Different forms of ovarian stimulation for IVF : *Terminology*

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Disclosures

None

The ISMAAR proposal on Terminology for Ovarian Stimulation for IVF

Rotterdam consensus group on Terminology for ovarian stimulation for IVF

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For the ISMAAR Consensus Group on Terminology for Ovarian Stimulation for IVF

Consensus on Terminology

Consistency is needed

- For clinical practice
- For research publications
- Patient understanding & communication
- For policy makers
- For public information

Terminology is focused on the meaning & conveyance of concepts

Definitions

Terminology	***Aim***	***Methodology***
Natural cycle IVF	*Single oocyte*	*No medication*
Modified Natural cycle IVF	*Single oocyte*	*hCG only* *Antagonist & FSH/HMG add-back*
Mild IVF	*2-7 oocytes*	*Low dose FSH/HMG, oral compounds & antagonist*
Conventional IVF	*≥8 oocytes*	*Agonist or antagonist conventional FSH/HMG dose*

Terminology

Recommended	**To replace**
Natural cycle IVF	*Unstimulated, Spontaneous cycle IVF*
Modified Natural cycle IVF	*Semi-natural, Controlled natural cycle IVF*
Mild IVF	*Soft, Minimal stimulation, 'Friendly' IVF*
Conventional IVF	*Standard, Routine IVF , Controlled Ovarian Hyperstimulation (COH) IVF*

Natural cycle IVF

- Spontaneous cycle
- Single mature oocyte
- No medication used at any stage of cycle
- Monitoring with USS and or Hormone assay

Nargund et al: Human Reprod;2001;16:259-262

Modified Natural cycle IVF

- Spontaneous cycle
- Exogenous hormones used

Scenarios:

1. hCG only
2. GnRH antagonist ±FSH add-back & hCG
3. Luteal support

- Low risk of cancellation
- Commonly used method of natural cycle IVF

Rongieres-Bertrand et al:Hum Reprod,1999;14:683—688
Nargund & Frydman: RBM Online,2007;14;550-552

Mild IVF

- Lower doses of FSH or HMG (max 150iu/day)
- Oral compounds could be used
- Physiological approach to start of stimulation
- Shorter duration of stimulation
- GnRH antagonist cycle
- hCG to induce final oocyte maturation

Heijnen et al: Lancet 2007;369:743-749

Conventional IVF

- Most commonly used method in IVF
- GnRH agonist (downregulation) used
- Gn RH antagonist could be used
- Higher doses (up to 600iu/day) of FSH or HMG used
- Longer duration of stimulation
- Higher cumulative (total) dose of FSH or HMG

Nargund,Fauser,Macklon et al:Hum Reprod 2007

Time for a re-think?

- Revival of natural cycle IVF
- Concept of modified natural cycle IVF
- Development of protocols for Mild IVF
- Concerns about conventional stimulation IVF

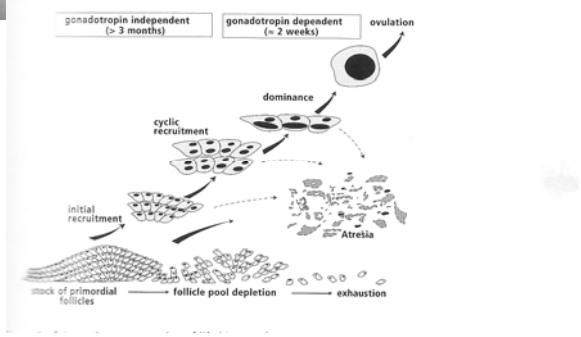
Conventional stimulation IVF:

- High number of oocytes & embryos
- Complex /unphysiological stimulation protocols
- Time consuming (up to 4-5 weeks)
- High costs (direct and indirect)
- Patient discomfort (prolonged injections)
- Menopausal symptoms
- Supra-physiological steroid levels
- OHSS/Thrombo-embolism
- Increase in chromosome abnormalities in oocytes & embryos
- Adverse endometrial conditions
- Long-term health consequences
- High drop-out rates

