burden - QoL - Patient preferences

Papers selected for this question that were already included in the evidence table of question 15	Type
Papanikolaou, E. G., Verpoest, W., Fatemi, H., Tarlatzis, B., Devroey, P., Tournaye, H. Fertil Steril 2011; 95(3): 1174-7. (20979997)	RCT

16.1 PROGESTERONE

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
van der Linden, M., Buckingham, K., Farquhar, C., Kremer, J. A. and Metwally, M. Cochrane Database Syst Rev. 2015; (7): Cd009154. (26148507)	SR	Cochrane review Progesterone vs placebo / no treatment 5 studies Total 642 patients	Im progesterone 50 mg / day or vaginal progesterone gel 90g / day. Oral dydrogestone 10 mg 1x3, Oral progesterone 200 mg x 4 or vag progesterone 100 mg x3 + e2 x 3.	CRP or ongoing pregnancy.	Pregnancy rate was higher in progesterone group vs no progesterone. live birth/ongoing pregnancy rate 5 RCT, OR 1.77, 95% CI 1.09-2.86, 642 women	Progesterone improves pregnancy rates in comparison to no progesterone.	GRADE evidence profile Progesterone vs placebo or no LPS

PROGESTERONE DOSAGE

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
van der Linden, M., Buckingham, K., Farquhar, C., Kremer, J. A. and Metwally, M. Cochrane Database Syst Rev. 2015; (7): Cd009154. (26148507)	SR	Cochrane review 5 studies Total 3720 patients	Five studies compared a low dose (≤ 100 mg) with a high dose (≥ 100 mg)	CRP or ongoing pregnancy.	no difference in live birth/ongoing pregnancy rate (5 RCT, OR 0.97, 95% CI 0.84-1.11, 3720 women)		GRADE evidence profile Dosage
Aslih, N., Ellenbogen, A., Shavit, T., Michaeli, M., Yakobi, D. and Shalom-Paz, E. Gynecol Endocrinol. 2017; 33 (8): 602-606. (28277886)	RCT	Pilot study. Dosage of P. Does addition of P dosage improve the outcome with patients with low levels (under 15 ng/ml) of P week after ET.	146 patients received routine P Endometrin suppositories 200 mg daily. 75 had normal levels of P Low levels of P (71 pat) were randomized to N 36 Continue with 200 mg P N 35 Increase dosage of P to 300 mg until pregnancy test	PR, CPR and live birth rate	**Group 1 vs 2** LBR 25% (9/36) vs. 17.1% (6/35)	Altering the mid-luteal dosage of P on patients with P <15 ng/ml week after ET does not improve PR, CPR or LBR. Suggest a cut off limit of 17 ng/ml for normal P-levels and prediction of the outcome.	The sample size was to small to make accurate statistical analysis. 70 patients in each group would have been needed for the analysis.
Michnova, L., Dostal, J., Kudela, M., Hamal, P. and Langova, K. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2017; 161 (1): 86-91. (28323291)	RCT	This study compared the efficiency, safety and tolerance of two vaginal micronized progesterones, Utrogestan and Crinone 8%Prospective randomized study. 111 patients	Utrogestan 200 mg 1x2 n 58 Crinone gel 90 mg n 53 LPS begun 2 days after OR and was continued until week 10.	pregnancy rate (PR), take home baby rate (THBR), number of cryopreserved embryos, pregnancies after 12th week of pregnancy, OHSS, Also vaginal microbes and patient satisfaction was evaluated.	**Group 1 vs 2** LBR: (52.8% (28/53) vs. 42.6% (20/47) Crinone 8% exhibited less subjective complaints than Utrogestan.	The outcomes of this study suggest that a vaginal gel with micronized progesterone (Crinone 8%) is the optimal choice at this time for luteal support.	Include, though the conclusions from the study might be based on patient preferences (since there is no difference in other outcomes).

PROGESTERONE TIMING ADMINISTRATION

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Baruffi R, Mauri AL, Petersen CG, Felipe V, Franco JG Jr. J Assist Reprod Genet. 2003; 20(12):517-20. (15035552)	RCT	103 patients Comparable age in both groups	OS with GnRH-a (400µg) and rFSH (150-300IU) trigger 5000-10.000IU hCG Group A: vaginal P 400mg start on evening of oocyte retrieval Group B: vaginal P 400 mg	No pre-defined outcome measures	**Group A vs B** Preg rate/transfer 27.4% vs. 28.8% NS	vaginal progesterone at the dose of 400 mg started on the day of oocyte retrieval did not increase implantation or pregnancy rates when compared to the same dose started on the day of	Included for start of LPS
Fanchin R, Righini C, de Ziegler D, Olivennes F, Ledée N, Frydman R. Fertil Steril. 2001 Jun;75(6):1136-40. (11384639)	RCT	84 infertile women Age 26-38 years Morphologically normal utery Groups were comparable at baseline	GnRHa triptorelin 3.0 mg im rFSH 225IU/d hCG 10.000IU im Group A: vaginal P (crinone 8%) immediately after oocyte retrieval		Group A vs B Clinical preg. Rate: 42% vs. 29% Ongoing preg rate 35% vs. 22%	vaginal progesterone administration starting 2 days before ET induces a significant reduction in uterine contraction frequency at the time of ET.	Included for start of LPS
Gao, J., Gu, F., Miao, B. Y., Chen, M. H., Zhou, C. Q. and Xu, Y. W. Fertil Steril. 2018; 109 (1): 97-103. (29175065)	RCT	233 patients Patient groups were similar.	Begin progesterone 1 day after OR 116 Begin progesterone on day of OR 117	CPR, miscarriage rate, implantation rate, LBR	The effect was similar in CPR 55.3% vs 51.5 NS LBR was similar 45,7 vs 46,6	The beginning of progesterone as LPS one day after OR does not have an effect on CPR, or LBR.	Include in beginning of LPS / progesterone

