Natural IVF cycles in poor responders on conventional stimulation protocols

ie Natural cycle IVF in normal vs. poor responders

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- *Maribor February 2009*

ISMAAR- International Society for Mild Approaches in Assisted Reproduction

- *Advances in embryology, ultrasound technology and endocrinology are making the natural cycle and mild stimulation IVF more successful and increasingly relevant to everyday practice.*
- *Tendency to shift from stronger to mild or minimal stimulation protocols*
- *Nargund G, Fauser BC, Macklon NS, Ombelet W, Nygren K, Frydman R; Rotterdam ISMAAR Consensus Group on Terminology for Ovarian Stimulation for IVF: The ISMAAR proposal on terminology for ovarian stimulation for IVF. Hum Reprod. 2007 Nov;22(11):2801-4.*

The ISMAAR terminology for ovarian stimulation in IVF

Terminology	*Aim*	*Methodology*
Natural cycle	*Single oocyte*	*No medication*
Modified natural cycle IVF	*Single oocyte*	*hCG only GnRH ant &FSH*
Mild stimulation IVF	*2-7 oocytes*	*Low dose FSH& antagonist*
Conventional high Stimulation IVF	*> 8 oocytes*	*Agonist or antag. & high dose FSH*

Problem of timing oocyte retrieval solved by administering hCG before natural LH surge (Paulson and co. 1989, Foulot and co. 1989) Modified natural cycle High cancellation rate - because high E2 levels were demanded for triggering hCG.

In 1994 we introduced lower minimal criteria to induce ovulation with hCG

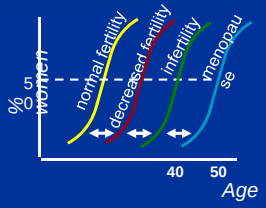
- *17 -18 days before expected bleeding*
- *E2: = > 0.4 nmol/l*
- *Φ of the dominant follicle: = > 16 mm*
- *Urinary LH neg*
- *Punctures performed 31-32 hours after hCG*
- *ET on the day 4*
- *Luteal supplementation with 1500 IU hCG on day 5*

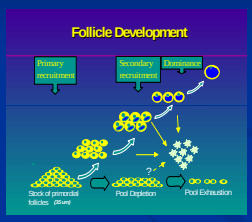
(Live birth per cycle was 28/196 cycles 14% Tomazevic et al: Assisted reproduction 1999; 149-56)

In 1999 we introduced ET on day five

Poor ovarian response to gonadotrophin stimulation The most frustrating problem of the COH . Ageing and the three phases of reproductive woman's life.

- *after Te Velde*





Causes

- *Advanced age*
- *Previous surgery*
- *Postinlammatory changes*
- *BMI*
- *Genetics*
- *Early ovarian ageing*

Prediction

- *Age*
- *Day 3 FSH*
- *Day 3 FSH + E2*
- *Inhibin B*
- *AMH*
- *Antral follicle count*
- *Clomiphene challenge*
- *GnRH agonist test*
- *FSH test*
- *Low or absent reponse to conventional ovarian stimulation*

Reduced number of high quality embryos

- *Reduced pregnancy rates and high abortion rates in both the index and subsequent cycles*
- *The need for higher gonadotrophin doses which may increase recruitment but do not necessarily translate in the higher pregnancy rates*
- *Natural IVF cycle in poor responders ??*

Natural cycle in poor responders ??

Yes

- Papaleo E et al Natural cycle as first approach in aged patients with elevated follicle-stimulating hormone undergoing intracytoplasmic sperm injection: a pilot study., Gynecol Endocrinol. 2006 Jul;22(7):381-4.
- Ubaldi FM et al. Management of poor responders in IVF. Review Reprod Biomed Online. 2005 ;10(2):235-46.
- Check JH.Modified natural cycle IVF for poor responders. Hum Reprod. 2005 Sep;20(9):2661
- Fasouliotis SJ et. al Evaluation and treatment of low responders in assisted reproductive technology: a challenge to meet. J Assist Reprod Genet. 2000 Aug;17(7):357-73.
- Morgia F et al.A controlled trial of natural cycle versus microdose gonadotropin-releasing hormone analog flare cycles in poor responders undergoing in vitro fertilization.
- Fertil Steril. 2004 Jun;81(6):1542-7.

No

- Phillips SJ et alControlled natural cycle IVF: experience in a world of stimulation.Reprod Biomed Online. 2007 Mar;14(3):356-9
- Kolibianakis E et al. Modified natural cycle for IVF does not offer a realistic chance of parenthood in poor responders with high day 3 FSH levels, as a last resort prior to oocyte donation. Hum Reprod. 2004 Nov;19(11):2545-9.

The lack of a clear cut definition of poor response

- *Makes it difficult to compare treatment outcomes, to counsell the patients, to develop protocols for prevention and management and to distiguish between good and bad prognosis in theese patients.*
- *<3 oocytes on conventional high dose stimulation*

Our way of using modified natural cycle a IVF with hCG only

Day 1 2 3 4 5 6 7 8 9 10 11 12 13 14
E_2 √ √ √ √ √
VUS when E_2 > 0,4 nmol/l √ √ √
Urinary LH √ √ √
HCG 5000 - IU ↓: when, follicle Φ: > 16 mm (17-21 mm), E_2 > 0,4 nmol/l
at the meeting point of three criteria E_2, follicle, duration cycle of minus 17-18days
Puncture 32 hours later

