



Annex 6: Literature study report

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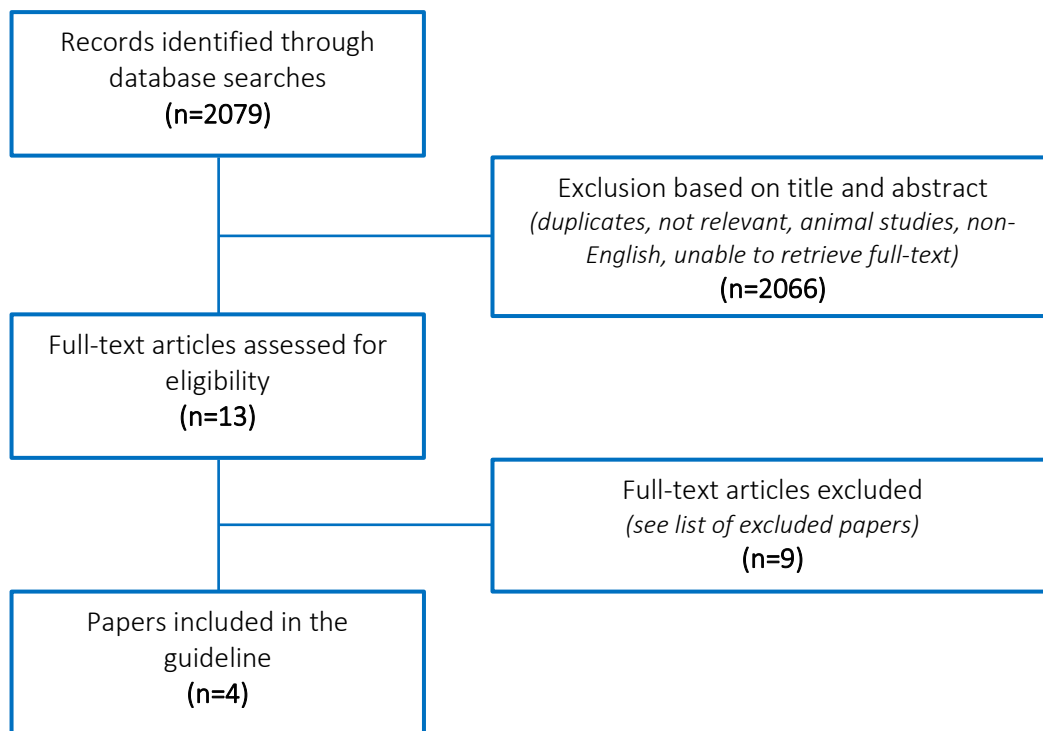


II. Diagnosis

II.1 Confirmation of ovulation

PICO QUESTION: WHICH IS THE RELIABILITY AND CONVENIENCE OF METHODS TO CONFIRM REGULAR OVULATION?

Flowchart



List of excluded papers

	Exclusion criterion
Broad, A., Biswakarma, R. and Harper, J. C. A survey of women's experiences of using period tracker applications: Attitudes, ovulation prediction and how the accuracy of the app in predicting period start dates affects their feelings and behaviours. <i>Womens Health (Lond)</i> . 2022; 18 17455057221095246.	Does not adequately assess the outcome of interest
Graham, F. M., Gosling, L. and France, J. T. An evaluation of teaching cervical mucus symptoms to ovulating infertile women. <i>Aust N Z J Obstet Gynaecol</i> . 1983; 23 (4): 226-30.	Descriptive study only
Lemay, A., Bastide, A., Lambert, R. and Rioux, J. E. Prediction of human ovulation by rapid luteinizing hormone (LH) radioimmunoassay and ovarian ultrasonography. <i>Fertil Steril</i> . 1982; 38 (2): 194-201.	Descriptive study only
Nulsen, J., Wheeler, C., Ausmanas, M. and Blasco, L. Cervical mucus changes in relationship to urinary luteinizing hormone. <i>Fertil Steril</i> . 1987; 48 (5): 783-6.	Non-comparative analysis
Quagliarello, J. and Arny, M. Inaccuracy of basal body temperature charts in predicting urinary luteinizing hormone surges. <i>Fertil Steril</i> . 1986; 45 (3): 334-7.	Descriptive analysis only



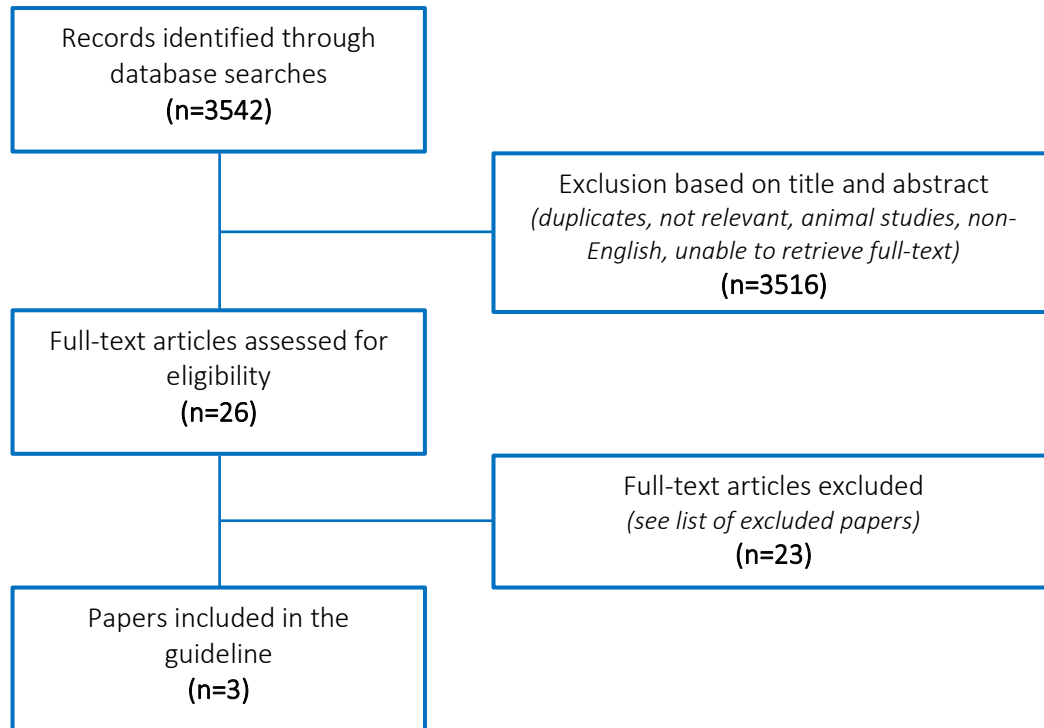
<p>Pillet, M. C., Wu, T. F., Adamson, G. D., Subak, L. L. and Lamb, E. J. Improved prediction of postovulatory day using temperature recording, endometrial biopsy, and serum progesterone. <i>Fertil Steril.</i> 1990; 53 (4): 614-9.</p>	<p>Objective was to determine next menses</p>
<p>Rollason, J. C., Outtrim, J. G. and Mathur, R. S. A pilot study comparing the DuoFertility® monitor with ultrasound in infertile women. <i>Int J Womens Health.</i> 2014; 6 657-62.</p>	<p>Descriptive analysis of a no longer existant technology</p>
<p>Sasaki, R. S., Approbato, M. S., Maia, M. C., Fleury, E. A., Giviziez, C. R. and Zanluchi, N. Patients' auto report of regularity of their menstrual cycles. Medical history is very reliable to predict ovulation. A cross-sectional study. <i>JBRA Assist Reprod.</i> 2016; 20 (3): 118-22.</p>	<p>Adequate confirmation of ovulation was lacking</p>
<p>Varma, T. R., Patel, R. H. and Everard, D. Determination with Hi-Gonavis of luteinizing hormone levels in urine compared with those in plasma. <i>Br J Obstet Gynaecol.</i> 1982; 89 (1): 87-90.</p>	<p>Non-comparative analysis</p>



II.2 Oocyte/corpus luteum quality

PICO QUESTION: WHAT IS THE RELIABILITY OF PARAMETERS DETECTING GOOD OOCYTE/ CORPUS LUTEUM QUALITY?

Flowchart



List of excluded papers

Reference	Exclusion criterion
Bassil, R., Casper, R., Samara, N., Hsieh, T. B., Barzilay, E., Orvieto, R. and Haas, J. Does the endometrial receptivity array really provide personalized embryo transfer? <i>J Assist Reprod Genet.</i> 2018; 35 (7): 1301-1305.	Women undergoing frozen blastocyst transfers, comparing agreement between endometrial phase examined by ERA or Noyes criteria. Not about corpus luteum function.
Bongso, A., Chye, N. S., Ratnam, S., Sathananthan, H. and Wong, P. C. Chromosome anomalies in human oocytes failing to fertilize after insemination in vitro. <i>Hum Reprod.</i> 1988; 3 (5): 645-9.	No comparison between age and chromosome status as determinants of oocyte quality.
Bonhoff, A., Johannisson, E. and Bohnet, H. G. Morphometric analysis of the endometrium of infertile patients in relation to peripheral hormone levels. <i>Fertil Steril.</i> 1990; 54 (1): 84-9.	No direct information on corpus luteum function.
Gerhard, I., Bechthold, E., Eggert-Kruse, W., Heberling, D. and Runnebaum, B. Value of endometrial biopsies and serum hormone determinations in women with infertility. <i>Hum Reprod.</i> 1990; 5 (8): 906-14.	Many factors investigated.
Haddad Filho, J., Cedenho, A. P. and de Freitas, V. Correlation between endometrial dating of luteal phase days 6 and 10 of the same menstrual cycle. <i>Sao Paulo Med J.</i> 1998; 116 (3): 1734-7.	Women with low P4 excluded and no direct analysis with P4
Hansen, K. R., Eisenberg, E., Baker, V., Hill, M. J., Chen, S., Talken, S., Diamond, M. P., Legro, R. S., Coutifaris, C., Alvero, R., Robinson, R. D., Casson, P., Christman, G. M., Santoro, N., Zhang, H. and Wild, R. A.	Progesterone measured in stimulated cycles.



Midluteal Progesterone: A Marker of Treatment Outcomes in Couples With Unexplained Infertility. <i>J Clin Endocrinol Metab.</i> 2018; 103 (7): 2743-2751.	
Kaye, L., Griffin, D., Thorne, J., Neuber, E., Nulsen, J., Benadiva, C. and Engmann, L. Independent serum markers of corpora lutea function after gonadotropin-releasing hormone agonist trigger and adjuvant low dose human chorionic gonadotropin in in vitro fertilization. <i>Fertil Steril.</i> 2019; 112 (3): 534-544.	Progesterone measured in stimulated cycles.
Kusuhara, K. Clinical importance of endometrial histology and progesterone level assessment in luteal-phase defect. <i>Horm Res.</i> 1992; 37 Suppl 1 53-8.	Endometrial biopsy, not serum progesterone.
Laatikainen, T., Andersson, B., Kärkkäinen, J. and Wahlström, T. Progesterin receptor levels in endometria with delayed or incomplete secretory changes. <i>Obstet Gynecol.</i> 1983; 62 (5): 592-5.	Endometrial biopsy
Leiva, R., Bouchard, T., Boehringer, H., Abulla, S. and Ecochard, R. Random serum progesterone threshold to confirm ovulation. <i>Steroids.</i> 2015; 101 125-9.	Progesterone to confirm ovulation
Lim, A. S. and Tsakok, M. F. Age-related decline in fertility: a link to degenerative oocytes? <i>Fertil Steril.</i> 1997; 68 (2): 265-71.	No comparison between age and chromosome status as determinants of oocyte quality.
Ma, S., Kalousek, D. K., Yuen, B. H., Gomel, V., Katagiri, S. and Moon, Y. S. Chromosome investigation in in vitro fertilization failure. <i>J Assist Reprod Genet.</i> 1994; 11 (9): 445-51.	No comparison between age and chromosome status as determinants of oocyte quality.
Macas, E., Floersheim, Y., Hotz, E., Imthurn, B., Keller, P. J. and Walt, H. Abnormal chromosomal arrangements in human oocytes. <i>Hum Reprod.</i> 1990; 5 (6): 703-7.	No comparison between age and chromosome status as determinants of oocyte quality.
Munné, S., Dailey, T., Sultan, K. M., Grifo, J. and Cohen, J. The use of first polar bodies for preimplantation diagnosis of aneuploidy. <i>Hum Reprod.</i> 1995; 10 (4): 1014-20.	No comparison between age and chromosome status as determinants of oocyte quality.
Pellestor, F., Andréo, B., Arnal, F., Humeau, C. and Demaille, J. Maternal aging and chromosomal abnormalities: new data drawn from in vitro unfertilized human oocytes. <i>Hum Genet.</i> 2003; 112 (2): 195-203.	No comparison between age and chromosome status as determinants of oocyte quality.
Perez, R. J., Plurad, A. V. and Palladino, V. S. The relationship of the corpus luteum and the endometrium in infertile patients. <i>Fertil Steril.</i> 1981; 35 (4): 423-7.	Correlation between progesterone and ovulation
Petsos, P., Mamtora, H., Ratcliffe, W. A. and Anderson, D. C. Inadequate luteal phase usually indicates ovulatory dysfunction: observations from serial hormone and ultrasound monitoring of 115 cycles. <i>Gynecol Endocrinol.</i> 1987; 1 (1): 37-45.	Correlation between progesterone and ovulation
Portuondo, J. A., Agustin, A., Herran, C. and Echanojauregui, A. D. The corpus luteum in infertile patients found during laparoscopy. <i>Fertil Steril.</i> 1981; 36 (1): 37-40.	compares whether visualization of ovulatory stigma during laparoscopy is correlated with observation of secretory endometrium in EMB
Shangold, M., Berkeley, A. and Gray, J. Both midluteal serum progesterone levels and late luteal endometrial histology should be assessed in all infertile women. <i>Fertil Steril.</i> 1983; 40 (5): 627-30.	Correlation between serum P and endometrial histology
Staessen, C., Platteau, P., Van Assche, E., Michiels, A., Tournaye, H., Camus, M., Devroey, P., Liebaers, I. and Van Steirteghem, A. Comparison of blastocyst transfer with or without preimplantation genetic diagnosis for aneuploidy screening in couples with advanced maternal age: a prospective randomized controlled trial. <i>Human reproduction (Oxford, England).</i> 2004; 19 (12): 2849-2858.	No comparison between age and chromosome status as determinants of oocyte quality.
Sterzik, K., Abt, M., Grab, D., Schneider, V. and Strehler, E. Predicting the histologic dating of an endometrial biopsy specimen with the use of Doppler ultrasonography and hormone measurements in patients undergoing spontaneous ovulatory cycles. <i>Fertil Steril.</i> 2000; 73 (1): 94-8.	No direct information on corpus luteum function, women with in and out of phase endometrium in the luteal phase of a



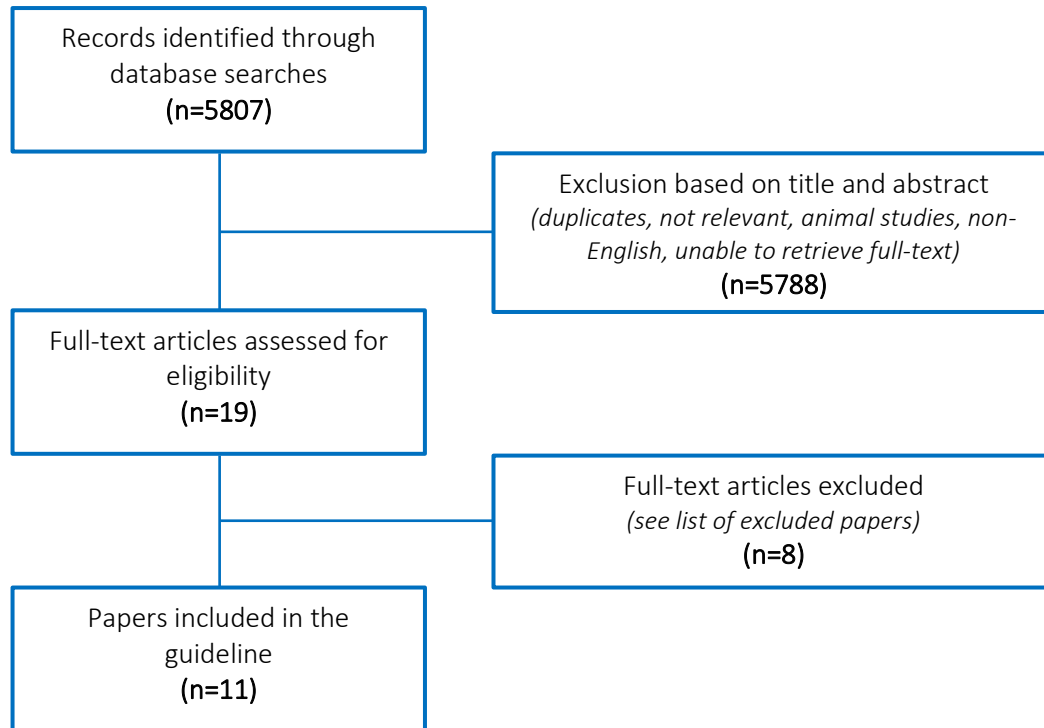
	spontaneous cycle have similar P4 levels.
Vialard, F., Gomes, D. M., Hammoud, I., Bergere, M., Wainer, R., Bailly, M., Lombroso, R. and Selva, J. Stability of aneuploidy rate in polar bodies in two cohorts from the same patient. <i>Reprod Biomed Online</i> . 2008; 17 (2): 213-9.	No comparison between age and chromosome status as determinants of oocyte quality.
Wu, C. H. and Minassian, S. S. The integrated luteal progesterone: an assessment of luteal function. <i>Fertil Steril</i> . 1987; 48 (6): 937-40.	Relies on endometrial dating by histology



II.3 Ovarian reserve

PICO QUESTION: SHOULD ONE OR MORE TESTS OF OVARIAN RESERVE BE INCLUDED IN THE DIAGNOSTIC WORK-UP?

Flowchart



List of excluded papers

Reference	Exclusion criterion
Erdem, M., Erdem, A., Guler, I. and Atmaca, S. Role of antral follicle count in controlled ovarian hyperstimulation and intrauterine insemination cycles in patients with unexplained subfertility. <i>Fertil Steril</i> . 2008; 90 (2): 360-6.	Difference between AFC in women with UI who got pregnant with IUI and who did not
Leach, R. E., Moghissi, K. S., Randolph, J. F., Reame, N. E., Blacker, C. M., Ginsburg, K. A. and Diamond, M. P. Intensive hormone monitoring in women with unexplained infertility: evidence for subtle abnormalities suggestive of diminished ovarian reserve. <i>Fertil Steril</i> . 1997; 68 (3): 413-20.	Very small sample, inappropriate statistics.
Moro, F., Tropea, A., Scarinci, E., Leoncini, E., Boccia, S., Federico, A., Alesiani, O., Lanzone, A. and Apa, R. Anti-Müllerian hormone concentrations and antral follicle counts for the prediction of pregnancy outcomes after intrauterine insemination. <i>Int J Gynaecol Obstet</i> . 2016; 133 (1): 64-8.	Comparing or markers between women with UI who got an ongoing pregnancy and did not
Ng, E. H., Yeung, W. S. and Ho, P. C. The significance of antral follicle count in controlled ovarian stimulation and intrauterine insemination. <i>J Assist Reprod Genet</i> . 2005; 22 (9-10): 323-8.	Comparing or markers between women with UI who got an ongoing pregnancy and did not
Steiner, A. Z., Herring, A. H., Kesner, J. S., Meadows, J. W., Stanczyk, F. Z., Hoberman, S. and Baird, D. D. Antimüllerian hormone as a predictor of natural fecundability in women aged 30-42 years. <i>Obstet Gynecol</i> . 2011; 117 (4): 798-804.	Small sample, unknown fertility status, those conceived within 3 months excluded



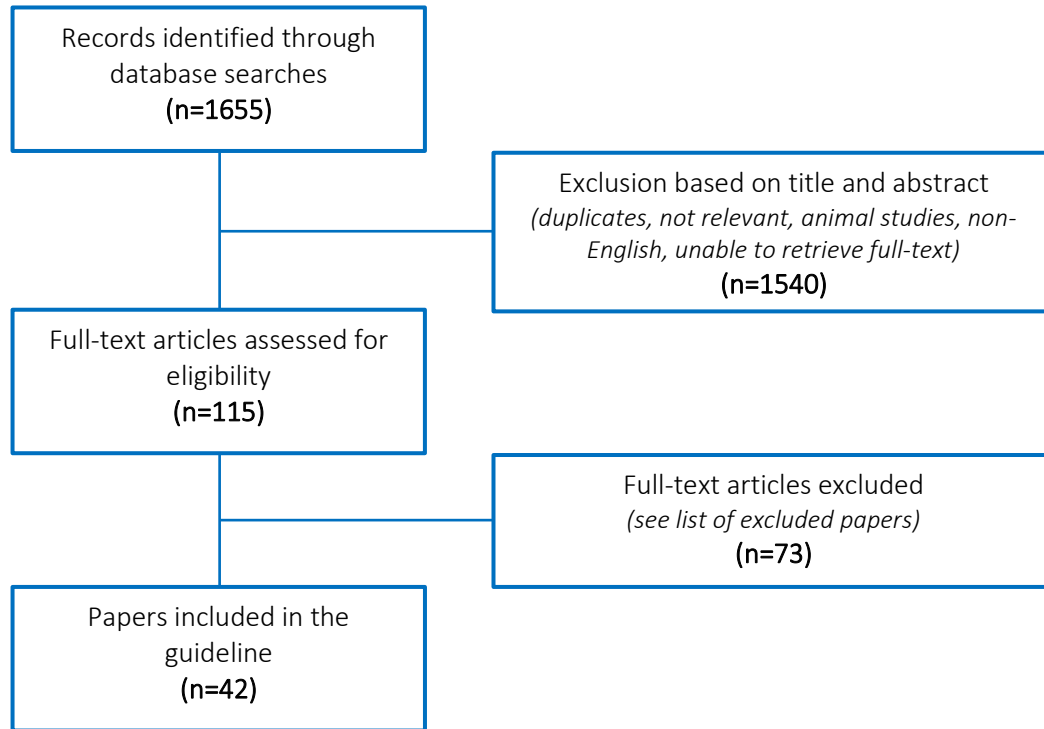
<p>van der Steeg, J. W., Steures, P., Eijkemans, M. J., Habbema, J. D., Hompes, P. G., Broekmans, F. J., Bouckaert, P. X., Bossuyt, P. M., van der Veen, F. and Mol, B. W. Predictive value and clinical impact of Basal follicle-stimulating hormone in subfertile, ovulatory women. <i>J Clin Endocrinol Metab.</i> 2007; 92 (6): 2163-8.</p>	<p>Very complicated design, difficult to draw conclusions on a general association between FSH and pregnancy.</p>
<p>Vagios, S., Hsu, J. Y., Sacha, C. R., Dimitriadis, I., Christou, G., James, K. E., Bormann, C. L. and Souter, I. Pretreatment antimüllerian hormone levels and outcomes of ovarian stimulation with gonadotropins/intrauterine insemination cycles. <i>Fertil Steril.</i> 2021; 116 (2): 422-430.</p>	<p>Not exclusively unexplained infertility</p>
<p>Yarde, F., Voorhuis, M., Dólleman, M., Knauff, E. A., Eijkemans, M. J. and Broekmans, F. J. Antimüllerian hormone as predictor of reproductive outcome in subfertile women with elevated basal follicle-stimulating hormone levels: a follow-up study. <i>Fertil Steril.</i> 2013; 100 (3): 831-8.</p>	<p>Women with FSH >12 included and underwent different treatments</p>



II.4 Tubal factor

PICO QUESTION: WHAT IS THE ACCURACY OF COMMONLY USED TESTS OF TUBAL PATENCY?