Mochtar, M. H., Van Wely, M. and Van der Veen, F. Hum Reprod. 2006; 21 (4): 905-8. (16373409)	RCT	385 patients Age, parity, indication for IVF and the total motile sperm count were equally divided between the three groups.	Vaginal P 400mg in 2 doses Group A: start at evening of hCG Group B: start at evening of oocyte retrieval Group C: start at evening of ET	Ongoing pregnancy rate	**Group B vs A vs C** Clinical pregnancy: 36/128 (28.1%) vs 30/130 (23.1%) vs 37/127 (29.1%) NS A vs B: RR 0.82 (95% CI 0.54-1.24) C vs B: RR 1.04 (95% CI 0.70-1.53) Ongoing pregnancy 29/128 (22.7%) vs 27/130 (20.8%) vs 30/127 (23.6%) NS A vs B: RR 0.92 (95% CI 0.58-1.45) C vs B: RR 1.04 (95% CI 0.66-1.62) Live birth 27/128 (21.1%) vs 26/130 (20.0%) vs 26/127 (20.5%) NS A vs B: RR 0.94 (95% CI 0.58-1.52) C vs B: RR 0.97 (95% CI 0.60-1.56)	Further studies are needed to explore whether timing of HCG according to predetermined criteria of follicular size, opposed to the until now rather loose criteria, leads to higher ongoing pregnancy rates in GnRH agonists down-regulated controlled ovarian hyperstimulation IVF/ET cycles.	Included for start of LPS
Sohn SH, Penzias AS, Emmi AM, Dubey AK, Layman LC, Reindollar RH, DeCherney AH. Fertil Steril. 1999 Jan;71(1):11-4 (9935109)	RCT	314 cycles Patient demographic characteristics, including age, primary diagnosis, number of oocytes retrieved and fertilized, and number of embryos transferred, were not different between the two groups.	Group A: 12.5 mg P i.m. in oil 12h before oocyte retrieval + dose on evening after OR After that 25mg daily Group B: 25 mg start at evening of OR	Clinical pregnancy	**Group A vs B** Clinical PR (per ET): 12.9% vs 24.6% (p=0.011)	for patients with the demographic characteristics of those in our study, providing progesterone supplementation before oocyte retrieval significantly adversely affected outcome.	Included for start of LPS
Williams, S. C., Oehninger, S., Gibbons, W. E., Van Cleave, W. C. and Muasher, S. J. Fertil Steril. 2001; 76 (6): 1140-3. (11730741)	RCT	126 women Cycle characteristics comparable between both groups except the day 6 group had more embryos cryopreserved compared with the day 3 group.	Long GnRHa protocol, GnRHa pre-treatment protocol, no downregulation or GnRHa flare protocol+rFSH 150-450IU Trigger: hCG 10.000IU Vaginal P 200 mg Group A: start morning of D3 after OR Group B: start morning of D6 after OR	Clinical pregnancy rate	**Group A vs B** Overall: Clinical pregnancy rate: 61.0% vs (p=0.05) Good responders with long GnRHa: Clinical pregnancy: 71.4% vs 47.5% p=0.03 Other protocols: NS		Included for start of LPS

PROGESTERONE ADMINISTRATION ROUTE

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Doblinger, J., Cometti, B., Trevisan, S. and Griesinger, G. PLoS One. 2016; 11 (3): e0151388. (26991890)	SR	Safety of subcutaneous progesterone. 2 trials. 1435 patients in study.	714 pat sc prog and 721 vaginal vagitorios	Ongoing pregnancy rate 10 w, LBR and risk OHSS.	**Sc vs vaginal** No effect on ongoing pregnancy rate No effect on LBR. 35.3% (252/714) vs 37.6% (271/721) risk difference -0.02, 95% CI -0.07-0.03 No impact on OHSS risk. (27/714 vs. 26/721; OR 1.04, 95% CI 0.60-1.81)	Sc progesterone is as efficient and safe as vaginal prog gel or vag capsules.	GRADE evidence profile Subcutaneous vs vaginal progesterone IPD meta-analysis
van der Linden, M., Buckingham, K., Farquhar, C., Kremer, J. A. and Metwally, M. Cochrane Database Syst Rev. 2015; (7): Cd009154. (26148507)	SR	Cochrane review	vaginal/rectal versus oral route, n=857 vaginal/rectal versus intramuscular route, n=2039	CRP or ongoing pregnancy.	**vaginal/rectal versus oral route** live birth/ongoing pregnancy rate (4 RCT, OR 1.19, 95% CI 0.83-1.69, 857 women) **vaginal/rectal versus intramuscular** live birth/ongoing pregnancy rate (7 RCT, OR 1.37, 95% CI 0.94 to 1.99, 2039 women)		GRADE evidence profile Progesterone vs placebo or no LPS Administration route

Iwase A, AndoH, Toda S, Ishimatsu S,Harata T, Kurotsuchi S, Shimomura Y, Goto M, Kikkawa F. Arch Gynecol Obstet. 2008;277(4):319–24. (17938943)	RCT	N=40 Inclusion: Infertile women of all ages undergoing IVF/ ICSI with (1) hMG for OS under GnRHa down-regulation (nafarelin acetate) and (2) a high response with a serum estradiol concentration of >2,000 pg/ml on the day of hCG administration, and (3) having at least one embryo transferred. The two groups were comparable in terms of age, dose of hMG used, duration of stimulation, estradiol level on the day of hCG administration, and the number of oocytes, embryos, and embryos transferred	Long and short GnRHa protocol + hMG 300IU Trigger: 10.000IU hCG P oral: 12 mg/day P i.m: 25 mg/day (day 2-6) P i.m.: 50 mg/day (day 7-14) Starting on day of ET	CPR LBR OHSS	**i.m. vs oral** clinical pregnancy 5/20 (25%) vs. 4/20 (20%) NS Live birth rate 3/20 (15%) vs. 4/20 (20%) NS OHSS 1/20 vs. 1/20 NS	Oral progesterone not inferior to IM progesterone in terms of endometrial thickness, implantation rate, and pregnancy rate as far as the normal and high responders were concerned.	Administration route
Zargar, M, Saadati, N and Ejtahed, Ms. International Journal of Pharmaceutical Research and Allied Sciences. 2016; 5 (3): 229-36. (CN-01158533)	CT RCT	Randomized double blinded CT conducted on 612 infertile women. 3 groups. Pat charasterics were similar, but the age of the groups differed. Mean age in DG was higher p<0.0001 Oral dydrogestone, 30.02 ± 5.02y, vaginal prgesterone 31.92 ± 4.82 and IMP 28.04 ± 5.04 <0.0001	Oral dydrogestone 30 mg 212 pat vaginal progesterone suppository (800 mg, n = 200 progesterone ampule 100 mg	PR and miscarriage rate	**intramuscular vs vaginal route** Clinical pregnancy rate (26.5% (53/200) vs. 26.5% (53/200), NS	The pregnancy rate and miscarriage rate was similar in all of the regiments (oral , vaginal and im). Dydrogestone may be consired as a regimen for LPS after IVF / ICSI:	ADMIN ROUTE IM vs vaginal

