Natural cycle IVF : Is it Effective and Cost-effective?

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Disclosures

None

BIRTH OF LOUISE BROWN: 25th July 1978

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

Effectiveness: The Definition

- Efficiency: doing things in the most economical way (good input to output ratio)
- Efficacy: getting things done, i.e. meeting targets
- Effectiveness: doing "right" things, i.e. setting right targets to achieve an overall goal (the *effect*)

Cost-Effectiveness

Cost-Effectiveness Analysis (CEA)

Is a form of economic analysis that compares the relative expenditure (costs) and outcomes (effects) of two or more courses of action.

Natural /Modified natural cycle IVF

- Cohort studies
- Cumulative data
- In selected population

1. Poor responders
2. Failed implantation
3. Older women
4. Cancer risk group

The ISMAAR proposal on Terminology for Ovarian Stimulation for IVF

Rotterdam consensus group on Terminology for ovarian stimulation for IVF

Nargund G , Fauser BCJM , Macklon NS , Ombelet W , Nygren K and Frydman R

Human Reproduction 2007;22(11) 2801-2804

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*

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

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

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 (downregulation & high stimulation) approaches:

- Complex /unphysiological/unnecessary/unpleasant
- Time consuming (up to 4-5 weeks)
- High costs (direct and indirect)
- Patient discomfort (prolonged injections)
- Menopausal symptoms, Headaches
- 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 (psychological burden)

Development of Superovulation IVF protocols

- To block premature LH surge
- To avoid cancellation of cycles
- To plan weekly schedules in clinics
- Due to relative inefficiency of single embryo transfer
- To allow multiple fresh embryo transfer

Why Now?

- Single Embryo Transfer
- Clinical availability of antagonists
- Advances in Endocrinology
- Latest Ultrasound Technology
- Improved Embryology
- Concerns about embryo & endometrial quality
- Cancer survivors requiring ART
- *"Cost"* of conventional IVF
- Increased demand in public health service

Natural/Modified natural cycle IVF:

Patient selection - Current practice

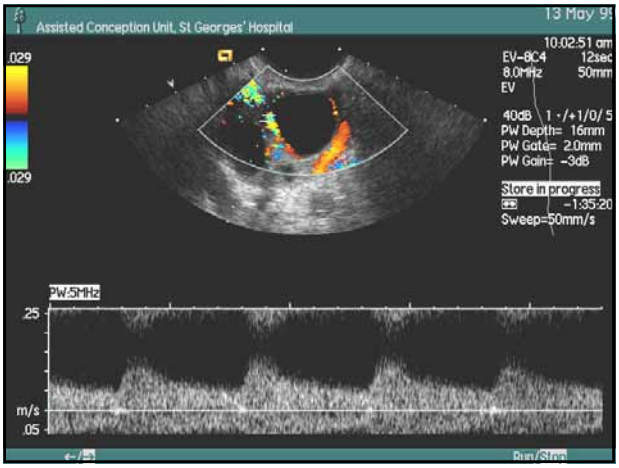
- In cancer patients & those with family H/O cancer
- Poor responders
- Older women
- Failed implantation
- With severe endometriosis
- For those who want to avoid drugs

Monitoring & Optimisation of cycles

- Normal cycle length
- Follicular-Endometrial synchronisation
- Ovulation jumping
- Single ovary

Synchronising Follicular & Endometrial growth & maturity

- Growth of follicle &Thickness of endometrium (early scan)
- Volume & follicular blood flow and Endometrial morphology & blood flow
- Peri- ovulatory follicle, Endometrial morphology & cervical mucus



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

Current success rates –
No down-regulation/No cancellation
No OHSS/Low cost

Create Health success rates for 2007

MILD STIMULATION IVF/ICSI		NATURAL/MODIFIED NATURAL CYCLE IVF/ICSI	
<35 Years	52.6%/ET	<37 Year	18.2 % /ET
35-37 Years	45.3%/ET	38 & 39 Years	18.2%/ET
38-39 Years	29.5%/ET	40 -45 Years	17.2% ET
40 -45 Years	22.6%/ET	Total - All ages	17.2% /ET
Total - All ages	37.7%/ET	Total no of egg collections	142
Total no of egg collections	347		