Flowchart



List of excluded papers

Reference	Exclusion criterion
Alborzi, S., Dehbashi, S. and Khodaei, R. Sonohysterosalpingographic screening for infertile patients. <i>Int J Gynaecol Obstet.</i> 2003; 82 (1): 57-62.	No raw data to calculate sensitivity, specificity, PPV, NPV
Alcázar, J. L., Martínez-Astorquiza Corral, T., Orozco, R., Domínguez-Piriz, J., Juez, L. and Errasti, T. Three-Dimensional Hysterosalpingo-Contrast-Sonography for the Assessment of Tubal Patency in Women with Infertility: A Systematic Review with Meta-Analysis. <i>Gynecol Obstet Invest.</i> 2016; 81 (4): 289-95.	More recent systematic review available.
Anestad, G., Lunde, O., Moen, M. and Dalaker, K. Infertility and chlamydial infection. <i>Fertil Steril.</i> 1987; 48 (5): 787-90.	Included in systematic review Mol et al., 1995
Bjercke, S. and Purvis, K. Characteristics of women under fertility investigation with IgA/IgG seropositivity for Chlamydia trachomatis. <i>Eur J Obstet Gynecol Reprod Biol.</i> 1993; 51 (2): 157-61.	Included in systematic review Mol et al., 1995
Chan, C. C., Ng, E. H., Tang, O. S., Chan, K. K. and Ho, P. C. Comparison of three-dimensional hysterosalpingo-contrast-sonography and diagnostic laparoscopy with chromopertubation in the assessment of tubal patency for the investigation of subfertility. <i>Acta Obstet Gynecol Scand.</i> 2005; 84 (9): 909-13.	Included in systematic review Wang et al., 2016
Cheng, Q., Wang, S. S., Zhu, X. S. and Li, F. Evaluation of Tubal Patency with Transvaginal Three-dimensional Hysterosalpingo-contrast Sonography. <i>Chin Med Sci J.</i> 2015; 30 (2): 70-5.	Included in systematic review Wang et al., 2016



Conway, D., Glazener, C. M., Caul, E. O., Hodgson, J., Hull, M. G., Clarke, S. K. and Stirrat, G. M. Chlamydial serology in fertile and infertile women. <i>Lancet</i> . 1984; 1 (8370): 191-3.	No raw data to calculate sensitivity, specificity, PPV, NPV
Coppus, S. F., Land, J. A., Opmeer, B. C., Steures, P., Eijkemans, M. J., Hompes, P. G., Bossuyt, P. M., van der Veen, F., Mol, B. W. and van der Steeg, J. W. Chlamydia trachomatis IgG seropositivity is associated with lower natural conception rates in ovulatory subfertile women without visible tubal pathology. <i>Hum Reprod</i> . 2011; 26 (11): 3061-7.	No raw data to calculate sensitivity, specificity, PPV, NPV
Czerwenka, K., Heuss, F., Hosmann, J., Manavi, M., Jelincic, D. and Kubista, E. Salpingitis caused by Chlamydia trachomatis and its significance for infertility. <i>Acta Obstet Gynecol Scand</i> . 1994; 73 (9): 711-5.	No raw data to calculate sensitivity, specificity, PPV, NPV
Darwish, A. M. and Youssef, A. A. Screening sonohysterography in infertility. <i>Gynecol Obstet Invest</i> . 1999; 48 (1): 43-7.	No raw data to calculate sensitivity, specificity, PPV, NPV
den Hartog, J. E., Lardenoije, C. M., Severens, J. L., Land, J. A., Evers, J. L. and Kessels, A. G. Screening strategies for tubal factor subfertility. <i>Hum Reprod</i> . 2008; 23 (8): 1840-8.	Included in systematic review Broeze et al., 2011
Dhaliwal, L. K., Khera, K. R., Gupta, I. and Gupta, A. N. Comparison of hysterosalpingography and laparoscopy in the evaluation of tubal factor. <i>Asia Oceania J Obstet Gynaecol</i> . 1987; 13 (1): 65-7.	very old paper, high risk of bias due to poor methodology, very high detection rate of tubal pathology and very high false-positive rate for HSG.
Dietrich, M., Suren, A., Hinney, B., Osmers, R. and Kuhn, W. Evaluation of tubal patency by hysterocontrast sonography (HyCoSy, Echovist) and its correlation with laparoscopic findings. <i>J Clin Ultrasound</i> . 1996; 24 (9): 523-7.	Included in systematic review Alcazar et al., 2020
Dijkman, A. B., Mol, B. W., van der Veen, F., Bossuyt, P. M. and Hogerzeil, H. V. Can hysterosalpingocontrast-sonography replace hysterosalpingography in the assessment of tubal subfertility? <i>Eur J Radiol</i> . 2000; 35 (1): 44-8.	Included in systematic review Alcazar et al., 2020
Duff, D. E., Fried, A. M., Wilson, E. A. and Haack, D. G. Hysterosalpingography and laparoscopy: a comparative study. <i>AJR Am J Roentgenol</i> . 1983; 141 (4): 761-3.	Inter-observer variance
El Hakim, E. A., Gordon, U. D. and Akande, V. A. The relationship between serum Chlamydia antibody levels and severity of disease in infertile women with tubal damage. <i>Arch Gynecol Obstet</i> . 2010; 281 (4): 727-33.	In the present study only women found to have tubal damage were studied, all other infertile women were excluded.
Exacoustos, C., Zupi, E., Carusotti, C., Lanzi, G., Marconi, D. and Arduini, D. Hysterosalpingo-contrast sonography compared with hysterosalpingography and laparoscopic dye perturbation to evaluate tubal patency. <i>J Am Assoc Gynecol Laparosc</i> . 2003; 10 (3): 367-72.	No raw data to calculate sensitivity, specificity, PPV, NPV
Frost, E., Collet, M., Reniers, J., Leclerc, A., Ivanoff, B. and Meheus, A. Importance of chlamydial antibodies in acute salpingitis in central Africa. <i>Genitourin Med</i> . 1987; 63 (3): 176-8.	All women had acute salpingitis.
Gao, Y. B., Yan, J. H., Yang, Y. D., Sun, J., Dong, J. Y. and Cui, G. H. Diagnostic value of transvaginal four-dimensional hysterosalpingo-contrast sonography combined with recanalization in patients with tubal infertility. <i>Niger J Clin Pract</i> . 2019; 22 (1): 46-50.	Included in systematic review Alcazar et al., 2020
Gijsen, A. P., Land, J. A., Goossens, V. J., Slobbe, M. E. and Bruggeman, C. A. Chlamydia antibody testing in screening for tubal factor subfertility: the significance of IgG antibody decline over time. <i>Hum Reprod</i> . 2002; 17 (3): 699-703.	No raw data to calculate sensitivity, specificity, PPV, NPV
Glatstein, I. Z., Sleeper, L. A., Lavy, Y., Simon, A., Adoni, A., Palti, Z., Hurwitz, A. and Laufer, N. Observer variability in the diagnosis and management of the hysterosalpingogram. <i>Fertil Steril</i> . 1997; 67 (2): 233-7.	No raw data to calculate sensitivity, specificity, PPV, NPV



Guerriero, S., Ajossa, S., Mais, V., Paoletti, A. M. and Melis, G. B. The screening of tubal abnormalities in the infertile couple. <i>J Assist Reprod Genet.</i> 1996; 13 (5): 407-12.	Included in systematic review Alcazar et al., 2020
Gump, D. W., Gibson, M. and Ashikaga, T. Evidence of prior pelvic inflammatory disease and its relationship to Chlamydia trachomatis antibody and intrauterine contraceptive device use in infertile women. <i>Am J Obstet Gynecol.</i> 1983; 146 (2): 153-9.	CAT from biopsies
Guyen, M. A., Dilek, U., Pata, O., Dilek, S. and Ciragil, P. Prevalance of Chlamydia trochomatis, Ureaplasma urealyticum and Mycoplasma hominis infections in the unexplained infertile women. <i>Arch Gynecol Obstet.</i> 2007; 276 (3): 219-23.	No raw data to calculate sensitivity, specificity, PPV, NPV
Hamilton, J. A., Larson, A. J., Lower, A. M., Hasnain, S. and Grudzinskas, J. G. Evaluation of the performance of hysterosalpingo contrast sonography in 500 consecutive, unselected, infertile women. <i>Hum Reprod.</i> 1998; 13 (6): 1519-26.	Included in systematic review Alcazar et al., 2020
He, Y., Ma, X., Xu, J., Li, S., Wu, H., Liu, Q., Kong, L., Luo, J. and Liu, H. Comparison of Assessment Methods for Fallopian Tubal Patency and Peritubal Adhesion Between Transvaginal 4-Dimensional Hysterosalpingo-Contrast Sonography and Laparoscopic Chromopertubation. <i>J Ultrasound Med.</i> 2017; 36 (3): 547-556.	Included in systematic review Alcazar et al., 2020
Henry-Suchet, J., Catalan, F., Loffredo, V., Serfaty, D., Siboulet, A., Perol, Y., Sanson, M. J., Debache, C., Pigeau, F., Coppin, R., de Brux, J. and Poynard, T. Microbiology of specimens obtained by laparoscopy from controls and from patients with pelvic inflammatory disease or infertility with tubal obstruction: Chlamydia trachomatis and Ureaplasma urealyticum. <i>Am J Obstet Gynecol.</i> 1980; 138 (7 Pt 2): 1022-5.	No raw data to calculate sensitivity, specificity, PPV, NPV
Henry-Suchet, J., Utzmann, C., De Brux, J., Ardoin, P. and Catalan, F. Microbiologic study of chronic inflammation associated with tubal factor infertility: role of Chlamydia trachomatis. <i>Fertil Steril.</i> 1987; 47 (2): 274-7.	Included in systematic review Mol et al., 1995
Hodgson, R., Driscoll, G. L., Dodd, J. K. and Tyler, J. P. Chlamydia trachomatis: the prevalence, trend and importance in initial infertility management. <i>Aust N Z J Obstet Gynaecol.</i> 1990; 30 (3): 251-4.	Included in systematic review Mol et al., 1995
Holst, N., Abyholm, T. and Borgersen, A. Hysterosalpingography in the evaluation of infertility. <i>Acta Radiol Diagn (Stockh).</i> 1983; 24 (3): 253-7.	No raw data to calculate sensitivity, specificity, PPV, NPV
Hubacher, D., Grimes, D., Lara-Ricalde, R., de la Jara, J. and Garcia-Luna, A. The limited clinical usefulness of taking a history in the evaluation of women with tubal factor infertility. <i>Fertil Steril.</i> 2004; 81 (1): 6-10.	No raw data to calculate sensitivity, specificity, PPV, NPV
Inki, P., Palo, P. and Anttila, L. Vaginal sonosalpingography in the evaluation of tubal patency. <i>Acta Obstet Gynecol Scand.</i> 1998; 77 (10): 978-82.	Included in systematic review Alcazar et al., 2020
Jain, M., Gupta, S., Singh, M. and Gulati, A. K. Chlamydial serology and laparoscopic findings in infertile women. <i>J Indian Med Assoc.</i> 1994; 92 (4): 108-9.	Included in systematic review Mol et al., 1995
Kalogeropoulos, A., Frantzydou, F., Klearchou, N., Diza, E., Kyriazopoulou, V. and Karagiannis, V. Chlamydia trachomatis in infertile Greek women. A serologic and laparoscopic study. <i>Eur J Obstet Gynecol Reprod Biol.</i> 1993; 48 (2): 107-10.	Included in systematic review Mol et al., 1995
Kane, J. L., Woodland, R. M., Forsey, T., Darougar, S. and Elder, M. G. Evidence of chlamydial infection in infertile women with and without fallopian tube obstruction. <i>Fertil Steril.</i> 1984; 42 (6): 843-8.	Included in systematic review Mol et al., 1995
Kasby, C. B. Hysterosalpingography: an appraisal of current indications. <i>Br J Radiol.</i> 1980; 53 (628): 279-82.	No raw data to calculate sensitivity, specificity, PPV, NPV
Kelver, M. E. and Nagamani, M. Chlamydial serology in women with tubal infertility. <i>Int J Fertil.</i> 1989; 34 (1): 42-5.	Included in systematic review Mol et al., 1995



Kleinkauf-Houcken, A., Hüneke, B., Lindner, C. and Braendle, W. Combining B-mode ultrasound with pulsed wave Doppler for the assessment of tubal patency. <i>Hum Reprod.</i> 1997; 12 (11): 2457-60.	Included in systematic review Alcazar et al., 2020
Kupesic, S. and Plavsic, B. M. 2D and 3D hysterosalpingo-contrast-sonography in the assessment of uterine cavity and tubal patency. <i>Eur J Obstet Gynecol Reprod Biol.</i> 2007; 133 (1): 64-9.	Included in systematic review Wang et al., 2016
Luciano, D. E., Exacoustos, C., Johns, D. A. and Luciano, A. A. Can hysterosalpingo-contrast sonography replace hysterosalpingography in confirming tubal blockage after hysteroscopic sterilization and in the evaluation of the uterus and tubes in infertile patients? <i>Am J Obstet Gynecol.</i> 2011; 204 (1): 79.e1-5.	Included in systematic review Alcazar et al., 2020
Lucisano, A., Morandotti, G., Marana, R., Leone, F., Branca, G., Dell'Acqua, S. and Sanna, A. Chlamydial genital infections and laparoscopic findings in infertile women. <i>Eur J Epidemiol.</i> 1992; 8 (5): 645-9.	Included in systematic review Mol et al., 1995
Ludwin, I., Ludwin, A., Wiechec, M., Nocun, A., Banas, T., Basta, P. and Pitynski, K. Accuracy of hysterosalpingo-foam sonography in comparison to hysterosalpingo-contrast sonography with air/saline and to laparoscopy with dye. <i>Hum Reprod.</i> 2017; 32 (4): 758-769.	Included in systematic review Alcazar et al., 2020
Maheux-Lacroix, S., Boutin, A., Moore, L., Bergeron, M. E., Bujold, E., Laberge, P., Lemyre, M. and Dodin, S. Hysterosalpingosonography for diagnosing tubal occlusion in subfertile women: a systematic review with meta-analysis. <i>Hum Reprod.</i> 2014; 29 (5): 953-63.	More recent systematic review available.
Martens, M. G., Young, R. L., Uribe, M., Buttram, V. C. and Faro, S. Presence of Chlamydia, Mycoplasma, ureaplasma, and other bacteria in the upper and lower genital tracts of fertile and infertile populations. <i>Infect Dis Obstet Gynecol.</i> 1993; 1 (2): 85-90.	No positive cultures for <i>C. trachomatis</i> found
Martin, D. C., Khare, V. K. and Miller, B. E. Association of Chlamydia trachomatis immunoglobulin gamma titers with dystrophic peritoneal calcification, psammoma bodies, adhesions, and hydrosalpinges. <i>Fertil Steril.</i> 1995; 63 (1): 39-44.	No raw data to calculate sensitivity, specificity, PPV, NPV
Meikle, S. F., Zhang, X., Marine, W. M., Calonge, B. N., Hamman, R. F. and Betz, G. Chlamydia trachomatis antibody titers and hysterosalpingography in predicting tubal disease in infertility patients. <i>Fertil Steril.</i> 1994; 62 (2): 305-12.	Included in systematic review Mol et al., 1995
Minassian, S. S., Wu, C. H., Jungkind, D., Gocial, B., Filer, R. B. and Glassner, M. Chlamydial antibody, as determined with an enzyme-linked immunosorbent assay, in tubal factor infertility. <i>J Reprod Med.</i> 1990; 35 (2): 141-5.	Included in systematic review Mol et al., 1995
Moore, D. E., Spadoni, L. R., Foy, H. M., Wang, S. P., Daling, J. R., Kuo, C. C., Grayston, J. T. and Eschenbach, D. A. Increased frequency of serum antibodies to Chlamydia trachomatis in infertility due to distal tubal disease. <i>Lancet.</i> 1982; 2 (8298): 574-7.	Included in systematic review Mol et al., 1995
Muzii, L., Marana, R. and Mancuso, S. Distal fallopian tube occlusion: false diagnosis with hysterosalpingography in cases of tubal diverticula. <i>Radiology.</i> 1996; 199 (2): 469-71.	No raw data to calculate sensitivity, specificity, PPV, NPV
Okonofua, F. E., Essen, U. I. and Nimalaraj, T. Hysterosalpingography versus laparoscopy in tubal infertility: comparison based on findings at laparotomy. <i>Int J Gynaecol Obstet.</i> 1989; 28 (2): 143-7.	No raw data to calculate sensitivity, specificity, PPV, NPV
Patton, D. L., Askienazy-Elbhar, M., Henry-Suchet, J., Campbell, L. A., Cappuccio, A., Tannous, W., Wang, S. P. and Kuo, C. C. Detection of Chlamydia trachomatis in fallopian tube tissue in women with postinfectious tubal infertility. <i>Am J Obstet Gynecol.</i> 1994; 171 (1): 95-101.	No raw data to calculate sensitivity, specificity, PPV, NPV
Piccioni, M. G., Riganelli, L., Filippi, V., Fuggetta, E., Colagiovanni, V., Imperiale, L., Caccetta, J., Panici, P. B. and Porpora, M. G. Sonohysterosalpingography: Comparison of foam and saline solution. <i>J Clin Ultrasound.</i> 2017; 45 (2): 67-71.	Included in systematic review Alcazar et al., 2020
Qu, E., Zhang, M., Ju, J., Chen, Y., Lin, X., Zhang, X. Is Hysterosalpingo-Contrast Sonography (HyCoSy) Using Sulfur Hexafluoride Microbubbles (SonoVue)	Includes only studies using SonoVue contrast medium



Sufficient for the Assessment of Fallopian Tube Patency? A Systematic Review and Meta-Analysis. <i>J Ultrasound Med</i> 2022; doi 10.1002/jum.15988	
Reis, M. M., Soares, S. R., Cancado, M. L. and Camargos, A. F. Hysterosalpingo contrast sonography (HyCoSy) with SH U 454 (Echovist) for the assessment of tubal patency. <i>Hum Reprod.</i> 1998; 13 (11): 3049-52.	Included in systematic review Alcazar et al., 2020
Reniers, J., Collet, M., Frost, Leclerc, A., Ivanoff, B. and Méheus, A. Chlamydial antibodies and tubal infertility. <i>Int J Epidemiol.</i> 1989; 18 (1): 261-3.	No raw data to calculate sensitivity, specificity, PPV, NPV
Reshef, E., Daniel, W. W., Foster, J. C., Bradley, E. L., Blackwell, R. E. and Younger, J. B. Comparison between 1-hour and 24-hour follow-up radiographs in hysterosalpingography using oil based contrast media. <i>Fertil Steril.</i> 1989; 52 (5): 753-5.	1-hour vs 24-hours follow-up
Shibahara, H., Takamizawa, S., Hirano, Y., Ayustawati, Takei, Y., Fujiwara, H., Tamada, S. and Sato, I. Relationships between Chlamydia trachomatis antibody titers and tubal pathology assessed using transvaginal hydrolaparoscopy in infertile women. <i>Am J Reprod Immunol.</i> 2003; 50 (1): 7-12.	All patients CAT positive at baseline.
Siassakos, D., Manley, K., Wardle, P. and Halawa, S. Chlamydia screening or prophylaxis before laparoscopy and dye hydrotubation: no readmissions, no worry, or is that so? <i>Int J STD AIDS.</i> 2007; 18 (12): 861-2.	No raw data to calculate sensitivity, specificity, PPV, NPV
Soliman, A. A., Shaalan, W., Abdel-Dayem, T., Awad, E. E., Elkassar, Y., Lüdders, D., Malik, E. and Sallam, H. N. Power Doppler flow mapping and four-dimensional ultrasound for evaluating tubal patency compared with laparoscopy. <i>Eur J Obstet Gynecol Reprod Biol.</i> 2015; 195 83-7.	No raw data to calculate sensitivity, specificity, PPV, NPV
Strandell, A., Bourne, T., Bergh, C., Granberg, S., Asztely, M. and Thorburn, J. The assessment of endometrial pathology and tubal patency: a comparison between the use of ultrasonography and X-ray hysterosalpingography for the investigation of infertility patients. <i>Ultrasound Obstet Gynecol.</i> 1999; 14 (3): 200-4.	Included in systematic review Broeze et al., 2011
Svenstrup, H. F., Fedder, J., Kristoffersen, S. E., Trolle, B., Birkelund, S. and Christiansen, G. Mycoplasma genitalium, Chlamydia trachomatis, and tubal factor infertility--a prospective study. <i>Fertil Steril.</i> 2008; 90 (3): 513-20.	No raw data to calculate sensitivity, specificity, PPV, NPV
Swart, P., Mol, B. W., van der Veen, F., van Beurden, M., Redekop, W. K. and Bossuyt, P. M. The accuracy of hysterosalpingography in the diagnosis of tubal pathology: a meta-analysis. <i>Fertil Steril.</i> 1995; 64 (3): 486-91.	More recent systematic review available.
Tamási, F., Weidner, A., Domokos, N., Bedros, R. J. and Bagdány, S. ECHOVIST-200 enhanced hystero-sonography: a new technique in the assessment of infertility. <i>Eur J Obstet Gynecol Reprod Biol.</i> 2005; 121 (2): 186-90.	No raw data to calculate sensitivity, specificity, PPV, NPV
Tanawattanacharoen, S., Suwajanakorn, S., Uerpaiojkit, B., Boonkasemsanti, W. and Virutamasen, P. Transvaginal hysterosalpingo-contrast sonography (HyCoSy) compared with chromolaparoscopy. <i>J Obstet Gynaecol Res.</i> 2000; 26 (1): 71-5.	Included in systematic review Alcazar et al., 2020
Thejls, H., Gnarpe, J., Lundkvist, O., Heimer, G., Larsson, G. and Victor, A. Diagnosis and prevalence of persistent chlamydia infection in infertile women: tissue culture, direct antigen detection, and serology. <i>Fertil Steril.</i> 1991; 55 (2): 304-10.	Included in systematic review Mol et al., 1995
Thomas, K., Coughlin, L., Mannion, P. T. and Haddad, N. G. The value of Chlamydia trachomatis antibody testing as part of routine infertility investigations. <i>Hum Reprod.</i> 2000; 15 (5): 1079-82.	No raw data to calculate sensitivity, specificity, PPV, NPV
Tjiam, K. H., Zeilmaker, G. H., Alberda, A. T., van Heijst, B. Y., de Roo, J. C., Polak-Vogelzang, A. A., van Joost, T., Stolz, E. and Michel, M. F. Prevalence of antibodies to Chlamydia trachomatis, Neisseria gonorrhoeae, and Mycoplasma hominis in infertile women. <i>Genitourin Med.</i> 1985; 61 (3): 175-8.	Included in systematic review Mol et al., 1995
Tüfekçi, E. C., Girit, S., Bayirli, E., Durmuşoğlu, F. and Yalti, S. Evaluation of tubal patency by transvaginal sonosalpingography. <i>Fertil Steril.</i> 1992; 57 (2): 336-40.	Included in systematic review Alcazar et al., 2020



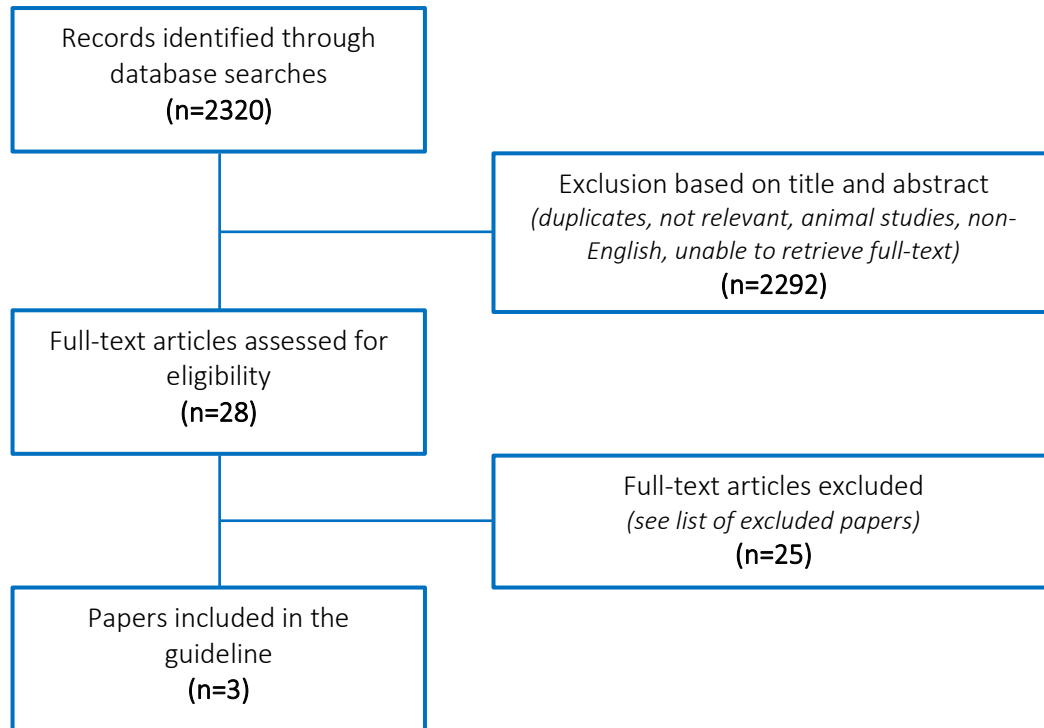
Van Schoubroeck, D., Van den Bosch, T., Meuleman, C., Tomassetti, C., D'Hooghe, T. and Timmerman, D. The use of a new gel foam for the evaluation of tubal patency. <i>Gynecol Obstet Invest.</i> 2013; 75 (3): 152-6.	Included in systematic review Alcazar et al., 2020
Volpi, E., De Grandis, T., Sismondi, P., Giacardi, M., Rustichelli, S., Patriarca, A. and Bocci, A. Transvaginal salpingo-sonography (TSSG) in the evaluation of tubal patency. <i>Acta Eur Fertil.</i> 1991; 22 (6): 325-8.	No raw data to calculate sensitivity, specificity, PPV, NPV
Wang, J., Li, J., Yu, L., Han, S., Shen, X. and Jia, X. Application of 3D-HyCoSy in the diagnosis of oviduct obstruction. <i>Exp Ther Med.</i> 2017; 13 (3): 966-970.	No raw data to calculate sensitivity, specificity, PPV, NPV
Wang, W., Zhou, Q., Gong, Y., Li, Y., Huang, Y. and Chen, Z. Assessment of Fallopian Tube Fimbria Patency With 4-Dimensional Hysterosalpingo-Contrast Sonography in Infertile Women. <i>J Ultrasound Med.</i> 2017; 36 (10): 2061-2069.	Included in systematic review Alcazar et al., 2020
Woolcott, R., Fisher, S., Thomas, J. and Kable, W. A randomized, prospective, controlled study of laparoscopic dye studies and selective salpingography as diagnostic tests of fallopian tube patency. <i>Fertil Steril.</i> 1999; 72 (5): 879-84.	No raw data to calculate sensitivity, specificity, PPV, NPV



II.5 Uterine factor

PICO QUESTION: WHICH DIAGNOSTIC PROCEDURES SHOULD BE PERFORMED TO CONFIRM A NORMAL UTERINE STRUCTURE/ANATOMY, UTERINE WALL/MYOMETRIUM?