PROGESTERONE DURATION

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Liu, X. R., Mu, H. Q., Shi, Q., Xiao, X. Q. and Qi, H. B. Reprod Biol Endocrinol. 2012; 10 107. (23237065)		6 RCTs	Progesterone LPS stop after pregnancy test Progesterone LPS continued until week 6/7	Live birth rate Ongoing pregnancy rate	**Stopping vs continuing** **Live birth rate** 77.3% (143/185) vs 81.5% (150/184); RR 0.95, 95% CI 0.86-1.05) **Ongoing pregnancy rate** 503/585 vs 514/581; RR 0.97, 95% CI 0.90-1.05), I^2=73%	we find no convincing evidence to support the routine use of P supplementation during early pregnancy in women undergoing IVF/ICSI	

16.2 Dydrogesterone

Progesterone versus dydrogesterone

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Barbosa, M. W. P., Valadares, N. P. B., Barbosa, A. C. P., Amaral, A. S., Iglesias, J. R., Nastri, C. O., Martins, W. P. and Nakagawa, H. M. JBRA Assist Reprod. 2018; 22 (2): 148-156. (29488367)	SR	Systematic review 9 RCTs; including 4,061 women	Studies included to the sr were ones comparing oral dydgrogesterone to vaginal progesterone capsules.	LBR, OPR, CPR, miscarriage rate	**Oral dydrogesterone vs vaginal progesterone** live birth/ongoing pregnancy (RR=1.08, 95%CI=0.92-1.26, I2=29%, 8 RCTs, 3,386 women) clinical pregnancy rates (RR 1.10, 95% CI 0.95 to 1.27; I2=43%; 9 RCTs; 4,061 women).).	Good quality evidence from RCTs suggest that oral dydrogesterone provides at least similar reproductive outcomes than vaginal progesterone capsules when used for LPS in women undergoing embryo transfers. Dydrogesterone is a reasonable option and the choice of either of the medications should be based on cost and side effects.	Include.
Griesinger, G., Blockeel, C., G, T. Sukhikh, Patki, A., Dhorepatil, B., Yang, D. Z., Chen, Z. J., Kahler, E., Pexman-Fieth, C. and Tournaye, H. Hum Reprod. 2018; (30304457)	RCT	1034 women undergoing IVF were randomized to 1:1 receive oral dydrogesterone 30mg or8% MVPgel 90mg daily. The groups were compararale.	Receive oral dydrogesterone (n = 520) MVP gel (n = 514) on the day of oocyte retrieval, and luteal phase support continued until 12 weeks of gestation	Presence of fetal heartbeatsat 12 weeks of gestation, as determined by transvaginal ultrasound.	Dydrogesterone vs progesterone CPR (12 weeks) 38.7% (191/494) and 35.0% (171/489) (adjusted difference, 3.7%; 95% CI: −2.3 to 9.7 Live birth rates in the FAS of 34.4% (170/494) and 32.5% (159/489) (adjusted difference 1.9%; 95% CI: −4.0 to 7.8).	Non-inferiority of oral dydrogesterone was demonstrated. This study demonstrates that oral dydrogesterone is a viable alternative to MVP gel, due to its comparable efficacy and tolerability profiles.	P vs dydro

DYDROGESTERONE VERSUS PLACEBO

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Kupferminc, M. J., Lessing, J. B., Amit, A., Yovel, I., David, M. P. and Peyser, M. R. Hum Reprod. 1990; 5 (3): 271-3. (2351709)	RCT	Prospective randomized study to test a need for LPS. 156 patients. Stimulated with HMG and triggered with 10 000 IU HCG. ET on day 2 and the patients were randomized to begin LPS.	Group 1 received (N=54) Dydrogestone 10 mg 1x3 Group 2 received (n=51) placebo tabl 3x daily Group 3 received (n=51) 2500 IU hCG on d 3, 6 and 10 following et.	PR,	**Dydrogesterone vs placebo** clinical pregnancy rate (29.6% (16/54) vs. 27.4% (14/51))	The data indicate that supplementation of the luteal phase may not improve the success rates of IVF-ET cycles.	

16.3 OESTRADIOL SUPPLEMENTATION

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
van der Linden, M., Buckingham, K., Farquhar, C., Kremer, J. A. and Metwally, M. Cochrane Database Syst Rev. 2015; (7): Cd009154. (26148507)	SR	Progesterone vs P+E2 16 RCTs, 2577 women.	Compared E2 + P(n=728) to P only (n=923) for LPS Oral E2 received 533 women from 2 to 6 mg daily. Compared to only P 733. Transdermal E2 received 111 women compared to 108 receiving only P. Vaginal E2 received 84 and were compared to 82 with only P.	Clinical pregnancy rate. Ongoing pregnancy over 12 weeks and LBR.	No differences were found between groups live birth/ongoing pregnancy (OR 1,12 95% cl 0,91 to 1,38) 9 RCTS 1651 women I2=0, low qual evidence) OHSS (OR 0,56 95% Cl 0,2 to 1.63, two RCTs, 461 women, low quality evidence.)	Addition of estrogen does not improve probability of pregnancy in IVF.	GRADE evidence profile Progesterone vs progesterone+estradiol
Gizzo, S., Andrisani, A., Esposito, F., Noventa, M., Di Gangi, S., Angioni, S., Litta, P., Gangemi, M. and Nardelli, G. B. Gynecol Endocrinol. 2014; 30 (12): 902-8. (25268567)	RCT	Dosage of P and addition of E2 best LPS (drugs association, daily dose and administration way) 360 women divided into subgroups by stimulation protocol 180 treated by long-GnRH agonist 90 by short-GnRH agonist 90 by shortGnRH antagonist protocol	From different stimulations subgroups were formed to receive low-dose P (200mg vaginal capsule twice daily) , 60+30+30 patients High dose P (200mg vaginal capsule three times daily plus 100mg intramuscular daily High dose P + E2 (200mg vaginal capsule three times daily plus 100mg intramuscular daily) in association with valerate E2 (2mg vaginal tablet twice daily). LPS began day after OR. Low dose P was the control.	CPR and ongoing PR Detect differences between the different LPS schemes (considering all stimulation protocols) in term of odds ratio (OR) to achieve clinical and ongoing pregnancy in cases of E2max at ovulation induction <5nmol/l, endometrial thickness at pick-up<10mm and woman age<35 years.	**P+E2 vs P** Clinical pregnancy rate - long GnRH agonist protocol 43.3% vs. 35% - GnRH antagonist protocol 60% vs. 36.6% - Short GnRH agonist protocol 43.3% vs 40%	High dose P increased the possibility of clinical and ongoing pregnancy rate. Addition of E2 does not have an effect on pregnancy rate. in short-GnRH-ag protocols the addiction of E2 to high-dose PG does not increase the clinical pregnancy rate.	