Live birth / cyle was 13 % in 286 cylces in women < 39 years of age

- ***Tomazevic T et. al. Age, oestradiol and blastocysts can predict success in natural cycle IVF-embryo transfer. Reprod Biomed Online. 2007 Aug;15(2):220-6***

When E_2 reaches 0.4 nmol/l one follicle gained dominance by a physiological process

Results of 397 natural IVF cycles with ET on day 5 (2000-2003)

Avg. number of IVF attempt : 5,3±3,4 FSH<10 IU, ICSI , male excluded

- *Cycles - women* — *397 cycles in 183 women*
- *Positive puncture (PP)* — *303/397 (76%)*
- *ET/PP* — *210/303 (69%)*
- *Clinical pregnancy* — *48*
- *Clinical pregnancy / cycle* — *48/397 (12%)*
- *Clinical pregnancy /ET* — *48/210 (23 %)*
- *Live birth / cycle* — *40/397 (10%)*
- *Live birth/ET* — *40/210 (19%)*
- *Live birth (woman)* — *40/183 (22%)*

48 pregnancies – 40 deliveries (83%) and 8 abortions (17%)

The aim : to evaluate six predictors of success by using modified natural IVF cycle and especially poor response to conventional stimulation

1. *The embryonic stage on the day 5*
2. *The womans age <39 years vs. = > 39 years*
3. *Natural cycle IVF only vs. natural cycle IVF in patients with 3-5 unsuccessful conventionally stimulated cycele*
4. *The number of oocytes retrieved in previous conventionally stimualted cycles . (<4 oocytesvs retrieved vs. = > 4 oocytes retrieved*
5. *Oestradiol on the day of hCG (0,4-0,6 nmol/l vs = >0,6 nmol/l)*
6. *Natural cycle IVF in patients with FSH = > 12 (2004-2006)*

Embryonic stage and the result of natural cycle IVF (2000-2003, FSH < 12)

Embryonic stage	*N*	*Pregnancy*	*Pregnancy/ET*
Blastocyst	*106 (51%)*	*39*	*37 %*
Morula	*92 (43%)*	*9*	*10%*
Lower stage	*25 (12%)*	*0*	*0%*

(p<0.001)

Woman s age and the result of natural IVF (2000-2003 , FSH <12)

Age - Years	*<=38*	*>=39*	*/*
Cycles	*286*	*111*	*/*
Positive puncture (PP)	*77%*	*75%*	*NS.*
ET/cycle	*57%*	*52%*	*NS.*
Blastocyst Development Rate	*55%*	*29%*	*P<0,001*
Pregnancy/Blastocyst	*39%*	*21%*	*NS.*
Pregnancy/ Morula	*13%*	*3%*	*N.S.*
Live birth/cycle	*13%*	*2%*	*P<0.001*

Patients with natural IVF only vs. patients with previously conventionally stimulated cycles (FSH<12) (2000-2003)

Natural IVF	No previous stimulated cycles	Previously stimulated cycles (3-5)	
Cycles	72	325	
Positive puncture (PP)	76 %	76 %	N.S
ET/cycle	61%	55%	N.S.
Blastocyst Development Rate	43 %	48%	N.S.
Pregnancy/Blastocyst	63%	34%	P< 0,02
Pregnancy/ Morula	14%	10%	N.S.
Live birth/Cycle	21%	9 %	P< 0,001

Number of oocytes retrieved in previous conventionally stimulated cycles and the results of IVF in natural cycle (2000-2003)

0ocytes in conventionally stimulated cycles	> 4 oocytes	=< 4 oocytes	/
Cycles	209	111	/
Positive puncture (PP)	82 %	65 %	P<0,001
ET/cycle	61%	45 %	P<0,004
Blastocyst Development Rate	51%	40%	NS.
Pregnancy/Blastocyst	38%	38%	N.S.
Pregnancy/ Morula	13%	0%	P<0,05.
Live birth/Cycle	11%	4%	P<0.05

Estradiol - day of hCG (all ages – FSH<12, 2000-2003)

Estradiol day of hCG	0,4-0,59 nmol/l	0,6-1,25 nmol/l	
Cycles	180	217	NS.
Positive Puncture (PP)	77%	76%	NS.
ET/cycle	58%	54%	NS.
Blastocyst Development	47%	49%	NS.
Pregnancy /ET of Blastocyst	37%	37%	NS.
Pregnancy/ ET of Morula	13%	6%	N.S.
Live birth/cycle	11%	10%	NS.

Results of natural cycle IVF - basal FSH >12 Positive Clomiphene test (2004 - 2006)

	FSH >12 –Positive Clomiphen test
Cycles	32
Positive puncture (PP)	87 %
ET/cycle	59 %
Blastocyst Development Rate	63%
Pregnancy/Blastocyst	0 %
Pregnancy/ Morula	0%
Live birth/Cycle	0%

Conclusions regarding poor responders

- Natural cycle IVF can be successfully used in patients with previously unsuccessfull conventionally stimulated IVF cycles .
- Patients with poor response to conventional ovarian hyperstimulastion can only occasionally profit of natural IVF cycle .
- The age of woman >=39 years unfavourably influences the success in natural IVF cycle. They can only occasionally profit of natural IVF cycle. IVF in natural cycle should not be recommended to age related poor responders
- IVF in natural cycle should not be recommended in poor responders with elevated FSH.

Conclusions regarding normal responders

- The use of natural cycle IVF in normal responders with respect to appropriate indications and age could provide good results with low costs of treatment.
- Complementary use of stimulated and unstimulated cycles in normal responders could possibly reduce costs and allow better cumulative success rates in the future.