Flowchart



List of excluded papers

Reference	Exclusion criterion
Aboulghar, M. M., Shoeir, I. K., Momtaz, M., Mohammady, M. E. and Ezzat, H. A comparative study of 2-dimensional sonohysterography versus 3-dimensional sonohysterography in infertile patients with uterine cavity lesions and abnormalities. Middle east fertility society journal. 2011; 16 (1): 67-71.	No comparison between 2D and 3D ultrasound
Apirakviriya, C., Rungruxsirivorn, T., Phupong, V. and Wisawasukmongchol, W. Diagnostic accuracy of 3D-transvaginal ultrasound in detecting uterine cavity abnormalities in infertile patients as compared with hysteroscopy. Eur J Obstet Gynecol Reprod Biol. 2016; 200 24-8.	No comparison between 2D and 3D ultrasound
Armstrong, S. C., Showell, M., Stewart, E. A., Rebar, R. W., Vanderpoel, S. and Farquhar, C. M. Baseline anatomical assessment of the uterus and ovaries in infertile women: a systematic review of the evidence on which assessment methods are the safest and most effective in terms of improving fertility outcomes. Hum Reprod Update. 2017; 23 (5): 533-547.	No comparison between 2D and 3D ultrasound
Bhatt, S., Sumbul, M., Rajpal, R. and Radhakrishnan, G. Value of "Three Dimensional Multidetector CT Hysterosalpingography" in Infertile Patients with Non-Contributory Hysterosalpingography: A Prospective Study. J Reprod Infertil. 2017; 18 (3): 323-332.	No comparison between 2D and 3D ultrasound
Bocca, S. M., Oehninger, S., Stadtmauer, L., Agard, J., Duran, E. H., Sarhan, A., Horton, S. and Abuhamad, A. Z. A study of the cost, accuracy, and benefits of 3-dimensional sonography compared with hysterosalpingography in women with uterine abnormalities. J Ultrasound Med. 2012; 31 (1): 81-5.	No comparison between 2D and 3D ultrasound



de Souza, N. M., Brosens, J. J., Schwieso, J. E., Paraschos, T. and Winston, R. M. The potential value of magnetic resonance imaging in infertility. <i>Clin Radiol.</i> 1995; 50 (2): 75-9.	No comparison between 2D ultrasound and MRI
El-Sherbiny, W., El-Mazny, A., Abou-Salem, N. and Mostafa, W. S. The diagnostic accuracy of two- vs three-dimensional sonohysterography for evaluation of the uterine cavity in the reproductive age. <i>J Minim Invasive Gynecol.</i> 2015; 22 (1): 127-31.	No comparison between 2D and 3D ultrasound
Grigore, M., Pristavu, A., Iordache, F., Gafitanu, D. and Ursulescu, C. Comparative Study of Hysteroscopy and 3D Ultrasound for Diagnosing Uterine Cavity Abnormalities. <i>Rev Med Chir Soc Med Nat Iasi.</i> 2016; 120 (4): 866-73.	No comparison between 2D and 3D ultrasound
Hamilton, J. A., Larson, A. J., Lower, A. M., Hasnain, S. and Grudzinskas, J. G. Routine use of saline hysterosonography in 500 consecutive, unselected, infertile women. <i>Hum Reprod.</i> 1998; 13 (9): 2463-73.	No comparison between 2D and 3D ultrasound
Inoue, T., Kitajima, M., Taniguchi, K. and Masuzaki, H. Three-dimensional saline-infusion sonohysterography is useful for the identification of endometrial polyp. <i>J Obstet Gynaecol Res.</i> 2016; 42 (7): 855-9.	No comparison between 2D ultrasound and MRI
Kim, M. J., Lee, Y., Lee, C., Chun, S., Kim, A., Kim, H. Y. and Lee, J. Y. Accuracy of three dimensional ultrasound and treatment outcomes of intrauterine adhesion in infertile women. <i>Taiwan J Obstet Gynecol.</i> 2015; 54 (6): 737-41.	No comparison between 2D and 3D ultrasound
Kiyokawa, K., Masuda, H., Fuyuki, T., Koseki, M., Uchida, N., Fukuda, T., Amemiya, K., Shouka, K. and Suzuki, K. Three-dimensional hysterosalpingo-contrast sonography (3D-HyCoSy) as an outpatient procedure to assess infertile women: a pilot study. <i>Ultrasound Obstet Gynecol.</i> 2000; 16 (7): 648-54.	No comparison between 2D and 3D ultrasound
Kupesic, S. and Plavsic, B. M. 2D and 3D hysterosalpingo-contrast-sonography in the assessment of uterine cavity and tubal patency. <i>Eur J Obstet Gynecol Reprod Biol.</i> 2007; 133 (1): 64-9.	No comparison between 2D and 3D ultrasound
Leonhardt, H., Gull, B., Stener-Victorin, E. and Hellström, M. Ovarian volume and antral follicle count assessed by MRI and transvaginal ultrasonography: a methodological study. <i>Acta Radiol.</i> 2014; 55 (2): 248-56.	Only ovarian morphology is assessed
Levaillant, J. M., Pasquier, M. and Massin, N. A novel concept for female infertility exploration: the Fertiliscan®, a dedicated all-in-one 3D ultrasound exploration. <i>J Gynecol Obstet Hum Reprod.</i> 2019; 48 (5): 363-367.	No comparison between 2D and 3D ultrasound
Liu, N. and Ren, Q. Magnetic Resonance Imaging Feature Analysis and Evaluation of Tubal Patency under Convolutional Neural Network in the Diagnosis of Infertility. <i>Contrast Media Mol Imaging.</i> 2021; 2021 5175072.	No comparison between 2D ultrasound and MRI
Ludwin, A., Ludwin, I., Kudla, M., Pitynski, K., Banas, T., Jach, R. and Knafel, A. Diagnostic accuracy of three-dimensional sonohysterography compared with office hysteroscopy and its interrater/intrarater agreement in uterine cavity assessment after hysteroscopic metroplasty. <i>Fertil Steril.</i> 2014; 101 (5): 1392-9.	No comparison between 2D and 3D ultrasound
Maged, A. M., Ramzy, A. M., Ghar, M. A., El Shenoufy, H., Gad Allah, S. H., Wahba, A. H., ElKateb, A. Y. and Hwedi, N. 3D ultrasound assessment of endometrial junctional zone anatomy as a predictor of the outcome of ICSI cycles. <i>Eur J Obstet Gynecol Reprod Biol.</i> 2017; 212 160-165.	No comparison between 2D and 3D ultrasound
Meylaerts, L. J., Wijnen, L., Ombelet, W., Bazot, M. and Vandersteen, M. Uterine junctional zone thickness in infertile women evaluated by MRI. <i>J Magn Reson Imaging.</i> 2017; 45 (3): 926-936.	No comparison between 2D ultrasound and MRI
Ni, J., Han, B., Liang, J. and Wang, F. Three-dimensional 3D ultrasound combined with power Doppler for the differential diagnosis of endometrial lesions among infertile women. <i>Int J Gynaecol Obstet.</i> 2019; 145 (2): 212-218.	No comparison between 2D and 3D ultrasound
Pleş, L., Alexandrescu, C., Ionescu, C. A., Arvătescu, C. A., Vladareanu, S. and Moga, M. A. Three-dimensional scan of the uterine cavity of infertile women before assisted reproductive technology use. <i>Medicine (Baltimore).</i> 2018; 97 (41): e12764.	2D and 3D-TVUS were used simultaneously. No comparison between 2D and 3D TVUS

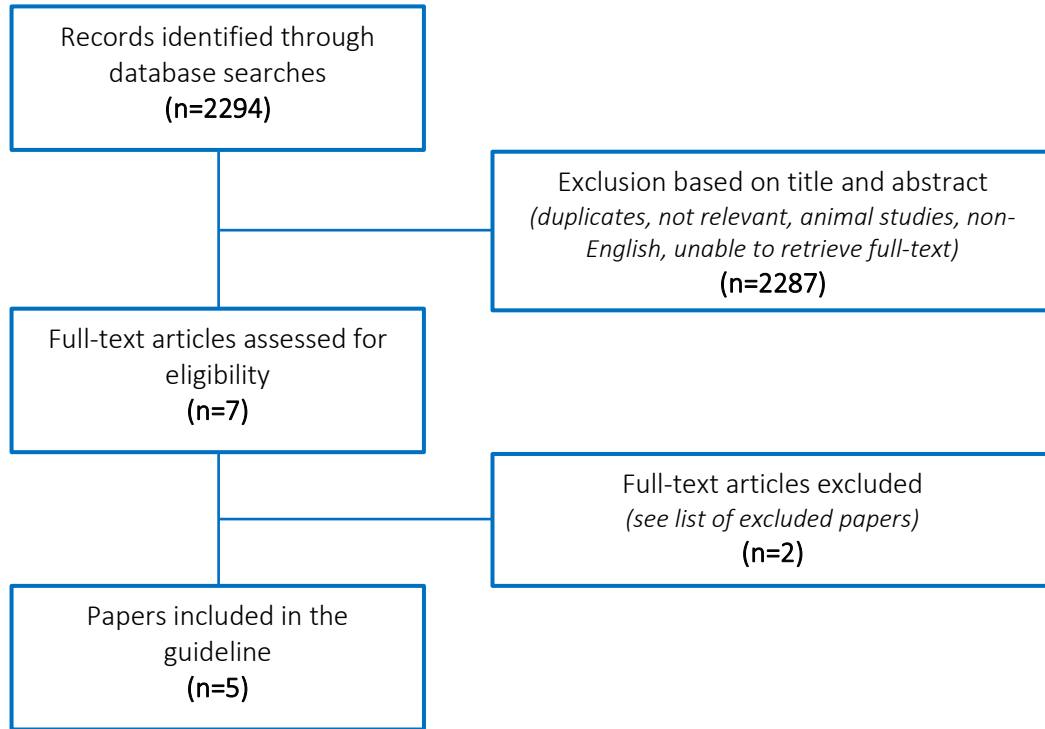


<p>Senoh, D., Tanaka, H., Akiyama, M., Yanagihara, T. and Hata, T. Saline infusion contrast intrauterine sonographic assessment of the endometrium with high-frequency, real-time miniature transducer in normal menstrual cycle: a preliminary report. <i>Hum Reprod.</i> 1999; 14 (10): 2600-3.</p>	<p>No comparison between 2D and 3D ultrasound</p>
<p>Silva, V., Ramos, F. F., Brás, A. F. M., Santos, R. F. S., Xavier, Msdpl and Miguelote, R. F. O. Junctional Zone in Infertile Women: A Three-dimensional Ultrasound Study. <i>Rev Bras Ginecol Obstet.</i> 2020; 42 (3): 152-159.</p>	<p>The interobserver and intraobserver agreements were analyzed (3D TVUS). No comparison between 2D and 3D TVUS</p>
<p>Sylvestre, C., Child, T. J., Tulandi, T. and Tan, S. L. A prospective study to evaluate the efficacy of two- and three-dimensional sonohysterography in women with intrauterine lesions. <i>Fertil Steril.</i> 2003; 79 (5): 1222-5.</p>	<p>No comparison between 2D and 3D ultrasound</p>
<p>Zinther, N. B., Zeuten, A., Marinovskij, E., Haislund, M. and Friis-Andersen, H. Detection of abdominal wall adhesions using visceral slide. <i>Surg Endosc.</i> 2010; 24 (12): 3161-6.</p>	<p>Detection of uterine wall adhesions</p>



PICO QUESTION: WHICH ADDITIONAL DIAGNOSTIC PROCEDURES SHOULD BE PERFORMED TO CONFIRM AN ANATOMICALLY NORMAL UTERINE CAVITY?

Flowchart



List of excluded papers

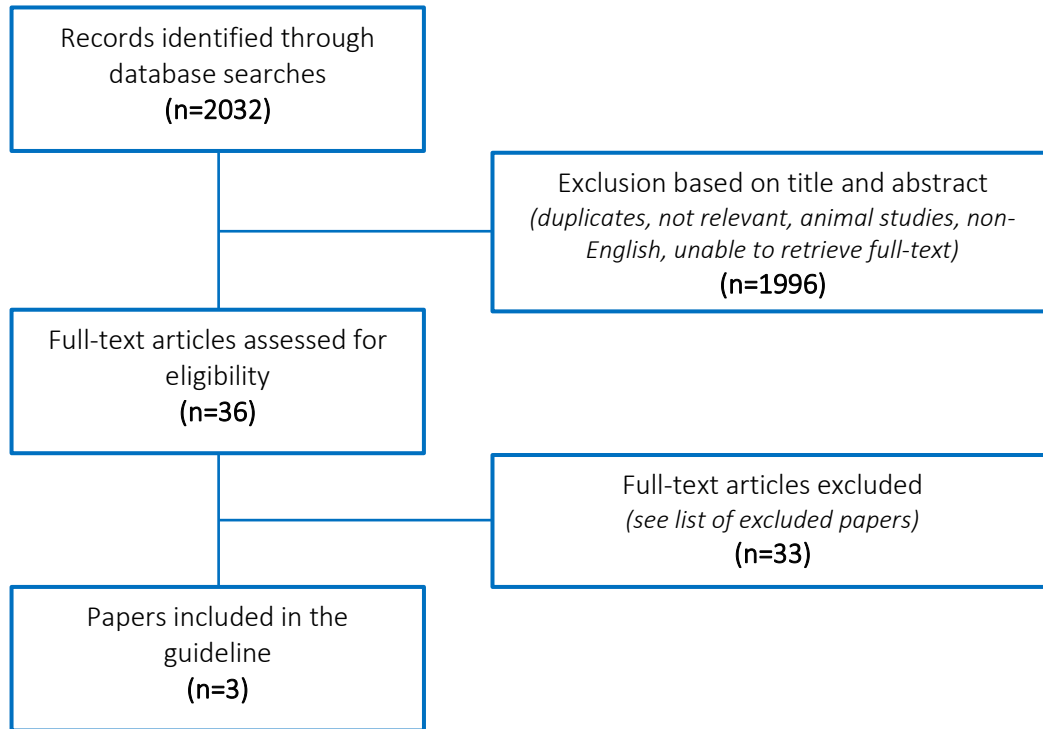
Reference	Exclusion criterion
Armstrong, S. C., Showell, M., Stewart, E. A., Rebar, R. W., Vanderpoel, S. and Farquhar, C. M. Baseline anatomical assessment of the uterus and ovaries in infertile women: a systematic review of the evidence on which assessment methods are the safest and most effective in terms of improving fertility outcomes. <i>Hum Reprod Update</i> . 2017; 23 (5): 533-547.	No calculation of accuracy in terms of sensitivity, specificity, PPV, NPV
Kamath, M. S., Bosteels, J., D'Hooghe, T. M., Seshadri, S., Weyers, S., Mol, B. W. J., Broekmans, F. J. and Sunkara, S. K. Screening hysteroscopy in subfertile women and women undergoing assisted reproduction. <i>Cochrane Database Syst Rev</i> . 2019; 4 (4): Cd012856.	No calculation of accuracy in terms of sensitivity, specificity, PPV, NPV



II.6 Laparoscopy

PICO QUESTION: SHOULD WOMEN UNDERGO A LAPAROSCOPY BEFORE BEING DIAGNOSED WITH UI?

Flowchart



List of excluded papers

Reference	Exclusion criterion
Badawy, A., Khiary, M., Ragab, A., Hassan, M. and Sherif, L. Laparoscopy--or not--for management of unexplained infertility. J Obstet Gynaecol. 2010; 30 (7): 712-5.	The author has published fraudulent papers (at least 9) and therefore the results of this study can not be taken as reliable
Bonneau, C., Chanelles, O., Sifer, C. and Poncelet, C. Use of laparoscopy in unexplained infertility. Eur J Obstet Gynecol Reprod Biol. 2012; 163 (1): 57-61.	although bilateral tubal patency was an inclusion criterium, 67 % of the patients had a subnormal HSG, including bilateral abnormalities.
Brosens, I., Gordts, S. and Campo, R. Transvaginal hydrolaparoscopy but not standard laparoscopy reveals subtle endometriotic adhesions of the ovary. Fertil Steril. 2001; 75 (5): 1009-12.	compares THL with DL
Campo, R., Gordts, S., Rombauts, L. and Brosens, I. Diagnostic accuracy of transvaginal hydrolaparoscopy in infertility. Fertil Steril. 1999; 71 (6): 1157-60.	compares THL with DL
Casa, A., Sesti, F., Marziali, M. and Piccione, E. Transvaginal hydrolaparoscopy vs. conventional laparoscopy for evaluating unexplained primary infertility in women. J Reprod Med. 2002; 47 (8): 617-20.	compares THL with DL
Corson, S. L., Cheng, A. and Gutmann, J. N. Laparoscopy in the "normal" infertile patient: a question revisited. J Am Assoc Gynecol Laparosc. 2000; 7 (3): 317-24.	No controls, publication-, attrition- and selectionbias. Confounding factors and a



	very small studygroup with no comparison.
Darai, E., Dessolle, L., Lecuru, F. and Soriano, D. Transvaginal hydrolaparoscopy compared with laparoscopy for the evaluation of infertile women: a prospective comparative blind study. <i>Hum Reprod.</i> 2000; 15 (11): 2379-82.	compares THL with DL
Dechaud, H., Ali Ahmed, S. A., Aligier, N., Vergnes, C. and Hedon, B. Does transvaginal hydrolaparoscopy render standard diagnostic laparoscopy obsolete for unexplained infertility investigation? <i>Eur J Obstet Gynecol Reprod Biol.</i> 2001; 94 (1): 97-102.	compares THL with DL
Dunphy, B. C. and Greene, C. A. Falloposcopic cannulation, oviductal appearances and prediction of treatment independent intrauterine pregnancy. <i>Hum Reprod.</i> 1995; 10 (12): 3313-6.	Not only patients with UI
Hauge, K., Flo, K., Riedhart, M. and Granberg, S. Can ultrasound-based investigations replace laparoscopy and hysteroscopy in infertility? <i>Eur J Obstet Gynecol Reprod Biol.</i> 2000; 92 (1): 167-70.	compares HyCoSy to DL
Hovav, Y., Hornstein, E., Almagor, M. and Yaffe, C. Diagnostic laparoscopy in primary and secondary infertility. <i>J Assist Reprod Genet.</i> 1998; 15 (9): 535-7.	compares patients with primary and secondary infertility
Ikechebelu, J. I. and Mbamara, S. U. Should laparoscopy and dye test be a first line evaluation for infertile women in southeast Nigeria? <i>Niger J Med.</i> 2011; 20 (4): 462-5.	Concerns routine DL in infertile women, not only those with normal findings on examination, standard work-up including ultrasound and HSG
Jayakrishnan, K., Koshy, A. K. and Raju, R. Role of laparohysteroscopy in women with normal pelvic imaging and failed ovulation stimulation with intrauterine insemination. <i>J Hum Reprod Sci.</i> 2010; 3 (1): 20-4.	Retrospective cohort after 3 x failed IUI. Selection of patients in whom no abnormalities were found in the work-up. However no mention of tubal patency tests
Kahyaoglu, S., Kahyaoglu, I., Yilmaz, B., Var, T., Ertas, I. E., Mollamahmutoglu, L. and Batioglu, S. Should diagnostic laparoscopy be performed initially or not, during infertility management of primary and secondary infertile women? A cross-sectional study. <i>J Obstet Gynaecol Res.</i> 2009; 35 (1): 139-44.	inclusion of patients with unexplained infertility, however it is not clearly stated that only patients with patent tubes on HSG were included. Table 2 suggests not, because 35 % had an abnormal HSG.
Komori, S., Fukuda, Y., Horiuchi, I., Tanaka, H., Kasumi, H., Shigeta, M., Tuji, Y. and Koyama, K. Diagnostic laparoscopy in infertility: a retrospective study. <i>J Laparoendosc Adv Surg Tech A.</i> 2003; 13 (3): 147-51.	Retrospective study including other causes than UI.
Mahran, A., Abdelraheim, A. R., Eissa, A. and Gadelrab, M. Does laparoscopy still has a role in modern fertility practice? <i>Int J Reprod Biomed.</i> 2017; 15 (12): 787-794.	Mixed population, not only UI
Milingos, S., Protopapas, A., Kallipolitis, G., Drakakis, P., Makrigiannakis, A., Liapi, A., Milingos, D., Antsaklis, A. and Michalas, S. Laparoscopic evaluation of infertile patients with chronic pelvic pain. <i>Reprod Biomed Online.</i> 2006; 12 (3): 347-53.	Cohort of patients with infertility and chronic pelvic pain
Moayeri, S. E., Lee, H. C., Lathi, R. B., Westphal, L. M., Milki, A. A. and Garber, A. M. Laparoscopy in women with unexplained infertility: a cost-effectiveness analysis. <i>Fertil Steril.</i> 2009; 92 (2): 471-80.	Does not involve only patients with UI
Nakagawa, K., Ohgi, S., Horikawa, T., Kojima, R., Ito, M. and Saito, H. Laparoscopy should be strongly considered for women with unexplained infertility. <i>J Obstet Gynaecol Res.</i> 2007; 33 (5): 665-70.	Cohort of patients with initially UI who underwent DL and subsequently ART (IVF), not natural



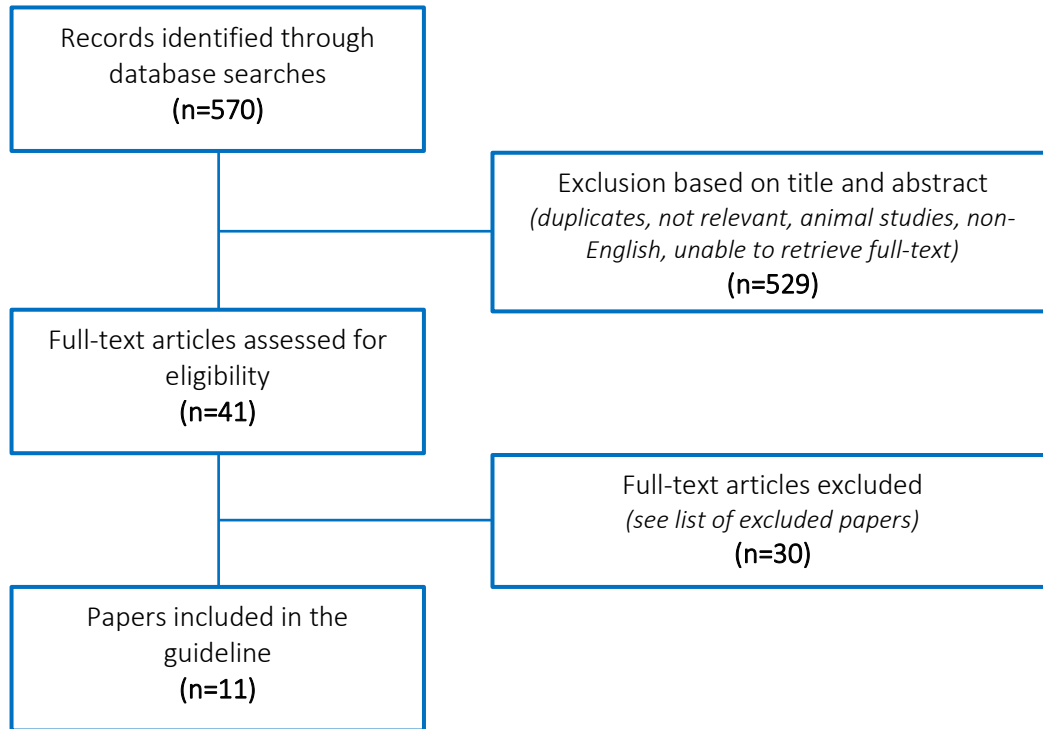
	conception, were analyzed. Only patients < 35 years old.
Nawroth, F., Foth, D., Schmidt, T. and Römer, T. Results of a prospective comparative study of transvaginal hydrolaparoscopy and chromolaparoscopy in the diagnostics of infertility. <i>Gynecol Obstet Invest.</i> 2001; 52 (3): 184-8.	compares THL with DL
Pantou, A., Simopoulou, M., Sfakianoudis, K., Giannelou, P., Rapani, A., Maziotis, E., Grigoriadis, S., Tsioulou, P., Syrkos, S., Souretis, K., Koutsilieris, M. and Pantos, K. The Role of Laparoscopic Investigation in Enabling Natural Conception and Avoiding in vitro Fertilization Overuse for Infertile Patients of Unidentified Aetiology and Recurrent Implantation Failure Following in vitro Fertilization. <i>J Clin Med.</i> 2019; 8 (4):	Not only patients with UI, also after failed IVF
Park, H., Ramirez, D., Noble, L., Saldivar, J. S. and Mulla, Z. Use of Laparoscopy in Unexplained Infertility in Historically Underserved Area. <i>J Minim Invasive Gynecol.</i> 2015; 22 (6s): S233-s234.	Cohort of patients with UI who underwent DL and treatment of endometriosis , pelvic adhesions and/or Tubal sides (90/100) and pregnancy outcome. No controls. Abstract only
Rapkin, A. J. Adhesions and pelvic pain: a retrospective study. <i>Obstet Gynecol.</i> 1986; 68 (1): 13-5.	Included patients with chronic pelvic pain and patients with infertility, not necessarily UI



II.7 Cervical/ vaginal factor

PICO QUESTION: WHAT IS THE NEED FOR FEMALE LOWER GENITAL TRACT INVESTIGATIONS?