Ismail Madkour, W. A., Noah, B., Abdel Hamid, A. M., Zaheer, H., Al-Bahr, A., Shaeer, M. and Moawad, A. Hum Fertil (Camb). 2016; 19 (2): 142-9. (27434094)	RCT	220 patients undergoing antagonist intracytoplasmic sperm injection (ICSI) cycles protocol. Randomized in 2 grouos	Group 1: vaginal progesterone alone (90mg once daily) starting on the day of oocyte retrieval for up to 12 weeks if pregnancy occurred. N = 110 Group 2 vaginal progesterone (90mg once daily) with oral e2 4 mg daily until week 7 starting on the day of oocyte retrieval for up to 12 weeks if pregnancy occurred. N = 110	Primary outcomes were pregnancy and ongoing pregnancy rates per embryo transfer. Secondary outcomes were implantation and early pregnancy loss rates	Group 1 vs 2 PR (39.09%) vs (43.63%) (p value¼0.3) ongoing pregnancy rate (32.7% vs 36.3%, p value¼0.1).	the addition of 4mg estrogen daily to progesterone for luteal support in antagonist ICSI cycles is not beneficial for pregnancy outcome.	P vs P+E2
Kutlusoy, F., Guler, I., Erdem, M., Erdem, A., Bozkurt, N., Biberoglu, E. H. and Biberoglu, K. O. Gynecol Endocrinol. 2014; 30 (5): 363-6. (24517720)	RCT	Effect of addition of E2 to progestin (P) for LPS on pregnancy outcome in IVF for poor responders. Total of 95 patients.	Group 1 (n=33) received only intravaginal progesterone gel (Crinone 8% gel). Group 2 (n=27) received intravaginal progesterone plus oral 2 mg estradiol hemihydrate Group 3 (n=35) received intravaginal progesterone plus oral 6mg estradiol hemihydrate,	CPR and PR	PR: Group 1: 18.2%, Group 2, 44.4% Group 34.3% p<0.05 CPR: Group 1: 12.1%, Group2: 37.0%, Group 3 25.7% p<0.05 LB: Group1: 12.1%, Group2: 37.0% Group3 22.9% p<0.05 Sample size is quite small.	Poor responders given 2mg/day Estradiol Hemihydrate in addition to progesterone for LPS significantly improved IVF outcome. The main restrictions of this study are the number of cases being rather small in the groups and the COH protocol applied being heterogeneous	P vs P+E2

Tonguc, E., Var, T., Ozyer, S., Citil, A. and Dogan, M. Eur J Obstet Gynecol Reprod Biol. 2011; 154 (2): 172-6. (21067858)	RCT	Prospective randomized study. 285 women tested dosage of E2 in LPS after long GnRH agonist protocol ICSI. Randomization on day of OPU and begun LPS. No placebo control group.	Group 1 Received Crinone gel 8% 90 mg daily + 2 mg E2 (Estrofem) Group 2 Received Crinone gel 8% 90 mg daily + 4 mg E2 Group 3 Received Crinone gel 8% 90 mg daily + 6 mg E2	CPR, IR (implantation rate), miscarriage rate, multiple pregnancy rate	CPR was not significant. 1. 31.6%, 2. 40%and 3. 32%, p= NS	Addition of E2 4-6 mg reduced miscarriage rate. Larger studies are needed in order to find the optimal dose of E2. Comment, no placebo control.	P+E2 dosage

16.4 HUMAN CHORIONIC GONADOTROPHIN (HCG)

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Pritts, E. A. and Atwood, A. K. Hum Reprod. 2002; 17 (9): 2287-99. (12202415)	SR	1 RCT including 91 women	hCG vsprogesterone+ E2	Clinical pregnancy rate	No difference in clinical pregnancy rate (RR 0.99, 95% CI 0.50-1.92)		GRADE evidence profile hCG vs progesterone+estradiol
van der Linden, M., Buckingham, K., Farquhar, C., Kremer, J. A. and Metwally, M. Cochrane Database Syst Rev. 2015; (7): Cd009154. (26148507)	SR	Cochrane systematic review hCG vs progesterone 4 studies hCG vs no treatment 3 RCTs 527 pat	Hcg or progesterone in LPS Hcg or no additional treatment in LPS	LB and CPR	**hCG vs placebo** LBR 3 RCT, OR 1.76, 95% CI 1.08-2.86, 527 women OHSS 1 RCT, OR 4.28, 95% CI 1.91-9.60, 387 women **hCG or hCG+P vs progesterone** LBR/ongoing PR 5 RCT, OR 0.95, 95% CI 0.65-1.38, 833 women OHSS 5 RCT, OR 0.46, 95% CI 0.30-0.71, 1293 women	No effect on LB or CPR in P is used. HCG increases risk of OHSS.	GRADE evidence profile hCG vs progesterone hCG vs no treatment