Aims of Mild stimulation

- Less complex
- More physiological
- Less time consuming (in a natural cycle)
- Reduced psychological burden
- Minimal monitoring
- Cheaper
- Reduced patient discomfort (less injections)
- Reduced OHSS/VTE
- Low drop-out rates
- Better (quality) oocytes and embryos
- Improved endometrial conditions
- Single embryo transfer/Term LBR
- Health Economics benefits

Life history of ovarian follicles



Revival of Natural cycle IVF

- 44 cycles
- 33 women (26-36 years)
- Single dose Cetrorelix & HMG (4.7±1.4 amps)
- 4 cycles cancelled
- 40 oocyte collections
- 10 cycles with no oocytes
- 22 embryo transfers
- 7 clinical pregnancies
- 32% clinical pregnancy per ET
- 17.5% clinical pregnancy per oocyte collection

Rongieres-Bertrand C et al Human Repro 1999:14 (3): 683-8

Natural Cycle IVF

Cumulative Conception & Live birth Rates:
Nargund et al Human Reprod 2001
-52 women &181 cycles (3.49 cycles/patient)
-Life table analysis
After 4 successive cycles of treatment
Cumulative probability of pregnancy -46%
Cumulative probability of Live birth -32%

Natural Cycle IVF

Nargund et al: Human Reprod 2001

Conclusions:
1.For maximum effectiveness, must be offered as a series of treatment cycles
2.Safer, less stressful and can be offered over consecutive cycles
3.Can be offered at ~23% of the cost of stimulated cycle

Minimal stimulation in Natural (Semi-Natural) Cycle

- More physiological
  Follows the path of follicular growth
- Minimal cost
- Fits into a spontaneous cycle
- Less stressful
- No cancellation/LH surge with antagonist
- Effective alternative

Modified Natural Cycle IVF

- *Feldman B et al: Gynae Endo 2001*
- *Nargund et al: Human Reprod 2001*
- *Ubaldi FM : RBM online 2005*

-Favourable in poor responders & failed implantation

-The use of antagonists did not change intrafollicular VEGF/Inhibin A levels

Semi-Natural Cycle IVF

For Poor responders/Low ovarian reserve/Failed implantation

1. Castlo-Branco,Frydman et al 2004
133 cycles/16.6% pregnancy/oocyte collection
2. Elizur S 2005 -540 cycles-Agonist/Antagonist/Natural IVF
10.6%/6.75%/10.2% pregnancy/cycle

Semi-Natural Cycle is a feasible alternative

Semi-Natural Cycle IVF

Pelinck MJ (Netherlands): Human Reprod 2005

-Late follicular start FSH/Antagonist
-50 patients/119 cycles (2.4 cycles/pt)
-52 Embryo Transfers
-17 ongoing pregnancies
-PR = 32.7%/ET
Cumulative ongoing pregnancy rate
-After 3 cycles: 34%
-Live Birth Rate per patient: 32%

Natural/Modified natural cycle IVF:

Patient selection - Current practice

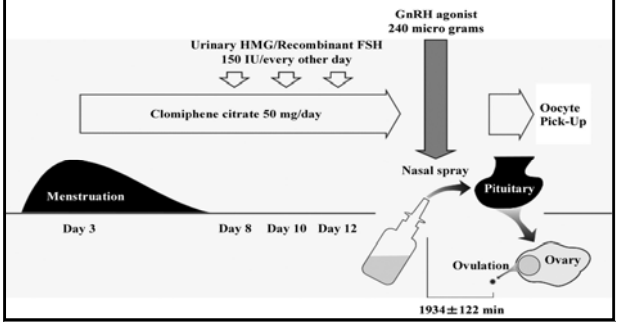
- In cancer patients
- Poor responders
- Failed implantation

Monitoring & Optimisation of cycles

- Cycle length
- Follicular-Endometrial synchronisation
- Ovulation jumping

Minimal ovarian stimulation with clomiphene citrate: a large-scale retrospective study

Teramoto S & Kato O:RBM Online 2007



Teramoto & Kato: RBM Online 2007

Age	27-29	30-32	33-35	36-38	39-41	42-44	45-47	Total
cycles	107	3335	6286	8465	10688	9732	4767	44345
ETs	499	1460	2671	3279	3447	2522	1011	14889
LBR/ Cycle (%)	14.6	13.5	10.5	7.4	3.1	1.0	0.1	5.2