Flowchart



List of excluded papers

Reference	Exclusion criterion
Babu, G., Singaravelu, B. G., Srikumar, R., Reddy, S. V. and Kokan, A. Comparative Study on the Vaginal Flora and Incidence of Asymptomatic Vaginosis among Healthy Women and in Women with Infertility Problems of Reproductive Age. <i>J Clin Diagn Res.</i> 2017; 11 (8): Dc18-dc22.	Not specifically unexplained infertility
Bernabeu, A., Lledo, B., Díaz, M. C., Lozano, F. M., Ruiz, V., Fuentes, A., Lopez-Pineda, A., Moliner, B., Castillo, J. C., Ortiz, J. A., Ten, J., Llacer, J., Carratala-Munuera, C., Orozco-Beltran, D., Quesada, J. A. and Bernabeu, R. Effect of the vaginal microbiome on the pregnancy rate in women receiving assisted reproductive treatment. <i>J Assist Reprod Genet.</i> 2019; 36 (10): 2111-2119.	women with infertility diagnosis, no stratification of infertility
Bracewell-Milnes, T., Saso, S., Nikolaou, D., Norman-Taylor, J., Johnson, M. and Thum, M. Y. Investigating the effect of an abnormal cervico-vaginal and endometrial microbiome on assisted reproductive technologies: A systematic review. <i>Am J Reprod Immunol.</i> 2018; 80 (5): e13037.	systematic review without meta-analysis
Brandão, P. and Gonçalves-Henriques, M. The Impact of Female Genital Microbiota on Fertility and Assisted Reproductive Treatments. <i>J Family Reprod Health.</i> 2020; 14 (3): 131-149.	systematic review without meta-analysis
Bush, M. R., Walmer, D. K., Couchman, G. M. and Haney, A. F. Evaluation of the postcoital test in cycles involving exogenous gonadotropins. <i>Obstet Gynecol.</i> 1997; 89 (5 Pt 1): 780-4.	no separate analysis of data by cause of infertility
Chen, C., Song, X., Wei, W., Zhong, H., Dai, J., Lan, Z., Li, F., Yu, X., Feng, Q., Wang, Z., Xie, H., Chen, X., Zeng, C., Wen, B., Zeng, L., Du, H., Tang, H., Xu, C., Xia, Y., Xia, H., Yang, H., Wang, J., Wang, J., Madsen, L., Brix, S., Kristiansen, K.,	samples of vagina, cervical canal, uterus, fallopian



Xu, X., Li, J., Wu, R. and Jia, H. The microbiota continuum along the female reproductive tract and its relation to uterine-related diseases. <i>Nat Commun.</i> 2017; 8 (1): 875.	tubes and peritoneal fluid were included in the study
Collins, J. A., So, Y., Wilson, E. H., Wrixon, W. and Casper, R. F. The postcoital test as a predictor of pregnancy among 355 infertile couples. <i>Fertil Steril.</i> 1984; 41 (5): 703-8.	included in systematic review by Oei et al., 1995
Daru, J., Williamson, H. O., Rust, P. F., Homm, R. J. and Mathur, S. A computerized postcoital test sperm motility: comparison with clinical postcoital test and correlations with sperm antibodies. <i>Arch Androl.</i> 1988; 21 (3): 189-203.	PCT vs. computerized PCT
Dunphy, B. C., Barratt, C. L., Kay, R., Jones, D. E. and Cooke, I. D. Postcoital test: which form of spermatozoal motility is associated with a good fertility outcome? <i>Andrologia.</i> 1990; 22 (3): 269-73.	Reproducibility: all conceptions were treatment independent
Eggert-Kruse, W., Gerhard, I., Tilgen, W. and Runnebaum, B. Clinical significance of crossed in vitro sperm-cervical mucus penetration test in infertility investigation. <i>Fertil Steril.</i> 1989; 52 (6): 1032-40.	in vitro testing of sperm ability to penetrate cervical mucus (CM) vs. PCT parameter, as a parameter of sperm function
Eimers, J. M., te Velde, E. R., Gerritse, R., van Kooy, R. J., Kremer, J. and Habbema, J. D. The validity of the postcoital test for estimating the probability of conceiving. <i>Am J Obstet Gynecol.</i> 1994; 171 (1): 65-70.	excluded from systematic review by Oei et al., 1995 because pregnancy rates could not be calculated for women with normal and abnormal PCT separately.
Haahr, T., Humaidan, P., Elbaek, H. O., Alsbjerg, B., Laursen, R. J., Rygaard, K., Johannesen, T. B., Andersen, P. S., Ng, K. L. and Jensen, J. S. Vaginal Microbiota and In Vitro Fertilization Outcomes: Development of a Simple Diagnostic Tool to Predict Patients at Risk of a Poor Reproductive Outcome. <i>J Infect Dis.</i> 2019; 219 (11): 1809-1817.	Not specifically unexplained infertility
Haahr, T., Zacho, J., Bräuner, M., Shathmigha, K., Skov Jensen, J. and Humaidan, P. Reproductive outcome of patients undergoing in vitro fertilisation treatment and diagnosed with bacterial vaginosis or abnormal vaginal microbiota: a systematic PRISMA review and meta-analysis. <i>Bjog.</i> 2019; 126 (2): 200-207.	Not specifically unexplained infertility
Harrison, R. F. The diagnostic and therapeutic potential of the postcoital test. <i>Fertil Steril.</i> 1981; 36 (1): 71-5.	included in systematic review by Oei et al., 1995
Hong, X., Ma, J., Yin, J., Fang, S., Geng, J., Zhao, H., Zhu, M., Ye, M., Zhu, X., Xuan, Y. and Wang, B. The association between vaginal microbiota and female infertility: a systematic review and meta-analysis. <i>Arch Gynecol Obstet.</i> 2020; 302 (3): 569-578.	Not specifically unexplained infertility
Hyman, R. W., Herndon, C. N., Jiang, H., Palm, C., Fukushima, M., Bernstein, D., Vo, K. C., Zelenko, Z., Davis, R. W. and Giudice, L. C. The dynamics of the vaginal microbiome during infertility therapy with in vitro fertilization-embryo transfer. <i>J Assist Reprod Genet.</i> 2012; 29 (2): 105-15.	Not specifically unexplained infertility
Kim, S. M., Won, K. H., Hong, Y. H., Kim, S. K., Lee, J. R., Jee, B. C., Suh, C. S. Microbiology of Human Follicular Fluid and the Vagina and Its Impact on in Vitro Fertilization Outcomes. <i>Yonsei Med J.</i> 2022; 63(10): 941-47	Results not stratified according to infertility diagnosis.
Koedooder, R., Singer, M., Schoenmakers, S., Savelkoul, P. H. M., Morré, S. A., de Jonge, J. D., Poort, L., Cuypers, Wjss, Beckers, N. G. M., Broekmans, F. J. M., Cohlen, B. J., den Hartog, J. E., Fleischer, K., Lambalk, C. B., Smeenk, Jmjs, Budding, A. E. and Laven, J. S. E. The vaginal microbiome as a predictor for outcome of in vitro fertilization with or without intracytoplasmic sperm injection: a prospective study. <i>Hum Reprod.</i> 2019; 34 (6): 1042-1054.	Not specifically unexplained infertility
Kong, Y., Liu, Z., Shang, Q., Gao, Y., Li, X., Zheng, C., Deng, X. and Chen, T. The Disordered Vaginal Microbiota Is a Potential Indicator for a Higher Failure of in vitro Fertilization. <i>Front Med (Lausanne).</i> 2020; 7 217.	Not specifically unexplained infertility



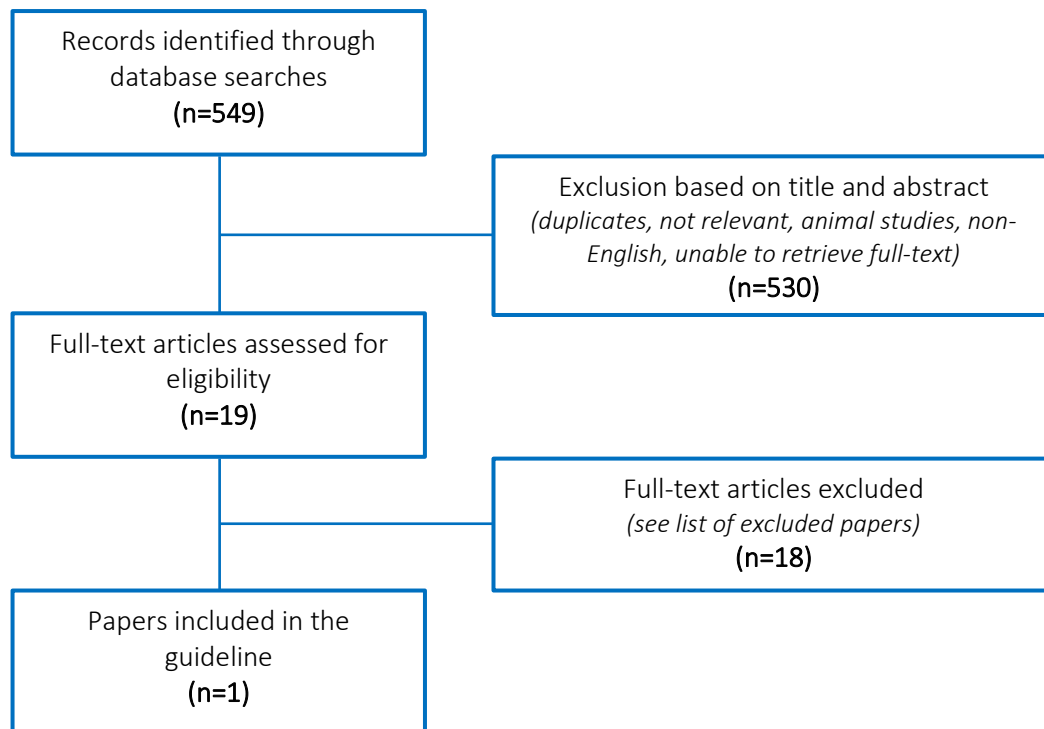
Kyono, K., Hashimoto, T., Nagai, Y. and Sakuraba, Y. Analysis of endometrial microbiota by 16S ribosomal RNA gene sequencing among infertile patients: a single-center pilot study. <i>Reprod Med Biol.</i> 2018; 17 (3): 297-306.	Not specifically unexplained infertility
Liversedge, N. H., Turner, A., Horner, P. J., Keay, S. D., Jenkins, J. M. and Hull, M. G. The influence of bacterial vaginosis on in-vitro fertilization and embryo implantation during assisted reproduction treatment. <i>Hum Reprod.</i> 1999; 14 (9): 2411-5.	Not specifically unexplained infertility
Lokken, E. M., Manhart, L. E., Kinuthia, J., Hughes, J. P., Jisuvei, C., Mwinyikai, K., Muller, C. H., Mandaliya, K., Jaoko, W. and McClelland, R. S. Association between bacterial vaginosis and fecundability in Kenyan women planning pregnancies: a prospective preconception cohort study. <i>Hum Reprod.</i> 2021;	non-infertility population
Matson, P. L., Tuvik, A. I., O'Halloran, F. and Yovich, J. L. The value of the postcoital test in predicting the fertilization of human oocytes. <i>J In Vitro Fert Embryo Transf.</i> 1986; 3 (2): 110-3.	Comparison between the fertilization rates of oocytes and the results of the PCT
Miron, N. D., Socolov, D., Mareş, M., Anton, G., Nastasa, V., Moraru, R. F., Virág, K., Anghelache-Lupaşcu, I. and Deák, J. Bacteriological agents which play a role in the development of infertility. <i>Acta Microbiol Immunol Hung.</i> 2013; 60 (1): 41-53.	Prevalence study
Ricci, S., De Giorgi, S., Lazzeri, E., Luddi, A., Rossi, S., Piomboni, P., De Leo, V. and Pozzi, G. Impact of asymptomatic genital tract infections on in vitro Fertilization (IVF) outcome. <i>PLoS One.</i> 2018; 13 (11): e0207684.	Not specifically unexplained infertility
Riganelli, L., Iebba, V., Piccioni, M., Illuminati, I., Bonfiglio, G., Neroni, B., Calvo, L., Gagliardi, A., Levrero, M., Merlino, L., Mariani, M., Capri, O., Pietrangeli, D., Schippa, S. and Guerrieri, F. Structural Variations of Vaginal and Endometrial Microbiota: Hints on Female Infertility. <i>Front Cell Infect Microbiol.</i> 2020; 10 350.	Not specifically unexplained infertility
Sabour, S., Arzanlou, M., Vaez, H., Rahimi, G., Sahebkar, A. and Khademi, F. Prevalence of bacterial vaginosis in pregnant and non-pregnant Iranian women: a systematic review and meta-analysis. <i>Arch Gynecol Obstet.</i> 2018; 297 (5): 1101-1113.	comparing BV in pregnant vs non-pregnant women, no stratification according to MAR or non-MAR or cause of infertility (not UI)
Steures, P., van der Steeg, J. W., Hompes, P. G., Bossuyt, P. M., Habbema, J. D., Eijkemans, M. J., Koks, C. A., Boudrez, P., van der Veen, F. and Mol, B. W. The additional value of ovarian hyperstimulation in intrauterine insemination for couples with an abnormal postcoital test and a poor prognosis: a randomized clinical trial. <i>Fertil Steril.</i> 2007; 88 (6): 1618-24.	subfertile couples with an abnormal postcoital test and a poor prognosis, were randomly allocated to three cycles of IUI with COH or three cycles of IUI without COH.
van Oostrum, N., De Sutter, P., Meys, J. and Verstraelen, H. Risks associated with bacterial vaginosis in infertility patients: a systematic review and meta-analysis. <i>Hum Reprod.</i> 2013; 28 (7): 1809-15.	Not specifically unexplained infertility
Wee, B. A., Thomas, M., Sweeney, E. L., Frentiu, F. D., Samios, M., Ravel, J., Gajer, P., Myers, G., Timms, P., Allan, J. A. and Huston, W. M. A retrospective pilot study to determine whether the reproductive tract microbiota differs between women with a history of infertility and fertile women. <i>Aust N Z J Obstet Gynaecol.</i> 2018; 58 (3): 341-348.	Not specifically unexplained infertility



II.8 Male genito-urinary anatomy

PICO QUESTION: SHOULD MEN UNDERGO ADDITIONAL DIAGNOSTIC PROCEDURES TO CONFIRM NORMAL GENITO-URINARY ANATOMY BEFORE BEING DIAGNOSED WITH UI?

Flowchart



List of excluded papers

Reference	Exclusion criterion
Abdelwahab, K., Eliwa, A. M., Seleem, M. M., El Galaly, H., Ragab, A., Desoky, E. A., Naguib, M., Ali, M. M., Saber, S. and Kamel, H. Role of Preoperative Testicular Shear Wave Elastography in Predicting Improvement of Semen Parameters After Varicocelectomy for Male Patients With Primary Infertility. <i>Urology</i> . 2017; 107 103-106.	Patients with clinically detectable varicocele and abnormal pre-operative semen parameters
Chen, S. S., Huang, W. J., Chang, L. S. and Wei, Y. H. 8-hydroxy-2'-deoxyguanosine in leukocyte DNA of spermatic vein as a biomarker of oxidative stress in patients with varicocele. <i>J Urol</i> . 2004; 172 (4 Pt 1): 1418-21.	Predictive value of Doppler ultrasound to detect varicocele
Cocuzza, M. S., Tiseo, B. C., Srougi, V., Wood, G. J. A., Cardoso, Jpgf, Esteves, S. C. and Srougi, M. Diagnostic accuracy of physical examination compared with color Doppler ultrasound in the determination of varicocele diagnosis and grading: Impact of urologists' experience. <i>Andrology</i> . 2020; 8 (5): 1160-1166.	Predictive value of Doppler ultrasound to detect varicocele
D'Andrea, S., Barbonetti, A., Castellini, C., Martorella, A., Minaldi, E., Viktor Giordano, A., Carducci, S., Necozone, S., Francavilla, F. and Francavilla, S. Reproductive hormones and sperm parameters after varicocele repair: An observational study. <i>Andrologia</i> . 2018; 50 (10): e13118.	Varicocele, abnormal semen analysis
D'Andrea, S., Barbonetti, A., Castellini, C., Nolletti, L., Martorella, A., Minaldi, E., Giordano, A. V., Carducci, S., Necozone, S., Francavilla, F. and Francavilla, S. Left spermatic vein reflux after varicocele repair predicts pregnancies and live births in subfertile couples. <i>J Endocrinol Invest</i> . 2019; 42 (10): 1215-1221.	Varicocele, abnormal semen analysis



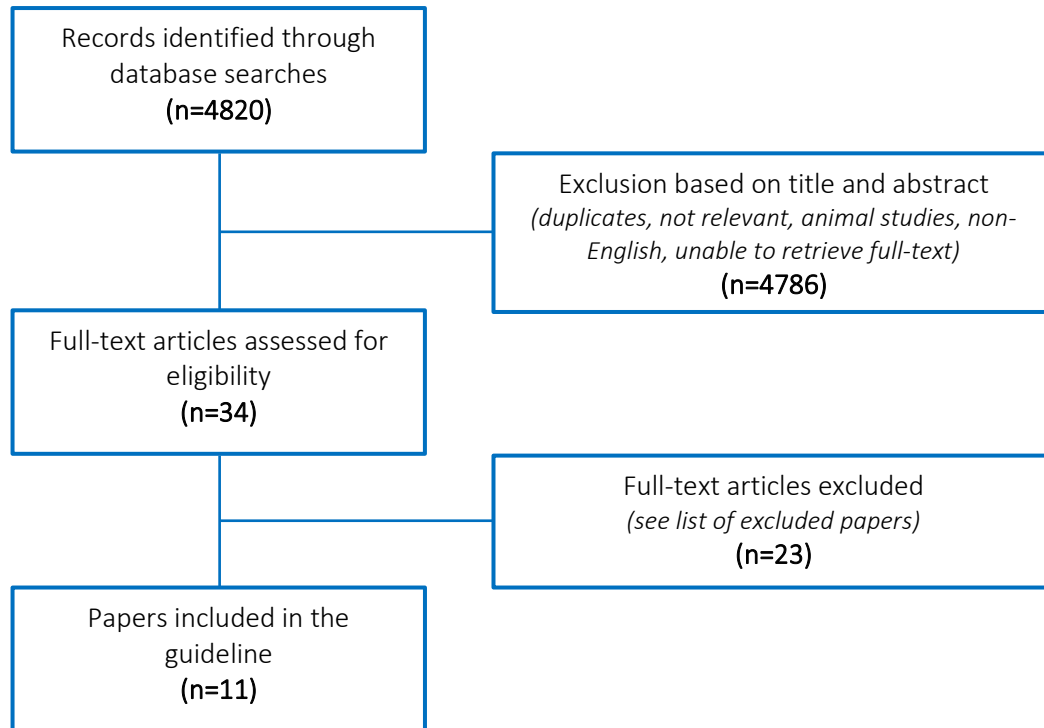
D'Andrea, S., Micillo, A., Barbonetti, A., Giordano, A. V., Carducci, S., Mancini, A., Necozone, S., Francavilla, F. and Francavilla, S. Determination of spermatic vein reflux after varicocele repair helps to define the efficacy of treatment in improving sperm parameters of subfertile men. <i>J Endocrinol Invest.</i> 2017; 40 (10): 1145-1153.	Varicocele, abnormal semen analysis
Erdoğan, H., Durmaz, M. S., Özbakır, B., Cebeci, H., Özkan, D. and Gökmen, İE. Experience of using shear wave elastography in evaluation of testicular stiffness in cases of male infertility. <i>Journal of ultrasound.</i> 2020; 23 (4): 529-534.	No semen parameters provided but seems that infertile men included in the study have at least some abnormal parameters
Eskew, L. A., Watson, N. E., Wolfman, N., Bechtold, R., Scharling, E. and Jarow, J. P. Ultrasonographic diagnosis of varicoceles. <i>Fertil Steril.</i> 1993; 60 (4): 693-7.	Predictive value of Doppler ultrasound to detect varicocele
Gomaa MD, Motawaa MA, Al-Nashar AM, El-Sakka AI. Impact of Subinguinal Varicolectomy on Serum Testosterone to Estradiol Ratio in Male Patients With Infertility. <i>Urology.</i> 2018 Jul;117:70-77.	Study and control groups are not comparable (varicocele with/without surgical removal vs fertile men)
Hussein, A. F. The role of color Doppler ultrasound in prediction of the outcome of microsurgical subinguinal varicolectomy. <i>J Urol.</i> 2006; 176 (5): 2141-5.	Varicocele, abnormal semen analysis
Lenz, S., Thomsen, J. K., Giwercman, A., Hertel, N. T., Hertz, J. and Skakkebaek, N. E. Ultrasonic texture and volume of testicles in infertile men. <i>Human reproduction (Oxford, England).</i> 1994; 9 (5): 878-881.	Varicocele, abnormal semen analysis
Lund, L. and Nielsen, A. H. Color Doppler sonography in the assessment of varicocele testis. <i>Scand J Urol Nephrol.</i> 1994; 28 (3): 281-5.	Predictive value of Doppler ultrasound to detect varicocele
Nieschlag, E., Hertle, L., Fishedick, A. and Behre, H. M. Treatment of varicocele: counselling as effective as occlusion of the vena spermatica. <i>Human reproduction (Oxford, England).</i> 1995; 10 (2): 347-353.	Left sided varicocele, abnormal semen analysis
Ortapamuk, H., Tekdogan, U. Y., Naldoken, S., Bulut, S. and Atan, A. Hemodynamic evaluation of varicocele: the role of scrotal scintigraphy and Doppler ultrasonography in the prediction of postoperative seminal improvement. <i>Ann Nucl Med.</i> 2005; 19 (7): 529-34.	Left sided varicocele and abnormal pre-operative semen parameters
Pezzella, A., Barbonetti, A., Micillo, A., D'Andrea, S., Necozone, S., Gandini, L., Lenzi, A., Francavilla, F. and Francavilla, S. Ultrasonographic determination of caput epididymis diameter is strongly predictive of obstruction in the genital tract in azospermic men with normal serum FSH. <i>Andrology.</i> 2013; 1 (1): 133-8.	Patient population of interest is only a subgroup and the focus of predictive value of the intervention was not on that subgroup
Preutthipan, S. and Nicholas, O. A. Comparative study between scrotal physical examination and scrotal ultrasonography in the detection of varicocele in men with infertility. <i>J Med Assoc Thai.</i> 1995; 78 (3): 135-9.	Varicocele, abnormal semen analysis
Rodriguez Peña, M., Alescio, L., Russell, A., Lourenco da Cunha, J., Alzu, G. and Bardoneschi, E. Predictors of improved seminal parameters and fertility after varicocele repair in young adults. <i>Andrologia.</i> 2009; 41 (5): 277-81.	Varicocele and semen parameters reported inadequately
Teixeira, T. A., Pariz, J. R., Dutra, R. T., Saldiva, P. H., Costa, E. and Hallak, J. Cut-off values of the Johnsen score and Copenhagen index as histopathological prognostic factors for postoperative semen quality in selected infertile patients undergoing microsurgical correction of bilateral subclinical varicocele. <i>Transl Androl Urol.</i> 2019; 8 (4): 346-355.	Patients who underwent microsurgical correction of subclinical bilateral varicocele; no data on semen parameters though methods state it was performed



II.9 Male additional tests

PICO QUESTION: IS THERE ADDED VALUE OF ADDITIONAL TESTS IN THE MALE WITH NORMAL WHO SEMEN ANALYSIS?