16.5 GnRH AGONIST

16.5.1 SINGLE GnRH AGONIST BOLUS SUPPLEMENTATION

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
van der Linden, M., Buckingham, K., Farquhar, C., Kremer, J. A. and Metwally, M. Cochrane Database Syst Rev. 2015; (7): Cd009154. (26148507)	SR	9 studies 5 single dose 1536 women (control 748 vs 788 study), 5 multiple dose 1325 (control 637 vs 688) (randomization?) Cochrane Database Syst Rev	Single GnRH-a on day of transfer D5/6 single dose	LBR/OBR	Live birth/ongoing pregnancy rates (OR 0.62, 95% CI 0.48 to 0.81, nine RCTs, 2861 women, I2 = 55%, random effects, low-quality evidence)	Heterogenous studies and low sample size.	GRADE evidence profile Progesterone+GnRHa vs progesterone
Razieh, D. F., Maryam, A. R. and Nasim, T. Taiwan J Obstet Gynecol. 2009; 48 (3): 245-8. (19797013)	RCT	Effect of gonadotropin-releasing hormone (GnRH) agonist triptorelin, administered in the luteal phase of ICSI. 180 patients The baseline characteristics of the two groups, especially age, duration of infertility, duration and dosage of hormonal stimulation, number of retrieved oocytes and transferred embryos, were not statistically different. 10.000IU hCG trigger	Study group n=90 single dose of triptorelin 0.1mg (Decapeptyl;) subcutaneously on day 3 after embryo transfer. Control group n=90 received placebo.	CPR	**GnRH agonist vs placebo** clinical pregnancy rate (25.5% vs. 10.0%; p=0.015	The results of this study showed a beneficial effect of GnRH agonist administration as luteal phase support on pregnancy outcomes in ART as in previous studies, but more studies investigating the optimal dose and exact mechanism of the beneficial effect of a GnRH agonist are needed.	

Zafardoust, S, Jeddi-Tehrani, M, Akhondi, Mm, Sadeghi, Mr, Kamali, K, Mokhtar, S, Badehnoosh, B, Arjmand-Teymouri, F, Fatemi, F and Mohammadzadeh, A. J Reprod Infertil. 2015; 16 (2): 96-101. (25927026)	RCT	This blind randomized controlled study evaluates the effect of GnRH agonist administration on ICSI outcome in antagonist ovarian stimulation protocol in women with 2 or more previous IVF/ICSI-ET failures. N=83 The study and control groups did not differ statistically significally. hCG 10.000IU trigger	Study group received single dose GnRH agonist (0.1 mg of Decapeptil) 6 days after OPU. N= 43 Control group did not receive anything. N = 40	clinical pregnancy rates	There was a significantly higher rate clinical pregnancy (27.9% (12/43 vs. 10% (4/40), OR=3.4, 95%CI, 1.01 to 11.9) in the GnRH agonist group.	One dose of Decapeptil 6 days after OR in women with previous history of 2 or more IVF/ICSI failures with good embryo quality, led to a significant improvement in implantation and pregnancy rates in ICSI cycles following ovarian stimulation with GnRH antagonist protocol.	small sample size.

16.5.2 REPEATED GNRH AGONIST

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
van der Linden, M., Buckingham, K., Farquhar, C., Kremer, J. A. and Metwally, M. Cochrane Database Syst Rev. 2015; (7): Cd009154. (26148507)	SR	9 studies 5 single dose 1536 women (control 748 vs 788 study) , 5 multiple dose 1325 (control 637 vs 688) (randomization?) Cochrane Database Syst Rev	1 Decapeptyl daily 14 days from ET 2. GnRHa daily 12 days from ET 3. Triptorelin 3 x from D 6	LBR/OBR higher in GnRH-a. No statistically significant difference single dose vs multiple dose.	LBR. 5 RCT, OR 0.64, 95% CI 0.42-0.98, 1325 women OHSS OR 1.00, 95% CI 0.33-3.01, 300 women	Heterogenous studies and low sample size.	GRADE evidence profile
Bar Hava, I., Blueshtein, M., Ganer Herman, H., Omer, Y. and Ben David, G. Fertil Steril. 2017; 107 (1): 130-135.e1. (28228316)	CS	Efficacy of repeated GnRHa as sole LPS after IVF / ICSI. A retrospective cohort study. 2529 cycles from 1479 women. The women in GnRHa were younger and had less IVF cycles, BMI and live childen did not differ. rhCG trigger	Study group received intranasal GnRH-a (nafareline 200 ugx2) as LPS for 2 weeks n=1436 The control group received vaginal P either Endometrin 200 mgx2 or Crinone 90 mg x1	PR, CPR, LB, miscarriage rate.	**GnRH agonist vs Progesterone** Positive b-hCG, n (%) 401 (27.9) vs 217 (19.8) p<.001 Chemical pregnancy 51/401 (12.7) vs 32/217 (14.7) P= .48 Live birth 254/401 (63.3) vs 108/217 (49.7) P=.001 The outcome was also better in older women in the GnRHa group.	Daily repeated intranasal GnRHa used as sole LPS after IVF/ICSI resulted in higher live birth rate than traditional progesterone. These findings should be investigated in prospective randomized study.	

16.6 LH SUPPLEMENTATION

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Papanikolaou, E. G., Verpoest, W., Fatemi, H., Tarlatzis, B., Devroey, P. and Tournaye, H. Fertil Steril. 2011; 95 (3): 1174-7. (20979997)	RCT	Addition of LH in GnRHa triggered cycles to improve PR. Pilot study. 1 hCG trigger 17 2 GnRHa trigger + LH 18	250 ug Ovitrelle + 600 mg micronized P Triptorelin 0,2 mg + 600 mg micronized P + 300 IU LH every second day after triggering until 10 days after OP	rate of OHSS. bichemical pregnancy in LH, delivery rates.	**Progesterone+LH vs progesterone** LBR 22.2% (4/18) vs. 23.5% (4/17) Number of oocytes retrieved 11.7±1.9 vs. 13.8±1.8	The role of LH support in LPS has to still be investigated. No conclusions can be drawn from stis study.	A pilot study, 17 and 18 patients in both arms, randomized controlled trial. Nurse randomized and doctor found out on day of trigger. Data poor.