A mild treatment strategy for in-vitro fertilisation: Randomised non-inferiority trial

Esther M E W Heijnen, Marinus J C Eijkemans, Cora De Klerk, Suzanne Polinder, Nicole G M Beckers, Ellen R Klinkert, Frank J Broekmans, Jan Passchier, Egbert R Te Velde, Nick S Macklon, Bart C J M Fauser

Lancet 2007;369:743-49

Cycle-specific characteristics of IVF cycles finished within 1 year

Heijnen et al **: Lancet 2007;369:743-49**

Mild treatment (n=444)	Standard treatment (n=325)		p
Duration of ovarian stimulation (days)	8·3 (2·2)	11·5 (3)	<0·001*
Duration of injections (days)	8·5 (2·7)	25·3 (6·8)	<0·001*
Total dose of follicle stimulating hormone (IU)	1307 (529)	1832 (758)	<0·001*
Cancellation of pregnancy cycle	80 (18·0%)	(8·3%)	<0·001†
Number of oocytes per retrieval	6·9 (4·8)	8·5 (4·3)	<0·001*
‡Number of embryos per retrieval	2·8 (2·7)	3·8 (2·9)	<0·001*
Number of cryopreserved embryos vs fresh embryos for transfer	0·9 (1·8)	0·6 (1·4)	0·04*
Continuing pregnancy per started cycle (fresh embryos)	78 (17·6%)	93 (28·6%)	<0·001†
Continuing pregnancy per started cycle (cryopreserved embryos)	6 (1·4%)	4 (1·2%)	0·8†
Term livebirth per started cycle (fresh embryos)	70 (15·8%)	78 (24·0%)	0·003†
Term livebirth per started cycle (cryopreserved embryos)	49 (1·1%)	3 (0·9%)	0·8†
§Ovarian hyper stimulation syndrome	6 (1·4%)	12 (3·7%)	0·04†

Pregnancy outcome after mild and standard IVF treatment

Heijnen et al **: Lancet 2007;369:743-49**

Mild strategy			**Standard strategy**	
Singleton	Multiple*		Singleton	Multiple
Live births (total)	91	1	76	26
Live born children	91	3	76	51†
Term live birth (≥37 weeks' gestation)	86	0	69	17
Late preterm live birth (32–37 weeks' gestation)	2	0	6	6
Early preterm live birth (<32 weeks' gestation)	3	1	1	3
Birth weight (kg)‡	3·34 (0·76)	1·34	3·35 (0·76)	2·34 (0·73)

Cost-Effectiveness of a mild compared with standard strategy for IVF:
A randomised comparison using cumulative term live birth as a primary endpoint

Polinder,S,Heijnen EMEW,Macklon NS,Hebbema JDF,Fauser BCJM & Eijkemans MJC

Human Reprod November 2007

Mild+ SET Vs Std +DET (205 cycles Vs 199 cycles)

- Over 1 year (4 Mild vs 3 Std cycles)
- Cost of IVF - €8337 Vs 10,745
- 6 vs 16 preterm livebirths (<37weeks)
- Obs/postnatal cost/preg -€1947 vs 4136
- Cost/Term live birth - €24k vs 19k
- Incremental cost-effectiveness ratio/extra pregnancy-Term livebirth €185k

Polinder et al: Human Reprod 2007

Natural/Mild (Friendly) IVF: Patient opinions

Despite cancellations & lower success rates per cycle, women prefer:

- Simplicity & short duration
- Treatment fitted in their spontaneous menstrual cycles
- No/Low hormone strategy
- No/Few injections
- No/Few side effects
- Fewer visits/blood tests
- No/Less interference with professional/social life

Hojaard et al,Hum Reprod 2001
Norman A & Nargund G (MSc Thesis) 2004
Pistorius EN et al ,Hum Fertil 2006
Sedbon E et al ,RBM Online 2006 (French data)
De clerk C et al ,Hum Reprod 2007
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