Flowchart



List of excluded papers

Reference	Exclusion criterion
Bibi, R., Jahan, S., Razak, S., Hammadeh, M. E., Almajwal, A. and Amor, H. Protamines and DNA integrity as a biomarkers of sperm quality and assisted conception outcome. <i>Andrologia</i> . 2022; e14418.	Clinical outcomes calculated on pooled data from all patient groups
Bungum, M., Humaidan, P., Axmon, A., Spano, M., Bungum, L., Erenpreiss, J. and Giwercman, A. Sperm DNA integrity assessment in prediction of assisted reproduction technology outcome. <i>Hum Reprod</i> . 2007; 22 (1): 174-9.	Includes patients with mild male factor without stratification of results
Collins, J. A., Barnhart, K. T. and Schlegel, P. N. Do sperm DNA integrity tests predict pregnancy with in vitro fertilization? <i>Fertil Steril</i> . 2008; 89 (4): 823-31.	More recent systematic review available
Cui, D., Han, G., Shang, Y., Liu, C., Xia, L., Li, L. and Yi, S. Antisperm antibodies in infertile men and their effect on semen parameters: a systematic review and meta-analysis. <i>Clin Chim Acta</i> . 2015; 444 29-36.	At least half of the studies includes men with abnormal semen parameters.
Culligan, P. J., Crane, M. M., Boone, W. R., Allen, T. C., Price, T. M. and Blauer, K. L. Validity and cost-effectiveness of antisperm antibody testing before in vitro fertilization. <i>Fertil Steril</i> . 1998; 69 (5): 894-8.	Only fertilisation rates reported, no pregnancy outcomes
Depuydt, C., Donders, G., Verstraete, L., Beert, J., Salembier, G., Bosmans, E., Dhont, N., Kerkhofs, C. and Ombelet, W. Negative Impact of Elevated DNA Fragmentation and Human Papillomavirus (HPV) Presence in Sperm on the Outcome of Intra-Uterine Insemination (IUI). <i>J Clin Med</i> . 2021; 10 (4):	Includes patients with mild male factor without stratification of results
Ford, W. C., Williams, K. M., McLaughlin, E. A., Harrison, S., Ray, B. and Hull, M. G. The indirect immunobead test for seminal antisperm antibodies and fertilization rates at in-vitro fertilization. <i>Hum Reprod</i> . 1996; 11 (7): 1418-22.	Only fertilisation rates reported, no pregnancy outcomes



Garcia, P. C., Rubio, E. M. and Pereira, O. C. M. Antisperm antibodies in infertile men and their correlation with seminal parameters. <i>Reprod Med Biol.</i> 2007; 6 (1): 33-38.	No reproductive outcomes reported.
Henkel, R., Morris, A., Vogiatzi, P., Saleh, R., Sallam, H., Boitrelle, F., Garrido, N., Arafa, M., Gül, M., Rambhatla, A., Maldonado Rosas, I., Agarwal, A., Leisegang, K., Siebert, T. I. Predictive value of seminal oxidation-reduction potential analysis for reproductive outcomes of ICSI. <i>Reprod Biomed Online</i> 2022	No stratification of results according to infertility diagnosis
Jaworek, H., Koudelakova, V., Oborna, I., Zborilova, B., Brezinova, J., Ruzickova, D., Vrbkova, J., Kourilova, P. and Hajduch, M. Impact of human papillomavirus infection on semen parameters and reproductive outcomes. <i>Reprod Biol Endocrinol.</i> 2021; 19 (1): 156.	Includes patients with mild male factor without stratification of results
Junk, S. M., Matson, P. L., Yovich, J. M., Bootsma, B. and Yovich, J. L. The fertilization of human oocytes by spermatozoa from men with antispermatozoal antibodies in semen. <i>J In Vitro Fert Embryo Transf.</i> 1986; 3 (6): 350-2.	Only fertilisation rates reported, no pregnancy outcomes
Malić Vončina, S., Golob, B., Ihan, A., Kopitar, A. N., Kolbezen, M. and Zorn, B. Sperm DNA fragmentation and mitochondrial membrane potential combined are better for predicting natural conception than standard sperm parameters. <i>Fertil Steril.</i> 2016; 105 (3): 637-644.e1.	Included male in the study cohort with abnormal semen parameters.
Moreno-Sepulveda, J. and Rajmil, O. Seminal human papillomavirus infection and reproduction: a systematic review and meta-analysis. <i>Andrology.</i> 2021; 9 (2): 478-502.	Includes studies with males with abnormal sperm parameters.
Nicopoulos, J., Vicens-Morton, A., Lewis, S. E. M., Lee, K., Larsen, P., Ramsay, J., Yap, T. and Minhas, S. Novel use of COMET parameters of sperm DNA damage may increase its utility to diagnose male infertility and predict live births following both IVF and ICSI. <i>Hum Reprod.</i> 2019; 34 (10): 1915-1923.	1 year of regular unprotected intercourse without pregnancy and no genetic abnormalities leading to male infertility other than anomalies in semen parameters
Osman, A., Alsomait, H., Seshadri, S., El-Toukhy, T. and Khalaf, Y. The effect of sperm DNA fragmentation on live birth rate after IVF or ICSI: a systematic review and meta-analysis. <i>Reprod Biomed Online.</i> 2015; 30 (2): 120-7.	Includes studies with abnormal sperm parameters without stratification of results
Rex, A. S., Wu, C., Aagaard, J. and Fedder, J. DNA Fragmentation in Human Spermatozoa and Pregnancy Rates after Intrauterine Insemination. Should the DFI Threshold Be Lowered? <i>J Clin Med.</i> 2021; 10 (6):	Includes patients with mild male factor without stratification of results
Ribas-Maynou, J., Yeste, M., Becerra-Tomás, N., Aston, K. I., James, E. R. and Salas-Huetos, A. Clinical implications of sperm DNA damage in IVF and ICSI: updated systematic review and meta-analysis. <i>Biol Rev Camb Philos Soc.</i> 2021; 96 (4): 1284-1300.	Includes patients with mild male factor without stratification of results
Rossato, M., Galeazzi, C., Ferigo, M., Foresta, C. Antisperm antibodies modify plasma membrane functional integrity and inhibit osmosensitive calcium influx in human sperm. <i>Hum Reprod.</i> 2004; 19(8): 1816-20.	No reproductive outcomes reported.
Sugihara, A., Van Avermaete, F., Roelant, E., Punjabi, U. and De Neubourg, D. The role of sperm DNA fragmentation testing in predicting intra-uterine insemination outcome: A systematic review and meta-analysis. <i>Eur J Obstet Gynecol Reprod Biol.</i> 2020; 244 8-15.	Includes studies with abnormal sperm parameters without stratification of results
Verheyen, G., Tournaye, H., Laurier, K., Devroey, P. and Van Steirteghem, A. Auto-controlled study on in-vitro fertilization performance with 'antibody-free' spermatozoa selected by immunobead adsorption from semen of patients with anti-sperm antibodies. <i>Hum Reprod.</i> 1994; 9 (6): 1119-26.	Study and control interventions are mixed in the outcomes
Vujisić, S., Lepej, S. Z., Jerković, L., Emedi, I. and Sokolić, B. Antisperm antibodies in semen, sera and follicular fluids of infertile patients: relation to reproductive outcome after in vitro fertilization. <i>Am J Reprod Immunol.</i> 2005; 54 (1): 13-20.	Included male in the study cohort with abnormal semen parameters.

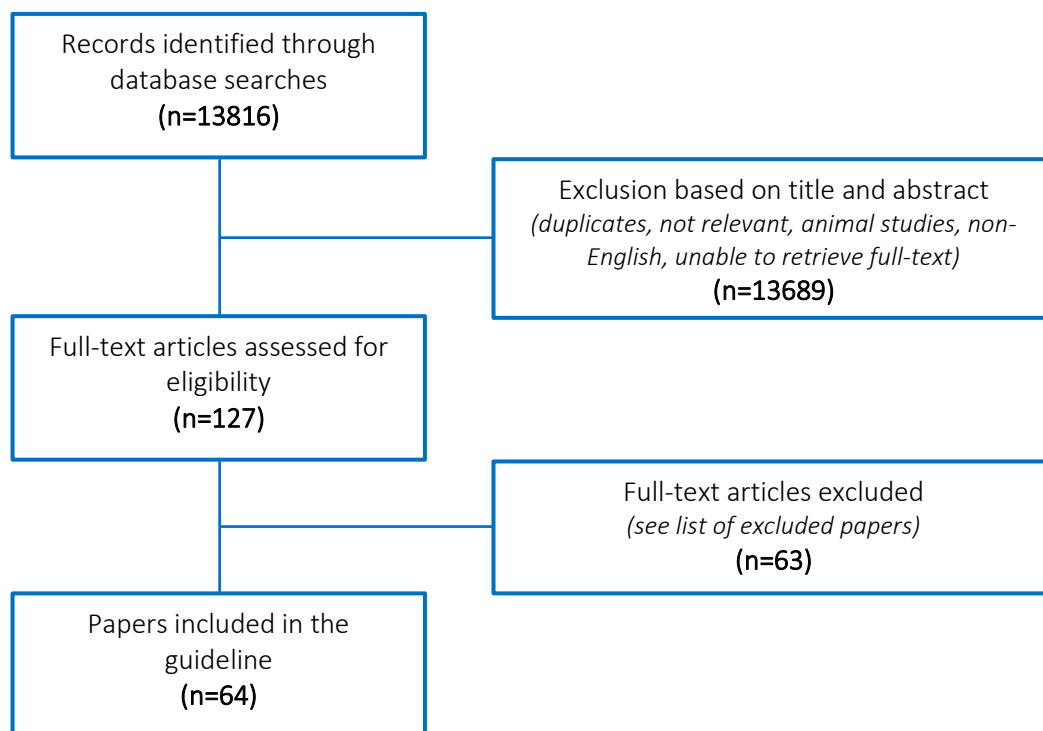


Weinberg, M., Sar-Shalom Nahshon, C., Feferkorn, I. and Bornstein, J. Evaluation of human papilloma virus in semen as a risk factor for low sperm quality and poor in vitro fertilization outcomes: a systematic review and meta-analysis. <i>Fertil Steril.</i> 2020; 113 (5): 955-969.e4.	Descriptive for clinical outcomes
Zhao, J., Zhang, Q., Wang, Y. and Li, Y. Whether sperm deoxyribonucleic acid fragmentation has an effect on pregnancy and miscarriage after in vitro fertilization/intracytoplasmic sperm injection: a systematic review and meta-analysis. <i>Fertil Steril.</i> 2014; 102 (4): 998-1005.e8.	Does not report on the critical outcomes of the guideline, i.e. LBR/OPR or multiple PR

II.10 Additional tests for systemic conditions

PICO QUESTION: SHOULD THERE BE ADDITIONAL EVALUATIONS OF POSSIBLE SYSTEMIC CAUSE OF UI IN THE COUPLE?

Flowchart



List of excluded papers

Reference	Exclusion criterion
Abalovich, M., Mittelberg, L., Allami, C., Gutierrez, S., Alcaraz, G., Otero, P. and Levalle, O. Subclinical hypothyroidism and thyroid autoimmunity in women with infertility. <i>Gynecol Endocrinol.</i> 2007; 23 (5): 279-83.	No control group
Andrisani, A., Sabbadin, C., Marin, L., Ragazzi, E., Dessole, F., Armanini, D., Donà, G., Bordin, L. and Ambrosini, G. The influence of thyroid autoimmunity on embryo quality in women undergoing assisted reproductive technology. <i>Gynecol Endocrinol.</i> 2018; 34 (9): 752-755.	No subdivision of UI in the results
Appasamy, M., Jauniaux, E., Serhal, P., Al-Qahtani, A., Groome, N. P. and Muttukrishna, S. Evaluation of the relationship between follicular fluid oxidative stress, ovarian hormones, and response to gonadotropin stimulation. <i>Fertil Steril.</i> 2008; 89 (4): 912-21.	No (fertile) controls



Ashrafi, M., Jahanian Sadatmahalleh, S., Akhoond, M. R., Ghaffari, F. and Zolfaghari, Z. ICSI Outcome in Infertile Couples with Different Causes of Infertility: A Cross-Sectional Study. <i>Int J Fertil Steril.</i> 2013; 7 (2): 88-95.	Subgroup of 34 were unexplained but groups were not identified separately in results
Aydemir, B., Kiziler, A. R., Onaran, I., Alici, B., Ozkara, H. and Akyolcu, M. C. Impact of Cu and Fe concentrations on oxidative damage in male infertility. <i>Biol Trace Elem Res.</i> 2006; 112 (3): 193-203.	UI but no sperm results not clearly stated as normal.
Ayvaliotis, B., Bronson, R., Rosenfeld, D. and Cooper, G. Conception rates in couples where autoimmunity to sperm is detected. <i>Fertil Steril.</i> 1985; 43 (5): 739-42.	No separate analysis for UI couples
Azem, F., Many, A., Ben Ami, I., Yovel, I., Amit, A., Lessing, J. B. and Kupfermenc, M. J. Increased rates of thrombophilia in women with repeated IVF failures. <i>Hum Reprod.</i> 2004; 19 (2): 368-70.	No separate analysis for UI couples
Bassey, I. E., Udoh, A. E., Essien, O. E., Isong, I. K., Gali, R. M. and Archibong, E. E. Thyroid hormones and prolactin levels in infertile women in southern Nigeria. <i>J Clin Diagn Res.</i> 2015; 9 (3): Oc13-5.	No separate analysis for UI couples
Belan, M., Carranza-Mamane, B., Pesant, M. H., AinMelk, Y., Duval, K., Jean-Denis, F., Langlois, M. F. and Baillargeon, J. P. Male partners of subfertile couples in which the spouse is obese display adverse weight and lifestyle associated with reduced sperm quality. <i>Obes Res Clin Pract.</i> 2019; 13 (3): 226-232.	No control group
Bianca, S., Barrano, B., Cutuli, N., Indaco, L., Cataliotti, A., Milana, G., Barone, C. and Ettore, G. Unexplained infertility and inherited thrombophilia. <i>Fertil Steril.</i> 2009; 92 (1): e4; author reply e5.	No separate analysis for UI couples
Chai, J., Yeung, W. Y., Lee, C. Y., Li, H. W., Ho, P. C. and Ng, H. Y. Live birth rates following in vitro fertilization in women with thyroid autoimmunity and/or subclinical hypothyroidism. <i>Clin Endocrinol (Oxf).</i> 2014; 80 (1): 122-7.	Very small subgroup of UI patients
Ciftci, H., Verit, A., Savas, M., Yeni, E. and Erel, O. Effects of N-acetylcysteine on semen parameters and oxidative/antioxidant status. <i>Urology.</i> 2009; 74 (1): 73-6.	UI in males, however, no data on the females.
Conway, D. I., Glazener, C. M., Kelly, N. and Hull, M. G. Routine measurement of thyroid hormones and FSH in infertility not worthwhile. <i>Lancet.</i> 1985; 1 (8435): 977-8.	No separate analysis for UI couples
Cramer, D. W., Sluss, P. M., Powers, R. D., McShane, P., Ginsburgs, E. S., Hornstein, M. D., Vitonis, A. F. and Barbieri, R. L. Serum prolactin and TSH in an in vitro fertilization population: is there a link between fertilization and thyroid function? <i>J Assist Reprod Genet.</i> 2003; 20 (6): 210-5.	166 patients had unexplained infertility but no subdivision of results
Dechaud, H., Anahory, T., Reyftmann, L., Loup, V., Hamamah, S. and Hedon, B. Obesity does not adversely affect results in patients who are undergoing in vitro fertilization and embryo transfer. <i>Eur J Obstet Gynecol Reprod Biol.</i> 2006; 127 (1): 88-93.	UI but no separation of results
Del Porto, F., Ferrero, S., Cifani, N., Sesti, G. and Proietta, M. Antiphospholipid antibodies and idiopathic infertility. <i>Lupus.</i> 2022; 31 (3): 347-353.	Chose patients with UI who had a positive aPL and we are not told what percentage that was. They recommend testing for aPL but cannot use this as no prevalence or comparison
Deroux, A., Dumestre-Perard, C., Dunand-Faure, C., Bouillet, L. and Hoffmann, P. Female Infertility and Serum Auto-antibodies: a Systematic Review. <i>Clin Rev Allergy Immunol.</i> 2017; 53 (1): 78-86.	UI selection unclear
Dhillon-Smith, R. K., Tobias, A., Smith, P. P., Middleton, L. J., Sunner, K. K., Baker, K., Farrell-Carver, S., Bender-Atik, R., Agrawal, R., Bhatia, K., Chu, J. J., Edi-Osagie, E., Ewies, A., Ghobara, T., Gupta, P., Jurkovic, D., Khalaf, Y., Mulbagal, K., Nunes, N., Overton, C., Quenby, S., Rai, R., Raine-Fenning, N., Robinson, L., Ross, J., Sizer, A., Small, R., Underwood, M., Kilby, M. D., Daniels,	No subdivision of UI in the results



J., Thangaratinam, S., Chan, S., Boelaert, K. and Coomarasamy, A. The Prevalence of Thyroid Dysfunction and Autoimmunity in Women With History of Miscarriage or Subfertility. <i>J Clin Endocrinol Metab.</i> 2020; 105 (8):	
Di Rosa, R., Ferrero, S., Cifani, N., Ferri, L., Proietta, M., Picchianti Diamanti, A. and Del Porto, F. In vitro fertilization and autoimmunity: Evidence from an observational study. <i>Eur J Obstet Gynecol Reprod Biol.</i> 2019; 234 137-142.	No subdivision of UI in the results
Dressler, N., Chandra, A., Aguirre Dávila, L., Spineli, L. M., Schippert, C. and von Versen-Höyneck, F. BMI and season are associated with vitamin D deficiency in women with impaired fertility: a two-centre analysis. <i>Arch Gynecol Obstet.</i> 2016; 293 (4): 907-14.	No control group, no separate analysis for UI and no clinical outcomes
Eggert-Kruse, W., Batschulat, K., Demirakca, T. and Strowitzki, T. Male immunity to the chlamydial 60 kDa heat shock protein (HSP 60) - associated with semen quality? <i>Andrologia.</i> 2015; 47 (1): 66-76.	No subdivision of UI in the results
Eldar-Geva, T., Shoham, M., Rösler, A., Margalioth, E. J., Livne, K. and Meirou, D. Subclinical hypothyroidism in infertile women: the importance of continuous monitoring and the role of the thyrotropin-releasing hormone stimulation test. <i>Gynecol Endocrinol.</i> 2007; 23 (6): 332-7.	No subdivision of UI in the results
Esteves, S. C., Schneider, D. T. and Verza, S., Jr. Influence of antisperm antibodies in the semen on intracytoplasmic sperm injection outcome. <i>Int Braz J Urol.</i> 2007; 33 (6): 795-802.	No subdivision of UI in the results
Feldthusen, A. D., Pedersen, P. L., Larsen, J., Toft Kristensen, T., Ellervik, C. and Kvetny, J. Impaired Fertility Associated with Subclinical Hypothyroidism and Thyroid Autoimmunity: The Danish General Suburban Population Study. <i>J Pregnancy.</i> 2015; 2015 132718.	No subdivision of UI in the results
Freischem, C. W., Knuth, U. A., Langer, K., Schneider, H. P. and Nieschlag, E. The lack of discriminant seminal and endocrine variables in the partners of fertile and infertile women. <i>Arch Gynecol.</i> 1984; 236 (1): 1-12.	UI but difficult to separate
Fumarola, A., Grani, G., Romanzi, D., Del Sordo, M., Bianchini, M., Aragona, A., Tranquilli, D. and Aragona, C. Thyroid function in infertile patients undergoing assisted reproduction. <i>Am J Reprod Immunol.</i> 2013; 70 (4): 336-41.	No subdivision of UI in the results
Garcia-Segura, S., Ribas-Maynou, J., Lara-Cerrillo, S., Garcia-Peiró, A., Castel, A. B., Benet, J. and Oliver-Bonet, M. Relationship of Seminal Oxidation-Reduction Potential with Sperm DNA Integrity and pH in Idiopathic Infertile Patients. <i>Biology (Basel).</i> 2020; 9 (9):	Males and no information on females
Genco, P. V., Mathur, S., Williamson, H. O., Rust, P. F., Glassman, A. B. and Fudenberg, H. H. Antibodies to A19 and Bw35 complexes of human leukocyte antigens are present in infertile subjects with sperm antibodies. <i>Fertil Steril.</i> 1984; 42 (4): 554-60.	No control subjects so no background rate
Gerhard, I., Lenhard, H. K., Eggert-Kruse, W. and Runnebaum, B. Routine hormone load tests are unnecessary in infertile men. <i>Andrologia.</i> 1992; 24 (4): 219-26.	30% of males had UI. No subdivision of infertility cause
Gracia, C. R., Morse, C. B., Chan, G., Schilling, S., Prewitt, M., Sammel, M. D. and Mandel, S. J. Thyroid function during controlled ovarian hyperstimulation as part of in vitro fertilization. <i>Fertil Steril.</i> 2012; 97 (3): 585-91.	No subdivision of UI in the results
Grassi, G., Balsamo, A., Ansaldi, C., Balbo, A., Massobrio, M. and Benedetto, C. Thyroid autoimmunity and infertility. <i>Gynecol Endocrinol.</i> 2001; 15 (5): 389-96.	No control group, no subdivision of UI in the results
Green, K. A., Werner, M. D., Franasiak, J. M., Juneau, C. R., Hong, K. H. and Scott, R. T., Jr. Investigating the optimal preconception TSH range for patients undergoing IVF when controlling for embryo quality. <i>J Assist Reprod Genet.</i> 2015; 32 (10): 1469-76.	No subdivision of UI in the results
Janssen, H. J., Bastiaans, B. A., Goverde, H. J., Hollanders, H. M., Wetzels, A. A. and Schellekens, L. A. Antisperm antibodies and in vitro fertilization. <i>J Assist Reprod Genet.</i> 1992; 9 (4): 345-9.	males with abnormal sperm parameters in the male and female positive groups



Hosen, M. B., Islam, M. R., Begum, F., Kabir, Y. and Howlader, M. Z. Oxidative stress induced sperm DNA damage, a possible reason for male infertility. <i>Iran J Reprod Med.</i> 2015; 13 (9): 525-32.	UI but vague information regarding female and male SA
Khan, H. L., Bhatti, S., Abbas, S., Kaloglu, C., Qurat-UI-Ain Zahra, S., Khan, Y. L., Hassan, Z., Turhan, NÖ and Aydin, H. H. Melatonin levels and microRNA (miRNA) relative expression profile in the follicular ambient microenvironment in patients undergoing in vitro fertilization process. <i>J Assist Reprod Genet.</i> 2021; 38 (2): 443-459.	No controls and only follicular fluid measured
Kim, N. Y., Cho, H. J., Kim, H. Y., Yang, K. M., Ahn, H. K., Thornton, S., Park, J. C., Beaman, K., Gilman-Sachs, A. and Kwak-Kim, J. Thyroid autoimmunity and its association with cellular and humoral immunity in women with reproductive failures. <i>Am J Reprod Immunol.</i> 2011; 65 (1): 78-87.	UI but mixed results with RSA and no controls
Lasa, J. S., Zubiaurre, I. and Soifer, L. O. Risk of infertility in patients with celiac disease: a meta-analysis of observational studies. <i>Arq Gastroenterol.</i> 2014; 51 (2): 144-50.	replaced by a more comprehensive systematic review
Li, Y., Yang, D. and Zhang, Q. Impact of overweight and underweight on IVF treatment in Chinese women. <i>Gynecol Endocrinol.</i> 2010; 26 (6): 416-22.	No subdivision of UI in the results
Liu, Y., Kong, X. D., Wu, Q. H., Li, G., Song, L. and Sun, Y. P. Karyotype analysis in large-sample infertile couples living in Central China: a study of 14965 couples. <i>J Assist Reprod Genet.</i> 2013; 30 (4): 547-53.	Not able to determine unexplained infertility. Males with normal count had prevalence of 1.69% which was less than other groups
Ludwig, M., Banz, C., Katalinic, A., Jacobeit, J. W., Epe, M., Von Zur Mühlen, A. and Schulte, H. M. The usefulness of a thyrotropin-releasing hormone stimulation test in subfertile female patients. <i>Gynecol Endocrinol.</i> 2007; 23 (4): 226-30.	No subdivision of UI in the results
Magri, F., Capelli, V., Gaiti, M., Brambilla, E., Montesion, L., Rotondi, M., Spinillo, A., Nappi, R. E. and Chiovato, L. Impaired outcome of controlled ovarian hyperstimulation in women with thyroid autoimmune disease. <i>Thyroid.</i> 2013; 23 (10): 1312-8.	No clear subdivision of UI in the results
Mansuri, T., Jadeja, S. H. D., Singh, M., Begum, R. and Robin, P. Phosphodiesterase 8B Polymorphism rs4704397 Is Associated with Infertility in Subclinical Hypothyroid Females: A Case-Control Study. <i>Int J Fertil Steril.</i> 2020; 14 (2): 122-128.	UI but hypothyroid and no controls
Micoogullari, U., Cakici, M. C., Kilic, F. U., Kisa, E., Ozcift, B., Caglayan, A., Neselioglu, S., Karatas, O. F. and Erel, O. Evaluation of the role of thiol / disulfide homeostasis in the etiology of idiopathic male infertility with a novel and automated assay. <i>Syst Biol Reprod Med.</i> 2022; 68 (2): 162-168.	No female data to establish UI
Mukheef, M. A., Ali, R. A. and Alheidery, H. H. A. Follicular fluid 8-Hydroxy-2-Deoxyguanosine (8-OHdG) as biomarker for oxidative stress in intracytoplasmic sperm injection. <i>J Med Invest.</i> 2022; 69 (1.2): 112-116.	No subdivision of UI in the results
Murakami, N., Kitajima, M., Ohyama, K., Aibara, N., Taniguchi, K., Wei, M., Kitajima, Y., Miura, K. and Masuzaki, H. Comprehensive immune complexome analysis detects disease-specific immune complex antigens in seminal plasma and follicular fluids derived from infertile men and women. <i>Clin Chim Acta.</i> 2019; 495 545-551.	Some UI but no control group
Olszak-Wąsik, K., Bednarska-Czerwińska, A., Olejek, A. and Tukiendorf, A. From "Every Day" Hormonal to Oxidative Stress Biomarkers in Blood and Follicular Fluid, to Embryo Quality and Pregnancy Success? <i>Oxid Med Cell Longev.</i> 2019; 2019 1092415.	No (fertile) controls
Orvieto, R., Meltcer, S., Nahum, R., Rabinson, J., Anteby, E. Y. and Ashkenazi, J. The influence of body mass index on in vitro fertilization outcome. <i>Int J Gynaecol Obstet.</i> 2009; 104 (1): 53-5.	UI at entry but no results