PART E: Prevention of OHSS

17. GnRH agonist triggering

KEY QUESTION: WHICH GNRH AGONIST MEDICATION AS A METHOD OF TRIGGERING WILL ADD TO THE PREVENTION OF THE OVARIAN HYPERSTIMULATION SYNDROME ALSO WITH REGARDS TO OVERALL EFFICACY

P	I	C	O
Women undergoing IVF/ICSI	GnRH agonist trigger	- hCG, 5.000 - hCG, 10.000 with freeze all embryo's - Coasting with hCG 10.000 - Coasting with hCG 5.000 - hCG with Cabergoline - hCG with I.V. Albumen - hCG trigger with Freeze all - AGO trigger with freeze all	Efficacy: - Cumulative (total) pregnancy rate /started cycle - Live birth rate/started cycle - Clinical pregnancy rate/ongoing pregnancy rate - Embryo utilization rate/frozen oocytes - Oocyte recovery rate (yield) Safety - Prevention of OHSS - Bleeding - Infection - Torsion - Long-term effect on maternal/child health Patient-related outcomes - Compliance - Drop-out rates - Patient burden - QoL - Patient preferences

Papers selected for this question that were already included in the evidence table of question 17	Type
Youssef, M. A., Van der Veen, F., Al-Inany, H. G., Mochtar, M. H., Griesinger, G., Nagi Mohesen, M., Aboulfoutouh, I. and van Wely, M. Cochrane Database Syst Rev. 2014; (10): Cd008046. (25358904)	SR
Humaidan, P., Polyzos, N. P., Alsbjerg, B., Erb, K., Mikkelsen, A. L., Elbaek, H. O., Papanikolaou, E. G. and Andersen, C. Y Hum Reprod. 2013; 28 (9): 2511-21. (23753114)	RCT

17.1 GnRH agonist trigger vs hCG trigger in (predicted) high responders

hCG vs GnRH agonist trigger in women at risk of OHSS without adjusted LPS

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Youssef, M. A., Van der Veen, F., Al-Inany, H. G., Mochtar, M. H., Griesinger, G., Nagi Mohesen, M., Aboulfoutouh, I., van Wely, M. Cochrane Database Syst Rev 2014; 10: Cd008046 (25358904)	SR			OHSS	OHSS (3 RCT, OR 0.06, 95%CI 0.01-0.34, 212 women)		Only included for OHSS No subgroup analysis for pregnancy outcomes
Babayof, R., Margalioth, E. J., Huleihel, M., Amash, A., Zylber-Haran, E., Gal, M., Brooks, B., Mimoni, T., Eldar-Geva, T. Hum Reprod 2006; 21(5): 1260-5 (16439507)	RCT	28 PCO women Patients with serum E2 concentration >17 000 pmol/l were excluded Groups were comparable at baseline	GnRH antagonist protocol (0.25mg) When at least 3 follicles reached 17 mm in diameter, rHCG trigger (Ovitrelle 250 µg) n=13 GnRH agonist trigger (Decapeptyl 0.2 mg). N=15	Number of oocytes retrieved Moderate-to-severe OHSS	**GnRH agonist vs hCG** No of oocytes retrieved 19.8 ± 2.5 vs 19.5 ± 1.9, NS OHSS 0/15 vs. 4/13, p<0.05 LBR 1/15 Vs. 2/13		

Engmann, L., DiLuigi, A., Schmidt, D., Nulsen, J., Maier, D., Benadiva, C. Fertil Steril 2008; 89(1):84-91 (17462639)	RCT	65 women Inclusion criteria: age 20–39 years at the time of screening, normal early follicular phase serum FSH concentration (%10.0 IU/L), and undergoing their first cycle of IVF with either PCOS or PCOM or undergoing a subsequent cycle with a history of high response in a previous IVF cycle. Groups were comparable at baseline	Long GnRH agonist protocol + GnRH antagonist Control group: hCG 3300-10.000 IU study group GnRH agonist (leuprolide 1mg)	OHSS Number of oocytes retrieved Ongoing pregnancy rate	GnRHa vs hCG OHSS Any form: 0% vs. 31% Moderate: 0 vs. 4/32 Severe: 0 vs. 1/32 Oocytes retrieved 20.2±9.9 18.8±10.4, NS Ongoing PR 16/30 (53.3) 14/29 (48.3), NS		
Humaidan, P., Polyzos, N. P., Alsbjerg, B., Erb, K., Mikkelsen, A. L., Elbaek, H. O., Papanikolaou, E. G. and Andersen, C. Y Hum Reprod. 2013; 28 (9): 2511-21. (23753114)	RCT	118 patients at risk of OHSS Group A: 60 women Group B: 58 women At risk of OHSS: >25 follicles ≥11 mm on day of trigger	Group A: 0.5 mg Buserelin with 1.500 hCG on day FA Group B: 5.000 hCG. Study duration 2 years, one cycle.	Outcome OHSS (moderate and severe, Navot) Ongoing Pregnancy rate	Ongoing Pregnancy rate Ago: 17/60: 28.3% hCG: 15/58: 25.9% RR: 1.09 (0.60-1.98) OHSS Ago: 0/60: 0% hCG: 2/58: 3.4 % RR: 0.24	GnRHa triggering followed by supplementation with one bolus of 1.500 IU hCG appears to reduce the OHSS incidence in the group at risk of OHSS when an upper limit of 25 follicles is used as a cut-off. Above this limit, to completely eliminate OHSS we recommend either an intensive luteal phase support strategy with E2 and progesterone	Fulfills meaning of Q12 GROUPS SIZES may limit final conclusion on equivalence of efficacy, as well as difference in Safety.

GnRH AGONIST TRIGGER FRESH TRANSFER VS FREEZE-ALL

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Aflatoonian A, Mansoori-Torshizi M, Farid Mojtahedi M, Aflatoonian B? Khalili MA, Amir-Arjmand MH, Soleimani M, Aflatoonian N, Oskouian H, Tabibnejad N, Humaidan P. Int J Reprod Biomed (Yazd). 2018;16(1):9-18. (29675483)	RCT	280 women at risk of OHSS 20-40y number of 14-25 follicles ≥12 mm on the day of trigger and a body mass index >18 and <35 kg/m2	GnRH antagonist+GnRHa (0.2mg) +freeze-all N=121 GnRH antagonist+GnRHa (0.2mg) +fresh transfer LPS: 1500IU hCG+ 2x400mg vaginal P N=119	CPR LBR OHSS	**FET vs fresh** **CPR** (ITT): 32.2% (39/121) vs 34.5% (41/119); OR 0.90 (0.52-1.54), NS **Ongoing PR** (ITT): 27.3% (33/121) vs 29.4% (35/119); OR 0.90 (0.51-1.57), NS **LBR** (ITT): 27.3% (33/121) vs 26.9% (32/119); OR 1.02 (0.57-1.80), NS **Mild OHSS**: 29.8% (36/212) vs 37% (44/119) **Moderate OHSS**: 5.8% (7/121) vs 5.9% (7/119), NS No cases of severe OHSS	in this study the clinical outcomes were similar between fresh and frozen transfer after GnRHa trigger, suggesting that GnRHa trigger followed by fresh transfer with modified luteal phase support in terms of a small hCG bolus is a good strategy to secure good live birth rates and a low risk of clinically relevant OHSS in IVF patients at risk of OHSS development.	
Karacan M, Erdem E, Usta A, Arvas A, Cebi Z, Camlibel T. Saudi Med J. 2017;38(6):586-591. (28578436)	CS	Retrospective cohort study High responder patients 122 women ≥15 follicles ≥ 12 mm and/or serum estradiol levels ≥3500 pg/ml on the day of GnRH agonist trigger Groups comparable at baseline	1: GnRHa trigger+hCG at oocyte retrieval + fresh transfer and standard LPS (50mg im P) N=74 2: GnRHa trigger+freeze-all LPS: 50mg im P+ 4mg E2 N=48	LBR Moderate/severe OHSS CPR	**Fresh vs FET** LBR: 40.5% (30/74) vs 41.7% (20/48), NS CPR: 45.9% (34/74) vs 43.8% (21/48), NS Severe/moderate OHSS: 2.7% (2/74) vs 0% (0/48), NS	the outcome of ICSI cycles with GnRH agonist triggering and concomitant use of 1500 IU of hCG immediately after oocyte retrieval is similar to that obtained with the freeze-all approach and FET in subsequent cycles in high responders.	

17.2 GnRH agonist vs hCG non-10.000 IU trigger

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Humaidan, P., Polyzos, N. P., Alsbjerg, B., Erb, K., Mikkelsen, A. L., Elbaek, H. O., Papanikolaou, E. G. and Andersen, C. Y. Hum Reprod. 2013; 28 (9): 2511-21. (23753114)	RCT	118 patients at risk of OHSS Group A: 60 women Group B: 58 women At risk of OHSS: >25 follicles ≥11 mm on day of trigger	Group A: 0.5 mg Buserelin with 1.500 hCG on day FA Group B: 5.000 hCG. Study duration 2 years, one cycle.	OHSS (moderate and severe, Navot) Ongoing Preg	Ong Preg Ago: 17/60: 28.3% hCG: 15/58: 25.9% RR: 1.09 (0.60-1.98) OHSS Ago: 0/60: 0% hCG: 2/58: 3.4 % RR: 0.24	GnRHa triggering followed by supplementation with one bolus of 1.500 IU hCG appears to reduce the OHSS incidence in the group at risk of OHSS when an upper limit of 25 follicles is used as a cut-off. Above this limit, to completely eliminate OHSS we recommend either an intensive luteal phase support strategy with E2 and progesterone	Fulfills meaning of Q12 GROUPS SIZES may limit final conclusion on equivalence of efficacy, as well as difference in Safety.

17.3 GnRH AGONIST TRIGGER + FREEZE-ALL VS hCG TRIGGER+FREEZE-ALL

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Borges, E., Jr., Braga, D. P., Setti, A. S., Vingris, L. S., Figueira, R. C., Iaconelli, A., Jr. JBRA Assist Reprod 2016; 20(1):8-12 (27203299)	CS	Case-control study 248 women at risk of OHSS Groups were comparable at baseline	GnRH antagonist protocol GnRHa trigger + freeze-all hCG trigger + freeze-all	No of oocytes retrieved Clinical pregnancy rate Cumulative pregnancy rate	**hCG vs GnRHa** retrieved oocytes 25.3 ± 9,6 vs. 30.8 ± 11.3, p<0.05 CPR 44.8% 50.0%, NS Cumulative PR 53.0% 59.5%, NS		
Tannus, S., Turki, R., Cohen, Y., Son, W. Y., Shavit, T., Dahan, M. H. Fertil Steril 2017; 107(6):1323-1328 (28501366)	CS	Retrospective study 272 hyper responders (542 cycles) Groups were comparable at baseline	GnRH antagonist protocol GnRHa trigger + freeze-all (buserelin 1 mg) ==168 (370 cycles) hCG trigger + freeze-all (hCG 5.000 or 10.000IU or 250µg rhCG) N=104 (172 cycles)	Cumulative live birth rate Number of oocytes retrieved	**GnRH a vs. hCG** Cumulative LBR 48.15% vs. 48.08%, NS Number of oocytes retrieved 22 (17–30) 21 (14–26), p<0.05		

17.4 GnRH AGONIST TRIGGER VS COASTING+hCG TRIGGER

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Herrero L, Pareja S, Losada C, Cobo AC, Pellicer A, Garcia-Velasco JA. Fertil Steril. 2011 Mar 1;95(3):1137-40. (21047635)	CS	Retrospective study 248 women at risk of OHSS Groups were comparable at baseline	GnRH antagonist+GnRHa trigger (0.2mg) Freeze-all N=96 Long GnRHa + Coasting hCG trigger (250µg) N=152	Cycle cancellation for OHSS risk CPR	**GnRHa trigger vs Coasting** Cycle cancellation: 8.3% (8/96) vs 19.7% (30/152) CPR: 50% (44/88) vs 29.5% (36/122), p<0.05	we confirm the usefulness of triggering with GnRH agonists to avoid OHSS in patients being treated with GnRH antagonist.	
DiLuigi AJ, Engmann L, Schmidt DW, Maier DB, Nulsen JC, Benadiva CA. Fertil Steril. 2010 Aug;94(3):1111-4 (20074722)	CS	Retrospective study 94 women at risk of OHSS	GnRH antagonist+GnRHa trigger LPS: P im (50mg) + E2 3x0.1mg N=61 GnRHa+coasting hCG trigger (3300-5000IU) LPS: P im (50mg) N=33	OHSS CPR Ongoing PR Cycle cancellation for OHSS risk	**Coasting vs GnRHa trigger** Cycle cancellation: 8/33 vs 0/61 OHSS: 0/33 vs 0/61 CPR: 27.2% vs 52.5% Ongoing PR: 24.4% vs 49.2%	Coasting is a valuable strategy for OHSS prevention but has recognized limitations, because it does not eliminate OHSS and may result in compromised cycle outcomes	

17.5 GnRH AGONIST TRIGGER VS hCG TRIGGER+CABERGOLINE/ALBUMIN

No relevant studies were identified

18. Freeze-all

KEY QUESTION: IS THE FREEZE-ALL PROTOCOL MEANINGFUL IN THE PREVENTION OF OVARIAN HYPER-STIMULATION SYNDROME ALSO WITH REGARD TO EFFICACY?