Paffoni, A., Ferrari, S., Mangiarini, A., Noli, S., Bulfoni, A., Vigano, P., Parazzini, F. and Somigliana, E. Concordance of vitamin D peripheral levels in infertile couples' partners. <i>Gynecol Endocrinol.</i> 2017; 33 (8): 649-652.	UI not defined and lumped with POI
Pagidas, K., Hemmings, R., Falcone, T. and Miron, P. The effect of antisperm autoantibodies in male or female partners undergoing in vitro fertilization-embryo transfer. <i>Fertil Steril.</i> 1994; 62 (2): 363-9.	comparison is with patients with antibodies and not against those without antibodies
Papanikolaou, E. G., Vernaev, V., Kolibianakis, E., Assche, E. V., Bonduelle, M., Liebaers, I., Van Steirteghem, A. and Devroey, P. Is chromosome analysis mandatory in the initial investigation of normovulatory women seeking infertility treatment? <i>Hum Reprod.</i> 2005; 20 (10): 2899-903.	No clear definition into UI in tables
Pasqualotto, F. F., Sharma, R. K., Nelson, D. R., Thomas, A. J. and Agarwal, A. Relationship between oxidative stress, semen characteristics, and clinical diagnosis in men undergoing infertility investigation. <i>Fertil Steril.</i> 2000; 73 (3): 459-64.	Subgroup of male idiopathic infertility but no female data
Pasqualotto, F. F., Sharma, R. K., Pasqualotto, E. B. and Agarwal, A. Poor semen quality and ROS-TAC scores in patients with idiopathic infertility. <i>Urol Int.</i> 2008; 81 (3): 263-70.	Idiopathic infertility but little detail
Rajah, S. V., Parslow, J. M., Howell, R. J. and Hendry, W. F. The effects on in-vitro fertilization of autoantibodies to spermatozoa in subfertile men. <i>Hum Reprod.</i> 1993; 8 (7): 1079-82.	potential selection bias: no clear inclusion criteria applied; groups are expected to not be comparable at clinical baseline level because of aetiology of infertility; no adjustment for confounders; small sample size in both groups
Rashad, N. M., El Shabrawy, R. M., Radwan, A. M., Allam, R. M., Abdul-Maksoud, R. S. and Sherif, M. M. Interferon-gamma Expression Profile as Diagnostic Signatures of Unexplained Infertility in Female Patients Suffer from Hashimoto's Thyroiditis. <i>Iran J Allergy Asthma Immunol.</i> 2021; 20 (4): 465-472.	Patients with Hashimoto's thyroiditis were chosen and then fertility looked at . Doesn't tell us if more common than other causes or controls
Rijal, B., Shrestha, R. and Jha, B. Association of thyroid dysfunction among infertile women visiting infertility center of Om Hospital, Kathmandu, Nepal. <i>Nepal Med Coll J.</i> 2011; 13 (4): 247-9.	No comparison to fertile controls
Selva, J., Martin-Pont, B., Hugues, J. N., Rince, P., Fillion, C., Herve, F., Tamboise, A. and Tamboise, E. Cytogenetic study of human oocytes uncleaved after in-vitro fertilization. <i>Hum Reprod.</i> 1991; 6 (5): 709-13.	Oocytes only and does not give information on the karyotype of the woman
Shah, D. K., Missmer, S. A., Berry, K. F., Racowsky, C. and Ginsburg, E. S. Effect of obesity on oocyte and embryo quality in women undergoing in vitro fertilization. <i>Obstet Gynecol.</i> 2011; 118 (1): 63-70.	UI at entry but no results
Signorini, C., Moretti, E., Noto, D., Micheli, L., Ponchia, R. and Collodel, G. Fatty Acid Oxidation and Pro-Resolving Lipid Mediators Are Related to Male Infertility. <i>Antioxidants (Basel).</i> 2022; 11 (1):	Unable to ascertain whether UI or not due to lack of female data
Skowronek, M. F., Velazquez, T., Mut, P., Figueiro, G., Sans, M., Bertoni, B. and Sapiro, R. Associations between male infertility and ancestry in South Americans: a case control study. <i>BMC Med Genet.</i> 2017; 18 (1): 78.	No fertile data
Tanacan, A. and Beksac, M. S. Spontaneous pregnancies in patients with at least one failed IVF cycle after the management of autoimmune disorders, hereditary thrombophilia, and methylation disorders. <i>JBRA Assist Reprod.</i> 2019; 23 (4): 361-366.	No controls
Unuane, D., Velkeniers, B., Anckaert, E., Schiettecatte, J., Tournaye, H., Haentjens, P. and Poppe, K. Thyroglobulin autoantibodies: is there any added	Subgroup of possible UI but not defined



value in the detection of thyroid autoimmunity in women consulting for fertility treatment? <i>Thyroid</i> . 2013; 23 (8): 1022-8.	
Yilmaz, N., Ersoy, E., Tokmak, A., Sargin, A., Ozgu-Erdinc, A. S., Erkaya, S. and Ibrahim Yakut, H. Do Serum Vitamin D Levels Have Any Effect on Intrauterine Insemination Success? <i>Int J Fertil Steril</i> . 2018; 12 (2): 164-168.	No subdivision of UI in the results
Yusuf, I. and Emokpae, M. A. Association between a marker of sperm DNA damage and sperm indices in infertile males in Benin City, Nigeria: A cross-sectional study. <i>Int J Reprod Biomed</i> . 2021; 19 (2): 137-146.	Unable to ascertain whether UI or not due to lack of female data

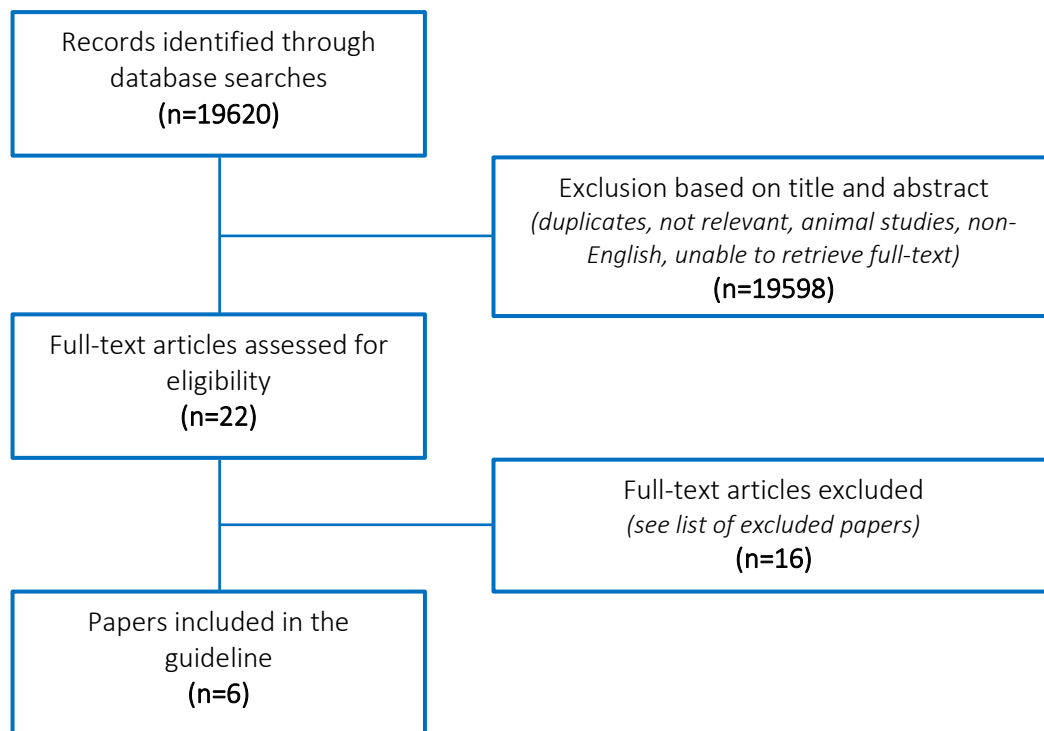


III. Treatment

III.1 Expectant management

PICO QUESTION: WHAT IS THE VALUE OF EXPECTANT MANAGEMENT COMPARED TO ACTIVE TREATMENT FOR PATIENTS WITH UI?

Flowchart



List of excluded papers

Reference	Exclusion criterion
Aboughar, M. A., Mansour, R. T., Serour, G. I., Amin, Y., Abbas, A. M. and Salah, I. M. Ovarian superstimulation and intrauterine insemination for the treatment of unexplained infertility. <i>Fertil Steril.</i> 1993; 60 (2): 303-6.	Cohort study in the presence of higher quality evidence
Brandes, M., Hamilton, C. J., van der Steen, J. O., de Bruin, J. P., Bots, R. S., Nelen, W. L. and Kremer, J. A. Unexplained infertility: overall ongoing pregnancy rate and mode of conception. <i>Hum Reprod.</i> 2011; 26 (2): 360-8.	Not a direct comparison. Treatment selected according to prognosis
Custers, I. M., van Rumste, M. M., van der Steeg, J. W., van Wely, M., Hompes, P. G., Bossuyt, P., Broekmans, F. J., Renckens, C. N., Eijkemans, M. J., van Dessel, T. J., van der Veen, F., Mol, B. W. and Steures, P. Long-term outcome in couples with unexplained subfertility and an intermediate prognosis initially randomized between expectant management and immediate treatment. <i>Hum Reprod.</i> 2012; 27 (2): 444-50.	Included in SR Ayeleke 2020
Deaton, J. L., Gibson, M., Blackmer, K. M., Nakajima, S. T., Badger, G. J. and Brumsted, J. R. A randomized, controlled trial of clomiphene citrate and intrauterine insemination in couples with unexplained infertility or surgically corrected endometriosis. <i>Fertil Steril.</i> 1990; 54 (6): 1083-8.	Included in SR Ayeleke 2020



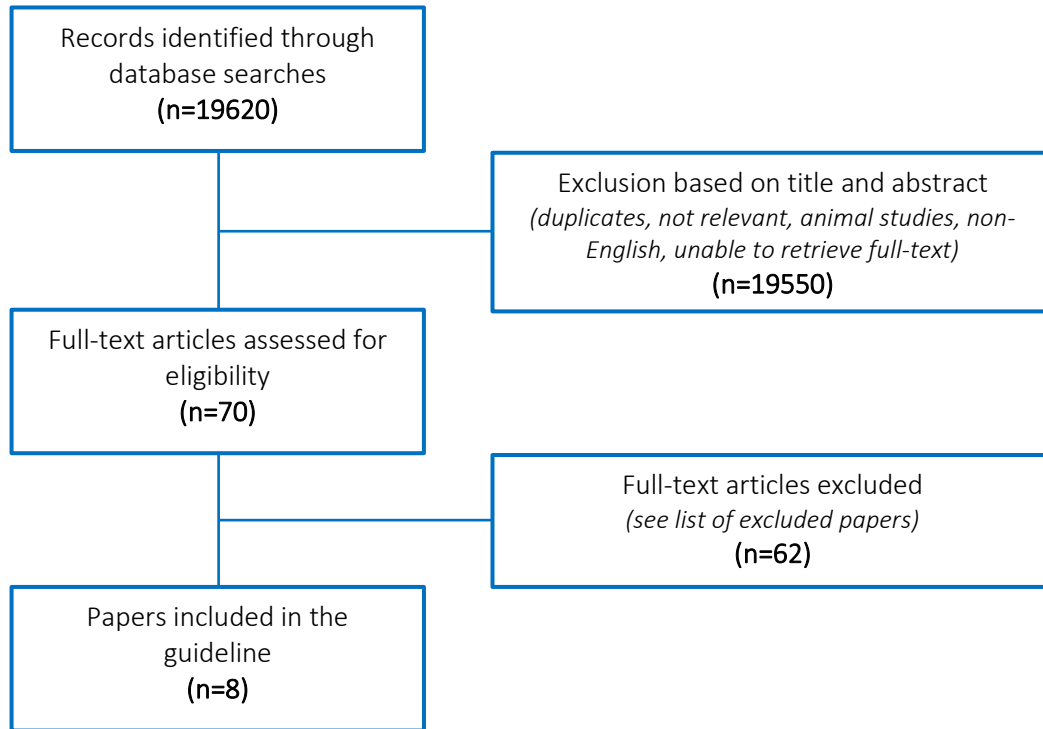
Farquhar, C. M., Liu, E., Armstrong, S., Arroll, N., Lensen, S. and Brown, J. Intrauterine insemination with ovarian stimulation versus expectant management for unexplained infertility (TUI): a pragmatic, open-label, randomised, controlled, two-centre trial. <i>Lancet</i> . 2018; 391 (10119): 441-450.	Included in SR Ayeleke 2020
Fisch, P., Casper, R. F., Brown, S. E., Wrixon, W., Collins, J. A., Reid, R. L. and Simpson, C. Unexplained infertility: evaluation of treatment with clomiphene citrate and human chorionic gonadotropin. <i>Fertil Steril</i> . 1989; 51 (5): 828-33.	No mention of expectant treatment
Glazener, C. M., Coulson, C., Lambert, P. A., Watt, E. M., Hinton, R. A., Kelly, N. G. and Hull, M. G. Clomiphene treatment for women with unexplained infertility: placebo-controlled study of hormonal responses and conception rates. <i>Gynecol Endocrinol</i> . 1990; 4 (2): 75-83.	unable to seerate data for first arm of crossover
Godart, E. S., Shin, D. H., Christensen, E., Thompson, E. R. and Turek, P. J. A study of pregnancy rates in "cleared" male factor couples. <i>Transl Androl Urol</i> . 2021; 10 (2): 620-625.	female not examined, not UI
Helmerhorst, F. M., Van Vliet, Haam, Gornas, T., Finken, M. J. and Grimes, D. A. Intra-uterine insemination versus timed intercourse or expectant management for cervical hostility in subfertile couples. <i>Cochrane Database of Systematic Reviews</i> . 2005; (4):	more recent SR on the topic available
Kersten, F. A. M., Nelen, Wldm, van den Boogaard, N. M., van Rumste, M. M., Koks, C. A., IntHout, J., Verhoeve, H. R., Pelinck, M. J., Boks, D. E. S., Gianotten, J., Broekmans, F. J. M., Goddijn, M., Braat, D. D. M., Mol, B. W. J. and Hermens, Rpgm. Implementing targeted expectant management in fertility care using prognostic modelling: a cluster randomized trial with a multifaceted strategy. <i>Hum Reprod</i> . 2017; 32 (8): 1648-1657.	Randomization not on patient level; inclusion criteria also include couples with mild known infertility factor + clinical outcomes are not analysed by type of treatment
Pandian, Z., Bhattacharya, S., Nikolaou, D., Vale, L. and Templeton, A. The effectiveness of IVF in unexplained infertility: a systematic Cochrane review. 2002. <i>Hum Reprod</i> . 2003; 18 (10): 2001-7.	more recent SR on the topic available
Peterson, C. M., Hatasaka, H. H., Jones, K. P., Poulson, A. M., Jr., Carrell, D. T. and Urry, R. L. Ovulation induction with gonadotropins and intrauterine insemination compared with in vitro fertilization and no therapy: a prospective, nonrandomized, cohort study and meta-analysis. <i>Fertil Steril</i> . 1994; 62 (3): 535-44.	no true comparison with expectant
Scholten, I., van Zijl, M., Custers, I. M., Brandes, M., Gianotten, J., van der Linden, P. J. Q., Hompes, P. G. A., van der Veen, F. and Mol, B. W. J. The effectiveness of intrauterine insemination: A matched cohort study. <i>Eur J Obstet Gynecol Reprod Biol</i> . 2017; 212 91-95.	no stratification according to infertility diagnosis
Steures, P., Berkhout, J. C., Hompes, P. G., van der Steeg, J. W., Bossuyt, P. M., van der Veen, F., Habbema, J. D., Eijkemans, M. J. and Mol, B. W. Patients' preferences in deciding between intrauterine insemination and expectant management. <i>Hum Reprod</i> . 2005; 20 (3): 752-5.	patient preference was guided by the physician providing prognosis and the recommended treatment for that.
Steures, P., van der Steeg, J. W., Hompes, P. G., Habbema, J. D., Eijkemans, M. J., Broekmans, F. J., Verhoeve, H. R., Bossuyt, P. M., van der Veen, F. and Mol, B. W. Intrauterine insemination with controlled ovarian hyperstimulation versus expectant management for couples with unexplained subfertility and an intermediate prognosis: a randomised clinical trial. <i>Lancet</i> . 2006; 368 (9531): 216-21.	Included in SR Ayeleke 2020
van Eekelen, R., van Geloven, N., van Wely, M., McLernon, D. J., Mol, F., Custers, I. M., Steures, P., Bhattacharya, S., Mol, B. W., van der Veen, F. and Eijkemans, M. J. Is IUI with ovarian stimulation effective in couples with unexplained subfertility? <i>Hum Reprod</i> . 2019; 34 (1): 84-91.	Cohort study in the presence of higher quality evidence



III.2 Active treatment

PICO QUESTION: IF ACTIVE TREATMENT IS PURSUED, WHICH TYPE OF ACTIVE TREATMENT FOR UI?

Flowchart



List of excluded papers

Reference	Exclusion criterion
Aboulghar, M. A., Mansour, R. T., Serour, G. I., Amin, Y., Ramzy, A. M., Sattar, M. A. and Kamal, A. Management of long-standing unexplained infertility: A prospective study. <i>Am J Obstet Gynecol.</i> 1999; 181 (2): 371-5.	Cohort study in the presence of higher quality evidence
Aboulghar, M., Mansour, R., Serour, G., Abdrzak, A., Amin, Y. and Rhodes, C. Controlled ovarian hyperstimulation and intrauterine insemination for treatment of unexplained infertility should be limited to a maximum of three trials. <i>Fertil Steril.</i> 2001; 75 (1): 88-91.	Cohort study in the presence of higher quality evidence
Abu-Heija, A. and Yates, R. Comparison of controlled ovarian superstimulation with or without intrauterine insemination for the treatment of unexplained infertility. <i>Ann Saudi Med.</i> 1995; 15 (5): 464-5.	Cohort study in the presence of higher quality evidence
Akbari Sene, A., Ghorbani, S. and Ashrafi, M. Comparison of the pregnancy outcomes and the incidence of fetal congenital abnormalities in infertile women treated with letrozole and clomiphene citrate. <i>J Obstet Gynaecol Res.</i> 2018; 44 (6): 1036-1041.	Cohort study in the presence of higher quality evidence
Arici, A., Byrd, W., Bradshaw, K., Kutteh, W. H., Marshburn, P. and Carr, B. R. Evaluation of clomiphene citrate and human chorionic gonadotropin treatment: a prospective, randomized, crossover study during intrauterine insemination cycles. <i>Fertil Steril.</i> 1994; 61 (2): 314-8.	Included in systematic review Ayeleke et al., 2020
Begum, M. R., Quadir, E., Begum, A., Begum, R. A. and Begum, M. Role of aromatase inhibitor in ovulation induction in patients with poor response to clomiphene citrate. <i>J Obstet Gynaecol Res.</i> 2006; 32 (5): 502-6.	Included women with anovulation



<p>Bensdorp, A. J., Tjon-Kon-Fat, R. I., Bossuyt, P. M., Koks, C. A., Oosterhuis, G. J., Hoek, A., Hompes, P. G., Broekmans, F. J., Verhoeve, H. R., de Bruin, J. P., van Golde, R., Repping, S., Cohlen, B. J., Lambers, M. D., van Bommel, P. F., Slappendel, E., Perquin, D., Smeenk, J. M., Pelinck, M. J., Gianotten, J., Hoozemans, D. A., Maas, J. W., Eijkemans, M. J., van der Veen, F., Mol, B. W., van Wely, M. Prevention of multiple pregnancies in couples with unexplained or mild male subfertility: randomised controlled trial of in vitro fertilisation with single embryo transfer or in vitro fertilisation in modified natural cycle compared with intrauterine insemination with controlled ovarian hyperstimulation. <i>Bmj.</i> 2015; 350: g7771</p>	<p>Included in systematic review Nandi et al., 2022</p>
<p>Bhattacharya, S., Harrild, K., Mollison, J., Wordsworth, S., Tay, C., Harrold, A., McQueen, D., Lyall, H., Johnston, L., Burrage, J., Grossett, S., Walton, H., Lynch, J., Johnstone, A., Kini, S., Raja, A. and Templeton, A. Clomifene citrate or unstimulated intrauterine insemination compared with expectant management for unexplained infertility: pragmatic randomised controlled trial. <i>Bmj.</i> 2008; 337 a716.</p>	<p>Included in systematic review Ayeleke et al., 2020</p>
<p>Brandes, M., Hamilton, C. J., van der Steen, J. O., de Bruin, J. P., Bots, R. S., Nelen, W. L. and Kremer, J. A. Unexplained infertility: overall ongoing pregnancy rate and mode of conception. <i>Hum Reprod.</i> 2011; 26 (2): 360-8.</p>	<p>Cohort study in the presence of higher quality evidence</p>
<p>Chaffkin, L. M., Nulsen, J. C., Luciano, A. A. and Metzger, D. A. A comparative analysis of the cycle fecundity rates associated with combined human menopausal gonadotropin (hMG) and intrauterine insemination (IUI) versus either hMG or IUI alone. <i>Fertil Steril.</i> 1991; 55 (2): 252-7.</p>	<p>Cohort study in the presence of higher quality evidence</p>
<p>Chambers, G. M., Sullivan, E. A., Shanahan, M., Ho, M. T., Priester, K. and Chapman, M. G. Is in vitro fertilisation more effective than stimulated intrauterine insemination as a first-line therapy for subfertility? A cohort analysis. <i>Aust N Z J Obstet Gynaecol.</i> 2010; 50 (3): 280-8.</p>	<p>Cohort study in the presence of higher quality evidence</p>
<p>Chung, C. C., Fleming, R., Jamieson, M. E., Yates, R. W. and Coutts, J. R. Randomized comparison of ovulation induction with and without intrauterine insemination in the treatment of unexplained infertility. <i>Hum Reprod.</i> 1995; 10 (12): 3139-41.</p>	<p>Included in systematic review Ayeleke et al., 2020</p>
<p>Costello, M. F. Systematic review of the treatment of ovulatory infertility with clomiphene citrate and intrauterine insemination. <i>Aust N Z J Obstet Gynaecol.</i> 2004; 44 (2): 93-102.</p>	<p>More recent systematic review available</p>
<p>Crosignani, P. G., Walters, D. E. and Soliani, A. The ESHRE multicentre trial on the treatment of unexplained infertility: a preliminary report. <i>European Society of Human Reproduction and Embryology. Hum Reprod.</i> 1991; 6 (7): 953-8.</p>	<p>Included in systematic review Ayeleke et al., 2020 and Nandi et al., 2022</p>
<p>Custers, I. M., König, T. E., Broekmans, F. J., Hompes, P. G., Kaaijk, E., Oosterhuis, J., Mochtar, M. H., Repping, S., van Wely, M., Steures, P., van der Veen, F. and Mol, B. W. Couples with unexplained subfertility and unfavorable prognosis: a randomized pilot trial comparing the effectiveness of in vitro fertilization with elective single embryo transfer versus intrauterine insemination with controlled ovarian stimulation. <i>Fertil Steril.</i> 2011; 96 (5): 1107-11.e1.</p>	<p>Included in systematic review Nandi et al., 2022</p>
<p>Danhof, N. A., van Wely, M., Repping, S., Koks, C., Verhoeve, H. R., de Bruin, J. P., Verberg, M. F. G., van Hooff, M. H. A., Cohlen, B. J., van Heteren, C. F., Fleischer, K., Gianotten, J., van Disseldorp, J., Visser, J., Broekmans, F. J. M., Mol, B. W. J., van der Veen, F. and Mochtar, M. H. Follicle stimulating hormone versus clomiphene citrate in intrauterine insemination for unexplained subfertility: a randomized controlled trial. <i>Hum Reprod.</i> 2018; 33 (10): 1866-1874.</p>	<p>Not within scope: comparison of stimulation protocol for IUI</p>
<p>Danhof, N. A., van Wely, M., Repping, S., van der Ham, D. P., Klijn, N., Janssen, Icah, Rijn-van Weert, J. M., Twisk, M., Traas, M. A. F., Pelinck, M. J., Perquin, D. A. M., Boks, D. E. S., Sluijmer, A., Mol, B. W. J., van der Veen, F. and Mochtar, M. H. Gonadotrophins or clomiphene citrate in couples with unexplained</p>	<p>Not within scope: comparison of stimulation protocol for IUI</p>



infertility undergoing intrauterine insemination: a cost-effectiveness analysis. <i>Reprod Biomed Online</i> . 2020; 40 (1): 99-104.	
Danhof, N. A., Wang, R., van Wely, M., van der Veen, F., Mol, B. W. J. and Mochtar, M. H. IUI for unexplained infertility-a network meta-analysis. <i>Hum Reprod Update</i> . 2020; 26 (1): 1-15.	Includes Martinez 1990, which does not allow extraction of data on UI alone
DiMarzo, S. J., Kennedy, J. F., Young, P. E., Hebert, S. A., Rosenberg, D. C. and Villanueva, B. Effect of controlled ovarian hyperstimulation on pregnancy rates after intrauterine insemination. <i>Am J Obstet Gynecol</i> . 1992; 166 (6 Pt 1): 1607-12; discussion 1612-3.	Cohort study in the presence of higher quality evidence
Elzeiny, H., Garrett, C., Toledo, M., Stern, K., McBain, J. and Baker, H. W. A randomised controlled trial of intra-uterine insemination versus in vitro fertilisation in patients with idiopathic or mild male infertility. <i>Aust N Z J Obstet Gynaecol</i> . 2014; 54 (2): 156-61.	Included in systematic review Nandi et al., 2022 and Pandian et al., 2015
Evans, J., Wells, C., Gregory, L. and Walker, S. A comparison of intrauterine insemination, intraperitoneal insemination, and natural intercourse in superovulated women. <i>Fertil Steril</i> . 1991; 56 (6): 1183-7.	Excluded from systematic review Ayeleke et al., 2020 because no pre-cross-over data available
Goldman, M. B., Thornton, K. L., Ryley, D., Alper, M. M., Fung, J. L., Hornstein, M. D. and Reindollar, R. H. A randomized clinical trial to determine optimal infertility treatment in older couples: the Forty and Over Treatment Trial (FORT-T). <i>Fertil Steril</i> . 2014; 101 (6): 1574-81.e1-2.	Included in systematic review Nandi et al., 2022
Goverde, A. J., McDonnell, J., Vermeiden, J. P., Schats, R., Rutten, F. F. and Schoemaker, J. Intrauterine insemination or in-vitro fertilisation in idiopathic subfertility and male subfertility: a randomised trial and cost-effectiveness analysis. <i>Lancet</i> . 2000; 355 (9197): 13-8.	Included in systematic review Ayeleke et al., 2020 and Nandi et al., 2022
Gowri, V., Al-Amri, A., Almamari, T. M. A., Al Khaduri, M., Jaju, S. The Success of Ovulation Induction with Letrozole and Gonadotropins in Obese and Nonobese Women: A Study from a Tertiary Center. <i>Int J Reprod Med</i> . 2022; 1931716	Includes mild male infertility in the UI group
Gregoriou, O., Vitoratos, N., Papadias, C., Konidaris, S., Gargaropoulos, A. and Louridas, C. Controlled ovarian hyperstimulation with or without intrauterine insemination for the treatment of unexplained infertility. <i>Int J Gynaecol Obstet</i> . 1995; 48 (1): 55-9.	Excluded from systematic review Ayeleke et al., 2020
Gunn, D. D. and Bates, G. W. Evidence-based approach to unexplained infertility: a systematic review. <i>Fertil Steril</i> . 2016; 105 (6): 1566-1574.e1.	More recent systematic review available
Guzick, D. S., Carson, S. A., Coutifaris, C., Overstreet, J. W., Factor-Litvak, P., Steinkampf, M. P., Hill, J. A., Mastroianni, L., Buster, J. E., Nakajima, S. T., Vogel, D. L. and Canfield, R. E. Efficacy of superovulation and intrauterine insemination in the treatment of infertility. National Cooperative Reproductive Medicine Network. <i>N Engl J Med</i> . 1999; 340 (3): 177-83.	Included in systematic review Ayeleke et al., 2020
Hewitt, J., Cohen, J., Krishnaswamy, V., Fehilly, C. B., Steptoe, P. C. and Walters, D. E. Treatment of idiopathic infertility, cervical mucus hostility, and male infertility: artificial insemination with husband's semen or in vitro fertilization? <i>Fertil Steril</i> . 1985; 44 (3): 350-5.	Cohort study in the presence of higher quality evidence
Huang, S., Wang, R., Li, R., Wang, H., Qiao, J. and Mol, B. W. J. Ovarian stimulation in infertile women treated with the use of intrauterine insemination: a cohort study from China. <i>Fertil Steril</i> . 2018; 109 (5): 872-878.	Cohort study in the presence of higher quality evidence
Hughes, E., Brown, J., Collins, J. J. and Vanderkerchove, P. Clomiphene citrate for unexplained subfertility in women. <i>Cochrane Database Syst Rev</i> . 2010; 2010 (1): Cd000057.	More recent systematic review available
Isaksson, R. and Tiitinen, A. Superovulation combined with insemination or timed intercourse in the treatment of couples with unexplained infertility and minimal endometriosis. <i>Acta Obstet Gynecol Scand</i> . 1997; 76 (6): 550-4.	Pseudo-randomised trial



Kalu, E., Thum, M. Y. and Abdalla, H. Intrauterine insemination in natural cycle may give better results in older women. <i>J Assist Reprod Genet.</i> 2007; 24 (2-3): 83-6.	Cohort study in the presence of higher quality evidence
Karlström, P. O., Bergh, T. and Lundkvist, O. A prospective randomized trial of artificial insemination versus intercourse in cycles stimulated with human menopausal gonadotropin or clomiphene citrate. <i>Fertil Steril.</i> 1993; 59 (3): 554-9.	Included in systematic review Ayeleke et al., 2020
Kaur, J., Suri, V., Gainer, S. and Arora, A. Prospective randomized trial comparing efficacy of letrozole step-up protocol with letrozole plus gonadotropins for controlled ovarian stimulation and intrauterine insemination in patients with unexplained infertility. <i>Arch Gynecol Obstet.</i> 2019; 300 (6): 1767-1771.	Not within scope: stimulation protocols for IUI
Kirby, C. A., Flaherty, S. P., Godfrey, B. M., Warnes, G. M. and Matthews, C. D. A prospective trial of intrauterine insemination of motile spermatozoa versus timed intercourse. <i>Fertil Steril.</i> 1991; 56 (1): 102-7.	No pre-cross-over data available
Magsi, S., Lashari, S., Shaikh, R., Magsi, I., Qureshi, S. G. Unexplained Infertility: comparison of Efficacy of Letrozole and Clomiphene Citrate. <i>Pakistan journal of medical and health sciences</i> 2022; 16(3): 109-11	Cohort study in the presence of higher quality evidence
Martinez, A. R., Bernardus, R. E., Voorhorst, F. J., Vermeiden, J. P. and Schoemaker, J. Intrauterine insemination does and clomiphene citrate does not improve fecundity in couples with infertility due to male or idiopathic factors: a prospective, randomized, controlled study. <i>Fertil Steril.</i> 1990; 53 (5): 847-53.	The 4 treatment modalities are not compared according to infertility diagnosis;
Martinez, A. R., Bernardus, R. E., Voorhorst, F. J., Vermeiden, J. P. and Schoemaker, J. Pregnancy rates after timed intercourse or intrauterine insemination after human menopausal gonadotropin stimulation of normal ovulatory cycles: a controlled study. <i>Fertil Steril.</i> 1991; 55 (2): 258-65.	Excluded from systematic review Ayeleke et al., 2020 for no pre-cross-over data available
Marschalek, J., Franz, M., Gonen, Y., Kruessel, J. S., Weichselbaum, A., Kuessel, L., Trofaier, M. L. and Ott, J. The effect of slow release insemination on pregnancy rates: report of two randomized controlled pilot studies and meta-analysis. <i>Arch Gynecol Obstet.</i> 2017; 295 (4): 1025-1032.	Includes only 2 studies with very small sample size
Mascarenhas, L., Khastgir, G., Davies, W. A. and Lee, S. Superovulation and timed intercourse: can it provide a reasonable alternative for those unable to afford assisted conception? <i>Hum Reprod.</i> 1994; 9 (1): 67-70.	Cohort study in the presence of higher quality evidence
Melis, G. B., Paoletti, A. M., Ajossa, S., Guerriero, S., Depau, G. F. and Mais, V. Ovulation induction with gonadotropins as sole treatment in infertile couples with open tubes: a randomized prospective comparison between intrauterine insemination and timed vaginal intercourse. <i>Fertil Steril.</i> 1995; 64 (6): 1088-93.	Included in systematic review Ayeleke et al., 2020
Merviel, P., Labarre, M., James, P., Bouée, S., Chabaud, J. J., Roche, S., Cabry, R., Scheffler, F., Lourdel, E., Benkhalifa, M., Copin, H., Drapier, H. and Beauvillard, D. Should intrauterine inseminations still be proposed in cases of unexplained infertility? Retrospective study and literature review. <i>Arch Gynecol Obstet.</i> 2022; 305 (5): 1241-1254.	Cohort study in the presence of higher quality evidence
Mukherjee, S., Sharma, S. and Chakravarty, B. N. Comparative evaluation of pregnancy outcome in gonadotrophin-clomiphene combination vs clomiphene alone in polycystic ovarian syndrome and unexplained infertility-A prospective clinical trial. <i>J Hum Reprod Sci.</i> 2010; 3 (2): 80-4.	Not within scope: CC+/- Gn
Nandi, A., Bhide, P., Hooper, R., Gudi, A., Shah, A., Khan, K. and Homburg, R. Intrauterine insemination with gonadotropin stimulation or in vitro fertilization for the treatment of unexplained subfertility: a randomized controlled trial. <i>Fertil Steril.</i> 2017; 107 (6): 1329-1335.e2.	Included in systematic review Nandi et al., 2022
Nulsen, J. C., Walsh, S., Dumez, S. and Metzger, D. A. A randomized and longitudinal study of human menopausal gonadotropin with intrauterine insemination in the treatment of infertility. <i>Obstet Gynecol.</i> 1993; 82 (5): 780-6.	Not a randomized trial



Pacu, I., Ionescu, C. A., Dimitriu, M., Banacu, M., Tarcomnicu, I., Calin, D., Socea, B., Pantea, A. S., Constantin, V. D., Paunica-Panea, G. and et al. Intrauterine insemination in idiopathic infertility. Archives of the balkan medical union. 2016; 51 (3): 334-339.	Cohort study in the presence of higher quality evidence
Qin, F., Zhou, Y., Huan, L. and Gui, W. Comparison of clomiphene and letrozole for superovulation in patients with unexplained infertility undergoing intrauterine insemination: A systematic review and meta-analysis. Medicine (Baltimore). 2020; 99 (31): e21006.	Not within scope: stimulation protocols for IUI
Reindollar, R. H., Regan, M. M., Neumann, P. J., Levine, B. S., Thornton, K. L., Alper, M. M. and Goldman, M. B. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. Fertil Steril. 2010; 94 (3): 888-99.	Included in systematic review Nandi et al., 2022
Rodriguez-Purata, J., Lee, J., Whitehouse, M., Sandler, B., Copperman, A. and Mukherjee, T. Comparison of Letrozole with Timed Intercourse Versus Clomiphene Citrate with Intrauterine Insemination in Patients with Unexplained Infertility. J Reprod Med. 2016; 61 (9-10): 425-430.	Cohort study in the presence of higher quality evidence
Serhal, P. F., Katz, M., Little, V. and Woronowski, H. Unexplained infertility--the value of Pergonal superovulation combined with intrauterine insemination. Fertil Steril. 1988; 49 (4): 602-6.	Cohort study in the presence of higher quality evidence
Simon, A., Avidan, B., Mordel, N., Lewin, A., Samueloff, A., Zajicek, G., Schenker, J. G. and Laufer, N. The value of menotrophin treatment for unexplained infertility prior to an in-vitro fertilization attempt. Hum Reprod. 1991; 6 (2): 222-6.	Cohort study in the presence of higher quality evidence
Soysal, C. and Ozmen, U. Intrauterine insemination in ovulatory infertile patients. Niger J Clin Pract. 2018; 21 (10): 1374-1379.	Cohort study in the presence of higher quality evidence
Steures, P., Berkhout, J. C., Hompes, P. G., van der Steeg, J. W., Bossuyt, P. M., van der Veen, F., Habbema, J. D., Eijkemans, M. J. and Mol, B. W. Patients' preferences in deciding between intrauterine insemination and expectant management. Hum Reprod. 2005; 20 (3): 752-5.	Cohort study in the presence of higher quality evidence
Tjon-Kon-Fat, R. I., Bendsdorp, A. J., Bossuyt, P. M., Koks, C., Oosterhuis, G. J., Hoek, A., Hompes, P., Broekmans, F. J., Verhoeve, H. R., de Bruin, J. P., van Golde, R., Repping, S., Cohlen, B. J., Lambers, M. D., van Bommel, P. F., Slappendel, E., Perquin, D., Smeenk, J., Pelinck, M. J., Gianotten, J., Hoozemans, D. A., Maas, J. W., Groen, H., Eijkemans, M. J., van der Veen, F., Mol, B. W. and van Wely, M. Is IVF-served two different ways-more cost-effective than IUI with controlled ovarian hyperstimulation? Hum Reprod. 2015; 30 (10): 2331-9.	Economic evaluation
Tjon-Kon-Fat, R. I., Tajik, P., Zafarmand, M. H., Bendsdorp, A. J., Bossuyt, P. M., Oosterhuis, G. J. E., van Golde, R., Repping, S., Lambers, M. D. A., Slappendel, E., Perquin, D., Pelinck, M. J., Gianotten, J., Maas, J. W. M., Eijkemans, M. J. C., van der Veen, F., Mol, B. W. and van Wely, M. IVF or IUI as first-line treatment in unexplained subfertility: the conundrum of treatment selection markers. Hum Reprod. 2017; 32 (5): 1028-1032.	Secondary analysis of the RCT by Bendsdorp et al., 2015
van Rumste, M. M., Custers, I. M., van Wely, M., Koks, C. A., van Weering, H. G., Beckers, N. G., Scheffer, G. J., Broekmans, F. J., Hompes, P. G., Mochtar, M. H., van der Veen, F. and Mol, B. W. IVF with planned single-embryo transfer versus IUI with ovarian stimulation in couples with unexplained subfertility: an economic analysis. Reprod Biomed Online. 2014; 28 (3): 336-42.	Economic evaluation
Wang, R., Danhof, N. A., Tjon-Kon-Fat, R. I., Eijkemans, M. J., Bossuyt, P. M., Mochtar, M. H., van der Veen, F., Bhattacharya, S., Mol, B. W. J. and van Wely, M. Interventions for unexplained infertility: a systematic review and network meta-analysis. Cochrane Database Syst Rev. 2019; 9 (9): Cd012692.	Replaced by a more recent systematic review
Welner, S., DeCherney, A. H. and Polan, M. L. Human menopausal gonadotropins: a justifiable therapy in ovulatory women with long-standing idiopathic infertility. Am J Obstet Gynecol. 1988; 158 (1): 111-7.	Cohort study in the presence of higher quality evidence

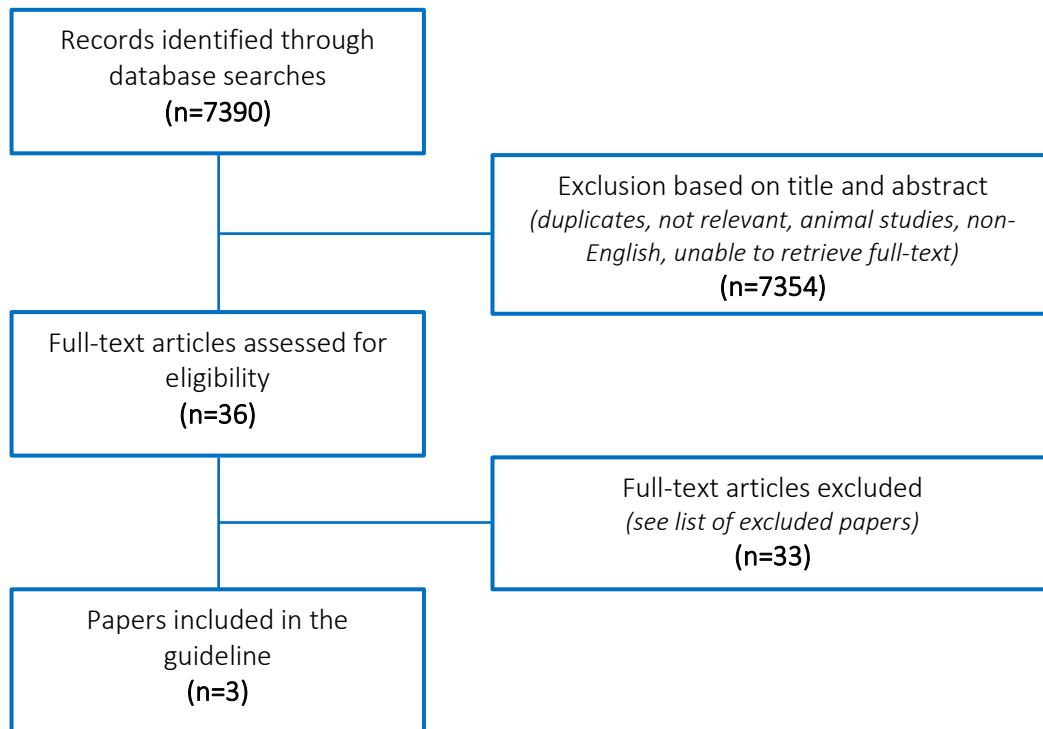


Wiser, A., Shalom-Paz, E., Reinblatt, S. L., Son, W. Y., Das, M., Tulandi, T. and Holzer, H. Ovarian stimulation and intrauterine insemination in women aged 40 years or more. <i>Reprod Biomed Online</i> . 2012; 24 (2): 170-3.	Cohort study in the presence of higher quality evidence
Zikopoulos, K., West, C. P., Thong, P. W., Kacser, E. M., Morrison, J., Wu, F. C. Homologous intra-uterine insemination has no advantage over timed natural intercourse when used in combination with ovulation induction for the treatment of unexplained infertility. <i>Hum Reprod</i> . 1993; 8 (4): 563-7.	excluded from systematic review Ayeleke et al., 2020 for no pre-cross-over data available
Zayed, F. Follow-up of patients with unexplained infertility who previously underwent natural cycle in vitro fertilization. <i>Gynecol Obstet Invest</i> . 2000; 49 (2): 127-31.	Cohort study in the presence of higher quality evidence
Zayed, F., Lenton, E. A. and Cooke, I. D. Comparison between stimulated in-vitro fertilization and stimulated intrauterine insemination for the treatment of unexplained and mild male factor infertility. <i>Hum Reprod</i> . 1997; 12 (11): 2408-13.	Cohort study in the presence of higher quality evidence



PICO QUESTION: WHAT IS THE VALUE OF IVF VERSUS ICSI?

Flowchart



List of excluded papers

	Exclusion criterion
Aboulghar, M. A., Mansour, R. T., Serour, G. I., Amin, Y., Ramzy, A. M., Sattar, M. A. and Kamal, A. Management of long-standing unexplained infertility: A prospective study. <i>Am J Obstet Gynecol.</i> 1999; 181 (2): 371-5.	Not a RCT
Aboulghar, M. A., Mansour, R. T., Serour, G. I., Sattar, M. A. and Amin, Y. M. Intracytoplasmic sperm injection and conventional in vitro fertilization for sibling oocytes in cases of unexplained infertility and borderline semen. <i>J Assist Reprod Genet.</i> 1996; 13 (1): 38-42.	Not a RCT
Biliangady, R., Kinila, P., Pandit, R., Tudu, N. K., Sundhararaj, U. M., Gopal, I. S. T. and Swamy, A. G. Are we Justified Doing Routine Intracytoplasmic Sperm Injection in Nonmale Factor Infertility? A Retrospective Study Comparing Reproductive Outcomes between In vitro Fertilization and Intracytoplasmic Sperm Injection in Nonmale Factor Infertility. <i>J Hum Reprod Sci.</i> 2019; 12 (3): 210-215.	Not a RCT
Bosch, E., Espinós, J. J., Fabregues, F., Fontes, J., García-Velasco, J., Llácer, J., Requena, A., Checa, M. A. and Bellver, J. ALWAYS ICSI? A SWOT analysis. <i>J Assist Reprod Genet.</i> 2020; 37 (9): 2081-2092.	SWOT analysis of IVF vs ICSI for non-male factor. 2 RCTs involving UI are included, these RCTs Bhattacharya 2001 & Foong 2006 are among the list of the 35 studies.
Bungum, L., Bungum, M., Humaidan, P. and Andersen, C. Y. A strategy for treatment of couples with unexplained infertility who failed to conceive after intrauterine insemination. <i>Reprod Biomed Online.</i> 2004; 8 (5): 584-9.	Not a RCT



Check, J. H., Bollendorf, A., Dix, E. and Katsoff, D. Effect of fertilization by intracytoplasmic sperm injection versus conventional insemination on embryo cleavage rates. <i>Clin Exp Obstet Gynecol.</i> 2010; 37 (3): 183-4.	Not a RCT
Check, J. H., Bollendorf, A., Summers-Chase, D., Horwath, D. and Hourani, W. Conventional oocyte insemination may result in a better pregnancy outcome than intracytoplasmic sperm injection (ICSI) for unexplained infertility. <i>Clin Exp Obstet Gynecol.</i> 2009; 36 (3): 150-1.	Not a RCT
Chung, C. H. S., Wong, A. W. Y., Yeung, Q. S. Y., Cheung, L. P. and Li, T. C. Is routine intracytoplasmic sperm injection justified in couples with unexplained infertility? A randomized controlled trial using sibling oocytes. <i>Journal of reproductive medicine.</i> 2018; 63 (4): 357-362.	Randomised sibling oocytes to IVF & ICSI
Drakopoulos, P., Garcia-Velasco, J., Bosch, E., Blockeel, C., de Vos, M., Santos-Ribeiro, S., Makrigiannakis, A., Tournaye, H. and Polyzos, N. P. ICSI does not offer any benefit over conventional IVF across different ovarian response categories in non-male factor infertility: a European multicenter analysis. <i>J Assist Reprod Genet.</i> 2019; 36 (10): 2067-2076.	Not a RCT
Eftekhari, M., Mohammadian, F., Yousefnejad, F., Molaei, B. and Aflatoonian, A. Comparison of conventional IVF versus ICSI in non-male factor, normoresponder patients. <i>Iran J Reprod Med.</i> 2012; 10 (2): 131-6.	Not a RCT
Farquhar, C. and Marjoribanks, J. Assisted reproductive technology: an overview of Cochrane Reviews. <i>Cochrane Database of Systematic Reviews.</i> 2018; (8): -	Summary of Cochrane reviews
Gennarelli, G., Carosso, A., Canosa, S., Filippini, C., Cesarano, S., Scarafia, C., Brunod, N., Revelli, A. and Benedetto, C. ICSI Versus Conventional IVF in Women Aged 40 Years or More and Unexplained Infertility: A Retrospective Evaluation of 685 Cycles with Propensity Score Model. <i>J Clin Med.</i> 2019; 8 (10):	Not a RCT
Gunn, D. D. and Bates, G. W. Evidence-based approach to unexplained infertility: a systematic review. <i>Fertil Steril.</i> 2016; 105 (6): 1566-1574.e1.	Systematic review without meta-analysis
Haas, J., Miller, T. E., Nahum, R., Aizer, A., Kirshenbaum, M., Zilberberg, E., Lebovitz, O. and Orvieto, R. The role of ICSI vs. conventional IVF for patients with advanced maternal age-a randomized controlled trial. <i>J Assist Reprod Genet.</i> 2021; 38 (1): 95-100.	Ovaries were randomized in stead of women
Isikoglu, M., Avci, A., Kendirci Ceviren, A., Aydinuraz, B. and Ata, B. Conventional IVF revisited: Is ICSI better for non-male factor infertility? Randomized controlled double blind study. <i>J Gynecol Obstet Hum Reprod.</i> 2020; 50 (7): 101990.	Sibling oocytes were randomised to IVF or ICSI, no separate result for UI cohort
Isikoglu, M., Ceviren, A. K., Cetin, T., Avci, A., Aydinuraz, B., Akgul, O. K. and Karaca, M. Comparison of ICSI and conventional IVF in non-male factor patients with less than four oocytes. <i>Arch Gynecol Obstet.</i> 2022;	Not a RCT
Iwamoto, A., Van Voorhis, B. J., Summers, K. M., Sparks, A., Mancuso, A. C. Intracytoplasmic sperm injection vs. conventional in vitro fertilization in patients with non-male factor infertility. <i>Fertil Steril</i> 2022; 118(3): 465-472	No stratification according to infertility diagnosis
Jaroudi, K., Al-Hassan, S., Al-Sufayan, H., Al-Mayman, H., Qeba, M. and Coskun, S. Intracytoplasmic sperm injection and conventional in vitro fertilization are complementary techniques in management of unexplained infertility. <i>J Assist Reprod Genet.</i> 2003; 20 (9): 377-81.	Sibling oocytes were randomised to IVF or ICSI
Khamsi, F., Yavas, Y., Roberge, S., Wong, J. C., Lacanna, I. C. and Endman, M. Intracytoplasmic sperm injection increased fertilization and good-quality embryo formation in patients with non-male factor indications for in vitro fertilization: a prospective randomized study. <i>Fertil Steril.</i> 2001; 75 (2): 342-7.	Randomised sibling oocytes to IVF & ICSI
Kim, J. Y., Kim, J. H., Jee, B. C., Lee, J. R., Suh, C. S. and Kim, S. H. Can intracytoplasmic sperm injection prevent total fertilization failure and enhance embryo quality in patients with non-male factor infertility? <i>Eur J Obstet Gynecol Reprod Biol.</i> 2014; 178 188-91.	Not a RCT



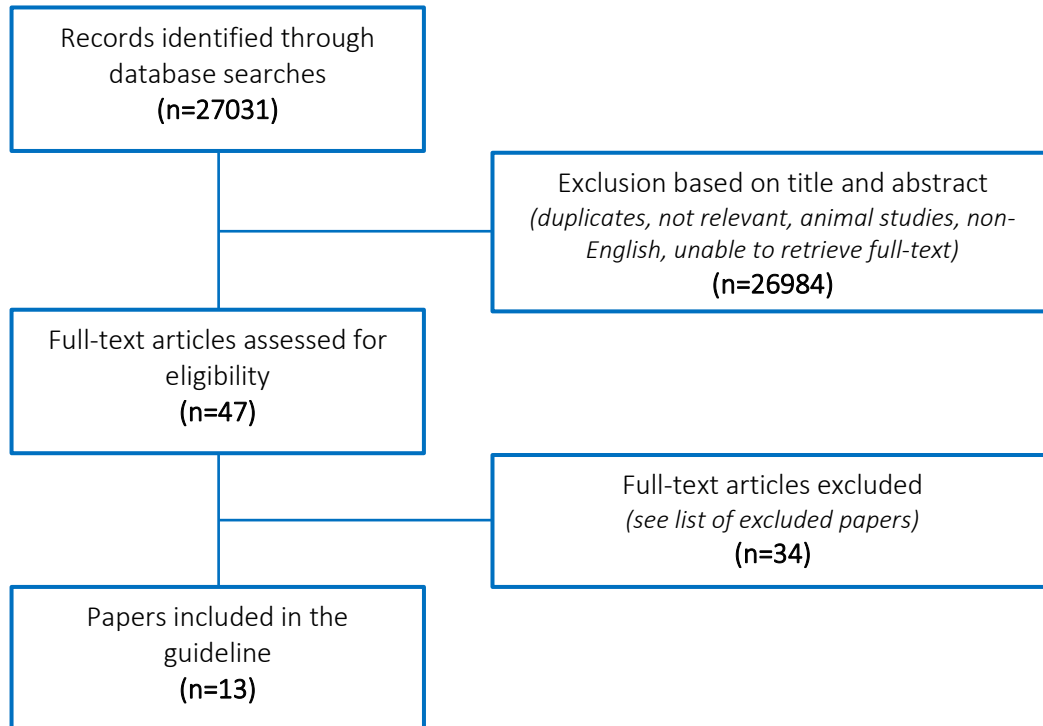
Li, Z., Lin, H., Xiao, W. and Wang, Y. Fertilization of IVF/ICSI using sibling oocytes from couples with subfertile male or unexplained infertility. <i>J Huazhong Univ Sci Technolog Med Sci.</i> 2004; 24 (4): 365-8, 384.	Randomised sibling oocytes to IVF & ICSI
Li, Z., Wang, A. Y., Bowman, M., Hammarberg, K., Farquhar, C., Johnson, L., Safi, N. and Sullivan, E. A. ICSI does not increase the cumulative live birth rate in non-male factor infertility. <i>Hum Reprod.</i> 2018; 33 (7): 1322-1330.	Not a RCT
Liu, L., Wang, H., Li, Z., Niu, J. and Tang, R. Obstetric and perinatal outcomes of intracytoplasmic sperm injection versus conventional in vitro fertilization in couples with nonsevere male infertility. <i>Fertil Steril.</i> 2020; 114 (4): 792-800.	Not a RCT
Miller, K. F., Falcone, T., Goldberg, J. M. and Attaran, M. Previous fertilization failure with conventional in vitro fertilization is associated with poor outcome of intracytoplasmic sperm injection. <i>Fertil Steril.</i> 1998; 69 (2): 242-5.	Not a RCT
Ruiz, A., Remohí, J., Minguez, Y., Guanes, P. P., Simón, C. and Pellicer, A. The role of in vitro fertilization and intracytoplasmic sperm injection in couples with unexplained infertility after failed intrauterine insemination. <i>Fertil Steril.</i> 1997; 68 (1): 171-3.	Randomised sibling oocytes to IVF & ICSI
Song, J., Liao, T., Fu, K. and Xu, J. ICSI Does Not Improve Live Birth Rates but Yields Higher Cancellation Rates Than Conventional IVF in Unexplained Infertility. <i>Front Med (Lausanne).</i> 2020; 7 614118.	Not a RCT
Takeuchi, S., Minoura, H., Shibahara, T., Shen, X., Futamura, N. and Toyoda, N. In vitro fertilization and intracytoplasmic sperm injection for couples with unexplained infertility after failed direct intraperitoneal insemination. <i>J Assist Reprod Genet.</i> 2000; 17 (9): 515-20.	Not a RCT
Sauerbrun-Cutler, M. T., Huber, W. J., 3rd, Has, P., Shen, C., Hackett, R., Alvero, R. and Wang, S. Is intracytoplasmic sperm (ICSI) better than traditional in vitro fertilization (IVF): confirmation of higher blastocyst rates per oocyte using a split insemination design. <i>J Assist Reprod Genet.</i> 2020; 37 (7): 1661-1667.	Not a RCT
van Rumste, M. M., Evers, J. L. and Farquhar, C. M. Intra-cytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in patients with non-male subfertility. <i>Cochrane Database Syst Rev.</i> 2003; (2): Cd001301.	Cochrane review included only 1 RCT of non-male factor infertility, this Bhattacharya 2001 is among the list of the 35 studies.
van Rumste, M. M., Evers, J. L. and Farquhar, C. M. ICSI versus conventional techniques for oocyte insemination during IVF in patients with non-male factor subfertility: a Cochrane review. <i>Hum Reprod.</i> 2004; 19 (2): 223-7.	Paper based on above Cochrane review van Rumste 2003.
Wyns, C., Vandermonde, J., Pirard, C., Demylle, D., Vanabelle, B. and Donnez, J. IVF and ICSI outcome in couples with unexplained infertility: a randomized study of 60 cases. <i>Jornal brasileiro de reproducao assistida.</i> 2004; 8 (5): 16-24.	Not addressing the specific key question of IVF vs ICSI.
Younes, G., Tannus, S., Son, W. Y. and Dahan, M. H. When to do intracytoplasmic sperm injection: a prospective comparison. <i>Arch Gynecol Obstet.</i> 2019; 300 (5): 1461-1471.	Not a RCT
Yovich, J. L., Conceicao, J. L., Marjanovich, N., Ye, Y., Hinchliffe, P. M., Dhaliwal, S. S. and Keane, K. N. An ICSI rate of 90% minimizes complete failed fertilization and provides satisfactory implantation rates without elevating fetal abnormalities. <i>Reprod Biol.</i> 2018; 18 (3): 301-311.	Not a RCT



III.3 Mechanical-surgical procedures

PICO QUESTION: WHAT IS THE VALUE OF MECHANICAL-SURGICAL PROCEDURES?