P	I	C	O
Women undergoing IVF/ICSI with excessive oocyte yield (>15 or 17 follicles larger than 11 mm)	Freeze-all protocol	Fresh transfer Other preventive measures (coasting, dopamine, antagonist initiation)	Efficacy: - cumulative LBR/cycle - Cumulative ongoing pregnancy rate /started cycle (fresh + frozen) - Clinical pregnancy rate/started cycle - Nr of Oocytes/ nr of MII oocyte recovery rate (yield) - number of embryo's (fresh+frozen) Safety - incidence of different grades of OHSS - grade of OHSS - incidence of cycle cancellation for hyper-response (predefined) - Bleeding - Infection - Torsion - Long-term effect on maternal/child health - other adverse events (treatment related) Patient-related outcomes - Compliance - Drop-out rates - Patient burden - QoL - Patient preferences

Reference	Study type	PATIENTS No. Of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
D'Angelo, A. and Amso, N. Cochrane Database Syst Rev. 2007; (3): Cd002806. (17636707)	SR	Only study by Shaker	See Shaker study details	OHSS mod sev CP	CPR: OR 0.06 (0.00 to 1.17) Mod Sev OHSS: OR 5.33 (0.51 to 56.24)	Insufficient evidence to support routine cryopreservation. Insufficient evidence for the relative merits of intra-venous albumin versus cryopreservation.	GRADE evidence profile Freeze-all vs albumin LOW qual
Wong, K.M., van Wely, M., Mol, F., Repping, S., Mastenbroek, S. Cochrane Database Syst Rev. 2017; Cd011184. (28349510)	SR	1892 participants in 4 RCTs, at risk for OHSS according to various criteria sets	Fresh ET versus Freeze all	- LBR cumulative for all embryo stages at transfer - OHHS rate per cycle	LBR: OR 1.09 (0.91-1.31) OPR: OR 1.05 (0.64-1.73) OHSS: OR 0.24 (0.15-0.38)	No difference in LBR, OPR, multiple pregnancy rate. Lower incidence of OHSS and miscarriage.	GRADE evidence profile Freeze-all vs Fresh MODERATE qual
Shi, Y., Sun, Y., Hao, C., Zhang, H., Wei, D., Zhang, Y., Zhu, Y., Deng, X., Qi, X., Li, H., Ma, X., Ren, H., Wang, Y., Zhang, D., Wang, B., Liu, F., Wu, Q., Wang, Z., Bai, H., Li, Y., Zhou, Y., Sun, M., Liu, H., Li, J., Zhang, L., Chen, X., Zhang, S., Sun, X., Legro, R. S. and Chen, Z. J. N Engl J Med. 2018; 378 (2): 126-136. (29320646)	RCT	2157 women Groups comparable at baseline	Fresh transfer, n=1080 Frozen transfer, n=1077	Live birth rate Moderate to severe OHSS	**Frozen vs fresh** LBR: 48.7% (525/1077) vs. 50.2% (542/1080); Rate Ratio 0.97, 95% CI 0.89-1.06) OHSS: 0.6% (7/1077) vs. 2.0% (22/1080); Rate Ratio 0.32, 95% CI 0.14-0.74)		Include

Vuong, L. N., Dang, V. Q., Ho, T. M., Huynh, B. G., Ha, D. T., Pham, T. D., Nguyen, L. K., Norman, R. J. and Mol, B. W. IVF New England journal of medicine. 2018; 378 (2): 137-147. (29320655)	RCT	782 women without PCOS First or second IVF cycle Groups comparable at baseline	Fresh transfer, n=391 Frozen transfer, n=391	Live birth rate Moderate to severe OHSS	**Frozen vs fresh** LBR: 33.8% (132/391) vs. 31.5% (123/391); RR 1.07, 95% CI 0.88-1.31 OHSS 0.8% (3/391) vs. 1% (4/391); RR 0.75 (0.17-3.33)	Results reflect clinical practice in Asia Results can be influence by the method of freezing	Include

Abbreviations

AFC	Antral follicle count
AMH	Anti-Müllerian hormone
ART	Assisted reproductive technology
BMI	Body mass index
CC	Clomiphene citrate
CI	Confidence interval
COC	Cumulus-oocyte complex
COCP	Combined oral contraceptive pill
DHEA	Dehydroepiandrosterone
Duostim	Double stimulation, ovarian stimulation during the follicular and luteal phase of the same cycle
EFORT	Exogenous follicle stimulating hormone ovarian reserve test
EMT	Endometrial thickness
FSH	Follicle stimulating hormone
GDG	Guideline development group
GH	Growth hormone
GnRH	Gonadotropin-releasing hormone
GPP	Good practice point
hCG	Human chorionic gonadotrophin
hMG	Human menopausal gonadotropin
hp-FSH	Highly purified follicle stimulating hormone
ICSI	Intracytoplasmic sperm injection
IPD	Individual patient data
IU	International unit
IUI	Intra-uterine insemination
IVF	In vitro fertilization
LBR	Live birth rate
LH	Luteinizing hormone
LPS	Luteal phase support
LR	Logistic regression
MD	Mean difference
MNC	Modified natural cycle
MPA	Medroxy progesterone acetate
OHSS	Ovarian hyperstimulation syndrome
OPU	Oocyte pick-up
OR	Odds ratio
OS	Ovarian stimulation
PCOM	Polycystic ovary morphology
PCOS	Polycystic ovary syndrome
p-FSH	Purified follicle stimulating hormone
pg	Pico gram
POI	Premature ovarian insufficiency
PR	Pregnancy rate
RCT	Randomized controlled trial
rFSH	Recombinant follicle stimulating hormone
rLH	Recombinant luteinizing hormone
ROC-AUC	Receiver operating characteristic – area under the curve
RR	Relative risk/risk ratio
SMD	Standardized mean difference