Flowchart



List of excluded papers

Reference	Exclusion criterion
Abdelhamid, A. M. The success rate of pregnancy in IUI cycles following endometrial sampling. A randomized controlled study: endometrial sampling and pregnancy rates. Arch Gynecol Obstet. 2013; 288 (3):673-8	Includes mild male factor infertility patients without stratifying results
Aflatoonian, A., Baradaran Bagheri, R. and Hosseiniadat, R. The effect of endometrial injury on pregnancy rate in frozen-thawed embryo transfer: A randomized control trial. Int J Reprod Biomed. 2016; 14 (7): 453-458.	Not stratifying results according to infertility diagnosis
Al-Fadhli, R., Sylvestre, C., Buckett, W. and Tulandi, T. A randomized study of laparoscopic chromopertubation with lipiodol versus saline in infertile women. Fertil Steril. 2006; 85 (2): 505-7.	Included in systematic review Wang et al., 2020
Alleyassin, A., Abiri, A., Agha-Hosseini, M. and Sarvi, F. The Value of Routine Hysteroscopy before the First Intracytoplasmic Sperm Injection Treatment Cycle. Gynecol Obstet Invest. 2017; 82 (2): 125-130.	Included in systematic review Kamath et al., 2019
Bahaa Eldin, A. M., Abdelmaabud, K. H., Laban, M., Hassanin, A. S., Tharwat, A. A., Aly, T. R., Elbohoty, A. E., Elsayed, H. M., Ibrahim, A. M., Ibrahim, M. E., Sabaa, H. M., Abdelrazik, A. A. and Abdelhady, I. Endometrial Injury May Increase the Pregnancy Rate in Patients Undergoing Intrauterine Insemination: An Interventional Randomized Clinical Trial. Reprod Sci. 2016; 23 (10): 1326-31.	Includes mild male factor infertility patients without stratifying results
Bosteels, J., Weyers, S., Mathieu, C., Mol, B. W. and D'Hooghe, T. The effectiveness of reproductive surgery in the treatment of female infertility: facts, views and vision. Facts Views Vis Obgyn. 2010; 2 (4): 232-52.	Replaced by a more recent systematic review Bafort et al., 2020.



Crosby, D. A., Glover, L. E., Downey, P., Mooney, E. E., McAuliffe, F. M., O'Farrelly, C., Brennan, D. J. and Wingfield, M. The impact of accurately timed mid-luteal endometrial injury in nulligravid women undergoing their first or second embryo transfer. <i>Ir J Med Sci.</i> 2021; 190 (3): 1071-1077.	Cohort study in the presence of higher quality evidence
El-Toukhy, T., Campo, R., Khalaf, Y., Tabanelli, C., Gianaroli, L., Gordts, S. S., Gordts, S., Mestdagh, G., Mardesic, T., Voboril, J., Marchino, G. L., Benedetto, C., Al-Shawaf, T., Sabatini, L., Seed, P. T., Gergolet, M., Grimbizis, G., Harb, H. and Coomarasamy, A. Hysteroscopy in recurrent in-vitro fertilisation failure (TROPHY): a multicentre, randomised controlled trial. <i>Lancet.</i> 2016; 387 (10038): 2614-2621.	Included in systematic review Kamath et al., 2019
Eskew, A. M., Reschke, L. D., Woolfolk, C., Schulte, M. B., Boots, C. E., Broughton, D. E., Jimenez, P. T., Omurtag, K. R., Keller, S. L., Ratts, V. S., Odem, R. R. and Jungheim, E. S. Effect of endometrial mechanical stimulation in an unselected population undergoing in vitro fertilization: futility analysis of a double-blind randomized controlled trial. <i>J Assist Reprod Genet.</i> 2019; 36 (2): 299-305.	No stratification according to infertility diagnosis
Frantz, S., Parinaud, J., Kret, M., Rocher-Escriva, G., Papaxanthos-Roche, A., Creux, H., Chansel-Debordeaux, L., Bénard, A. and Hocké, C. Decrease in pregnancy rate after endometrial scratch in women undergoing a first or second in vitro fertilization. A multicenter randomized controlled trial. <i>Hum Reprod.</i> 2019; 34 (1): 92-99.	No stratification according to infertility diagnosis
Goel, T., Mahey, R., Bhatla, N., Kalaivani, M., Pant, S. and Kriplani, A. Pregnancy after endometrial scratching in infertile couples undergoing ovulation induction and intrauterine insemination cycles-a randomized controlled trial. <i>J Assist Reprod Genet.</i> 2017; 34 (8): 1051-1058.	Includes mild male factor infertility patients without stratifying results
Hamdi, K., Nia, N. M., Hakimi, P. and Ghasemzadeh, A. The effects of endometrial scratch on pregnancy rate in iui cycles. <i>International journal of women's health and reproduction sciences.</i> 2019; 7 (3): 380-384.	no stratification acc to infertility diagnosis
Hebeisha, S. A., Moiety, F. S., Samir, M. and Hussein, M. Effect of endometrial injury on implantation and pregnancy rates: a randomised controlled trial. <i>Clinical and experimental obstetrics & gynecology.</i> 2018; 45 (1): 105-108.	no stratification acc to infertility diagnosis
Helmy, M. E. E., Maher, M. A., Elkhoully, N. I. and Ramzy, M. A randomized trial of local endometrial injury during ovulation induction cycles. <i>Int J Gynaecol Obstet.</i> 2017; 138 (1): 47-52.	no stratification acc to infertility diagnosis
Hodgson R.M., Hui L.L., Wang R., Mol B.W., Johnson N. Interventions for endometriosis-related infertility: a systematic review and network meta-analysis. <i>Fertil Steril.</i> 2020;113 (2):374-382	Replaced by the Cochrane systematic review Bafort et al., 2020
Kamath, M. S., Bosteels, J., D'Hooghe, T. M., Seshadri, S., Weyers, S., Mol, B. W. J., Broekmans, F. J. and Sunkara, S. K. Screening hysteroscopy in subfertile women and women undergoing assisted reproduction. <i>Cochrane Database Syst Rev.</i> 2019; 4 (4): Cd012856.	Fist IVF cycles, not specified unexplained infertility
Kang, Y., Wang, Z., Yang, Y., Liang, H., Duan, X., Gao, Q., Yin, Z. Impact of endometrial scratching on reproductive outcome in patients: A systematic review and meta-analysis. <i>Medicine (Baltimore)</i> 2022; 101(33): e30150	Includes mild male factor infertility patients without stratifying results
Letterie, G. S. and Rose, G. S. Pregnancy rates after the use of oil-based and water-based contrast media to evaluate tubal patency. <i>Southern medical journal.</i> 1990; 83 (12): 1402-1403.	Included in systematic review Wang et al., 2020
Liang, Y., Han, J., Jia, C., Ma, Y., Lan, Y., Li, Y. and Wang, S. Effect of Endometrial Injury on Secretion of Endometrial Cytokines and IVF Outcomes in Women with Unexplained Subfertility. <i>Mediators Inflamm.</i> 2015; 2015 757184.	Cohort study in the presence of higher quality evidence
Liu, W., Tal, R., Chao, H., Liu, M. and Liu, Y. Effect of local endometrial injury in proliferative vs. luteal phase on IVF outcomes in unselected subfertile women undergoing in vitro fertilization. <i>Reprod Biol Endocrinol.</i> 2017; 15 (1): 75.	Not stratifying results according to infertility diagnosis
Mahran, A., Ibrahim, M. and Bahaa, H. The effect of endometrial injury on first cycle IVF/ICSI outcome: a randomized controlled trial. <i>International journal of reproductive biomedicine.</i> 2016; 14 (3): 193-198.	Not stratifying results according to infertility diagnosis



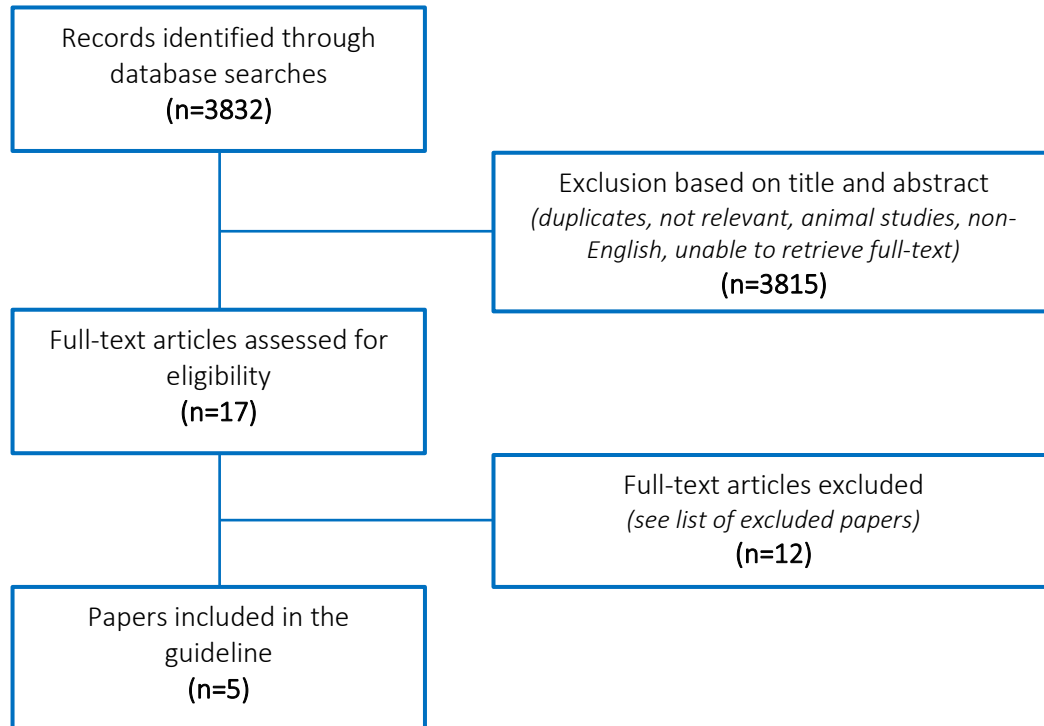
Moramezi, F., Barati, M., Mohammadjafari, R., Barati, S. and Hemadi, M. Effect of hysteroscopy before intra uterine insemination on fertility in infertile couples. Pak J Biol Sci. 2012; 15 (19): 942-6.	Randomisation and allocation concealment not provided. No power calculation. Not included in the Cochrane review.
Nugent, D., Watson, A. J., Killick, S. R., Balen, A. H. and Rutherford, A. J. A randomized controlled trial of tubal flushing with lipiodol for unexplained infertility. Fertil Steril. 2002; 77 (1): 173-5.	Included in systematic review Wang et al., 2020
Rama Raju GA, Shashi Kumari G, Krishna KM, Prakash GJ, Madan K. Assessment of uterine cavity by hysteroscopy in assisted reproduction programme and its influence on pregnancy outcome. Archives of Gynecology and Obstetrics 2006;274(3):160-4.	Included in systematic review Kamath et al., 2019
Shawki, H. E., Elmorsy, M. and Eissa, M. K. Routine office hysteroscopy prior to ICSI and its impact on assisted reproduction program outcome: a randomized controlled trial. Middle East Fertility Society journal. 2012; 17 (1): 14-21.	Included in systematic review Kamath et al., 2019
Sherif, A., Abou-Talib, Y., Ibrahim, M. and Arafat, R. The effect of day 6 endometrial injury of the ICSI cycle on pregnancy rate: a randomized controlled trial. Middle East Fertility Society journal. 2018; 23 (4): 292-296.	Not stratifying results according to infertility diagnosis
Shokeir, T., Ebrahim, M. and El - Mogy, H. Hysteroscopic-guided local endometrial injury does not improve natural cycle pregnancy rate in women with unexplained infertility: randomized controlled trial. Journal of obstetrics and gynaecology research. 2016; 42 (11): 1553-1557.	quasi-randomised trial
Smit, J. G., Kasius, J. C., Eijkemans, M. J. C., Koks, C. A. M., van Golde, R., Nap, A. W., Scheffer, G. J., Manger, P. A. P., Hoek, A., Schoot, B. C. and et al. Hysteroscopy before in-vitro fertilisation (inSIGHT): a multicentre, randomised controlled trial. Lancet (london, england). 2016; 387 (10038): 2622-2629.	Included in systematic review Kamath et al., 2019
Soliman, B. S. and Harira, M. Local endometrial scratching under ultrasound-guidance after failed intrauterine insemination and cycle outcome: a randomized controlled trial. Middle East Fertility Society journal. 2017; 22 (1): 60-66.	Includes mild male factor infertility patients without stratifying results
Wadhwa, L. and Mishra, M. Therapeutic Efficacy of Endometrial Scratching in Repeated Controlled Ovarian Stimulation (COS) Failure Cycles. J Hum Reprod Sci. 2018; 11 (1): 59-71.	Not stratifying results according to infertility diagnosis
Wadhwa, L., Pritam, A., Gupta, T., Gupta, S., Arora, S., Chandoke, R. Effect of endometrial biopsy on intrauterine insemination outcome in controlled ovarian stimulation cycle. J Hum Reprod Sci 2015, 8(3): 151-8.	Not stratifying results according to infertility diagnosis
Yavangi, M., Varmaghani, N., Pirdehghan, A., Varmaghani, M. and Faryadras, M. Comparison of pregnancy outcome in intrauterine insemination-candidate women with and without endometrial scratch injury: An RCT. Int J Reprod Biomed. 2021; 19 (5): 457-464.	Not stratifying results according to infertility diagnosis
Yeung, T. W., Chai, J., Li, R. H., Lee, V. C., Ho, P. C. and Ng, E. H. The effect of endometrial injury on ongoing pregnancy rate in unselected subfertile women undergoing in vitro fertilization: a randomized controlled trial. Hum Reprod. 2014; 29 (11): 2474-81.	Not stratifying results according to infertility diagnosis
Zarei, A., Alborzi, S., Dadras, N. and Azadi, G. The effects of endometrial injury on intrauterine insemination outcome: A randomized clinical trial. Iran J Reprod Med. 2014; 12 (9): 649-52.	Includes mild male factor infertility patients without stratifying results



III.4 Alternative therapeutic approaches

PICO QUESTION: WHAT IS THE EFFECTIVENESS OF ALTERNATIVE THERAPEUTIC APPROACHES?

Flowchart



List of excluded papers

Reference	Exclusion criterion
Badawy, A., Baker El Nashar, A. and El Totongy, M. Clomiphene citrate plus N-acetyl cysteine versus clomiphene citrate for augmenting ovulation in the management of unexplained infertility: a randomized double-blind controlled trial. <i>Fertil Steril.</i> 2006; 86 (3): 647-50.	Included in systematic review Showell et al., 2020
Cicek, N., Eryilmaz, O. G., Sarikaya, E., Gulerman, C. and Genc, Y. Vitamin E effect on controlled ovarian stimulation of unexplained infertile women. <i>J Assist Reprod Genet.</i> 2012; 29 (4): 325-8.	Included in systematic review Showell et al., 2020
Çoksüer, H., Barut, M. U., Bozkurt, M., Agacayak, E., Sak, S., Demir, M. and Caliskan, E. Acupuncture Enhances Chances of Pregnancy in Unexplained Infertile Patients Who Undergo A Blastocyst Transfer in A Fresh-Cycle. <i>Chin J Integr Med.</i> 2019; 25 (4): 298-302.	Very low quality study
Filipcikova, R., Oborna, I., Brezinova, J., Novotny, J., Wojewodka, G., De Sanctis, J. B., Radova, L., Hajduch, M. and Radzioch, D. Lycopene improves the distorted ratio between AA/DHA in the seminal plasma of infertile males and increases the likelihood of successful pregnancy. <i>Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.</i> 2015; 159 (1): 77-82.	Mixture of male infertility and UI but UI not defined to confirm actual UI
Legro, R. S., Hansen, K. R., Diamond, M. P., Steiner, A. Z., Coutifaris, C., Cedars, M. I., Hoeger, K. M., Usadi, R., Johnstone, E. B., Haisenleder, D. J., Wild, R. A., Barnhart, K. T., Mersereau, J., Trussell, J. C., Krawetz, S. A., Kris-Etherton, P. M., Sarwer, D. B., Santoro, N., Eisenberg, E., Huang, H. and Zhang, H. Effects of preconception lifestyle intervention in infertile women with obesity: The FIT-PLESE randomized controlled trial. <i>PLoS Med.</i> 2022; 19 (1): e1003883.	Not unexplained infertility (UI) as could have had unilat tubal blockage and only considered sperm total motile sperm in the



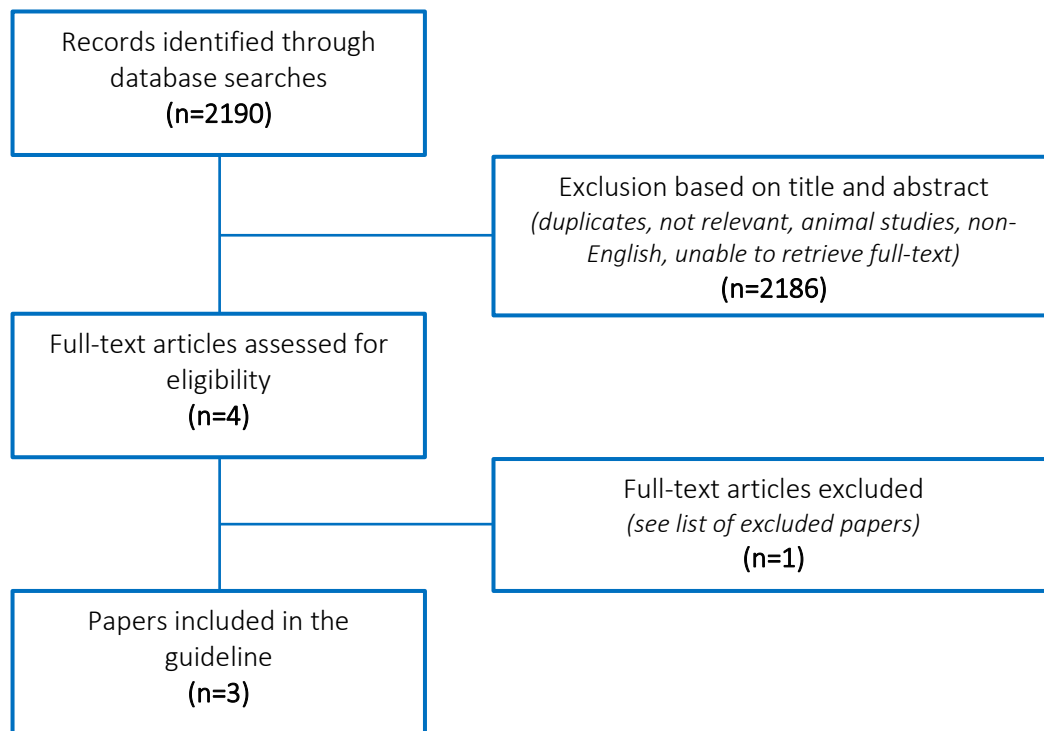
	ejaculate in evaluation of male semen analysis
Murto, T., Skoog Svanberg, A., Yngve, A., Nilsson, T. K., Altmäe, S., Wångren, K., Salumets, A. and Stavreus-Evers, A. Folic acid supplementation and IVF pregnancy outcome in women with unexplained infertility. <i>Reprod Biomed Online</i> . 2014; 28 (6): 766-72.	Not an intervention study
Neamtii, I. A., Surcel, M., Begum, T. F., A36Gurzau, E. S., Berindan-Neagoe, I., Braicu, C., Rotar, I., Muresan, D., Bloom, M. S. Specific lifestyle factors and in vitro fertilization outcomes in Romanian women: a pilot study. <i>OoerJ</i> 2022; 10: e14189	No stratification of results according to infertility diagnosis
Park, J. J., Kang, M., Shin, S., Choi, E., Kwon, S., Wee, H., Nam, B. and Kaptchuk, T. J. Unexplained infertility treated with acupuncture and herbal medicine in Korea. <i>J Altern Complement Med</i> . 2010; 16 (2): 193-8.	Combination of 2 interventions.
Salas-Huetos, A., Arvizu, M., Mínguez-Alarcón, L., Mitsunami, M., Ribas-Maynou, J., Yeste, M., Ford, J. B., Souter, I., Chavarro, J. E. Women's and men's intake of omega-3 fatty acids and their food sources and assisted reproductive technology outcomes. <i>Am J Obstet Gynecol</i> 2022; 227(2): 246.e1-246.e11	No stratification of results according to infertility diagnosis
Wang, B., Li, Z., Gao, W., Han, S., Li, Y. and Bai, C. Analysis of the application value of Dakundan combined with acupuncture in patients with infertility. <i>Minerva Surg</i> . 2021;	The interventions had additional treatments.
Wild, R. A., Edwards, R. K., Zhao, D., Kim, A. S., Hansen, K. R. Immediate weight loss before ovarian stimulation with intrauterine insemination is associated with a lower risk of preeclampsia in women with obesity and unexplained infertility. <i>F S Rep</i> 2022; 3(3): 264-268	Not unexplained infertility (UI) as could have had unilat tubal blockage and only considered sperm total motile sperm in the ejaculate in evaluation of male semen analysis
Youssef, M. A., Abdelmoty, H. I., Elashmwi, H. A., Abduljawad, E. M., Elghamary, N., Magdy, A., Mohesen, M. N., Abdella, R. M., Bar, M. A., Gouda, H. M., Ali, A. M., Raslan, A. N., Youssef, D., Sherif, N. A. and Ismail, A. I. Oral antioxidants supplementation for women with unexplained infertility undergoing ICSI/IVF: randomized controlled trial. <i>Hum Fertil (Camb)</i> . 2015; 18 (1): 38-42.	Compared 2 anti-oxidants against each other



IV. Quality of life

PICO QUESTION: IS THERE A DIFFERENCE IN QoL FOR PATIENTS WITH UNEXPLAINED VERSUS EXPLAINED INFERTILITY?

Flowchart



List of excluded papers

	Exclusion criterion
Krol, M., Nap, A., Michels, R., Veraart, C. and Goossens, L. Health state utilities for infertility and subfertility. <i>Reprod Health</i> . 2019; 16 (1): 47.	No distinction is made for QoL between explained and unexplained infertility.