Clinical Pregnancies per Embryo Transfer

Natural cycle IVF : Cost Effectiveness Analysis

- Daya et al: Human Reprod 1995
  240 cycles: 12% clinical pregnancy/cycle
  Despite the high failure rate at each step in the process, natural cycles are more cost-effective than stimulated cycles which incur an incremental cost per live birth of $48,000. Natural cycles offer a low-cost alternative that may be more accessible to patients
- Nargund et al: Human Reprod 2001
  181 cycles: Cumulative LBR -32% (4 cycles)
  Natural cycle IVF can be offered at 23% cost of stimulated cycle

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

Natural cycle IVF:
In Poor Responders

- Prospective study
- 22 poor responders over 1 year
- 44 NCIVF and 55 SIVF cycles
- 82% had one oocyte collected
- 41% had atleast 1 cycle with ET
- 9% had a live birth

Results of NCIVF & SIVF comparable

Feldman et al: Gynae Endocrinology 2001

Semi-Natural IVF:
In Poor prognosis patients

- Prospective study -133 cycles
- Altered ovarian status & Implantation failure
- 66 patients (AOS -47; IF-19)
- OPU rate (81.2%;61.1%)
- Clinical pregnancy rate/OPU (15.4%;16.6%)

Castelo-Branco A et al:Gynae Obstet Biol Reprod: 2004

Modified Natural cycle IVF:
In Poor Responders

- 540 cycles
- Retrospective evaluation
- MNIVF vs Antagonist SIVF vs LongSIVF
- 52 vs 200 vs 288 cycles
- 1.4 vs 2.3 vs 2.5 oocytes
- 10% vs 14.3% vs 6.75% implantation
- 10.2% vs 7.4% vs 10.6% pregnancies

Elizur et al: Assist Reprod Genetics 2005

Natural cycle IVF:
In Poor Responders

- 294 patients & 500 consecutive cycles
- ≤ 35 : 36-39 : ≥40 years old
- 18.1% : 11.7% : 5.8% pregnancy/cycle
- 29.2% : 20.6% : 10.5% pregnancy/ET
- 31.7% : 20.3% : 10.5% pregnancy/pt

NCIVF is an effective treatment.

Schimberni et al: Fertil Steril 2008

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%

Modified Natural cycle IVF:
Cumulative pregnancy rates

- 268 patients with sequential treatment
- MNC IVF followed by COS IVF
- Time to pregnancy -28.8 weeks
- 9 cycles of MNC followed by COSIVF
- Cumulative ongoing pregnancy 56.7%
- Cumulative LBR 50% per patient

Sequential treatment is patient-friendly,low-risk & has low twin pregnancy rate

Pellinck et al: Hum Reprod 2008

Natural /Modified Natural cycle IVF/ICSI:
In cancer risk women

- In BRCA1 & BRCA2 carriers
- H/O breast tumours
- Other oestrogen dependent tumours
- Prior to chemotherapy in other cancers
- Severe endometriosis

An effective & safe option

Hirt et al: Fertil steril 2008

Dor J : NCIVF abstracts :2006

Natural cycle IVF with IVM:
A New approach?

- In ovulatory Normal & PCO women
- hCG 10,000 IU
- 3 women
- 3 pregnancies
- 2 live births

Chain RC et al : Fertil Steril 2004

- 350 cycles
- 262 women
- 15.2% ongoing pregnancy rate

Benkhalifa M et al:RBM Online 2009

Natural/Modified Natural cycle IVF:
Patient opinions

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

- Natural selection
- 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
Pistonius EN et al ,Hum Fertil 2006
Sedbon E et al ,RBM Online 2006 (French data)
De clerk C et al ,Hum Reprod 2007
Verberg MF et al Hum Reprod 2008

What are the priorities for "results" of IVF?

For the Patient
- No side effects
- No OHSS
- Less interference
- Low cost
- No long-term concerns
- Healthy mother & Child

For the Service &State
- Low Cost/Economic loss
- Social responsibility
- No multiple pregnancy
- No OHSS & future risks
- Healthy mother & child
- Suitable for developing & developed world

Safety and Comfort

Quality NOT Quantity

Mild Vs Standard Strategy Heijnen et al: Lancet 2007

Mild Strategy
- 444 cycles
- SET
- Term live birth rate 43.4%
- OHSS -1.4%
- Mean cycle -2.3

Standard Strategy
- 325 cycles
- DET
- Term live birth rate 44.7%
- OHSS – 3.7%
- Mean cycle – 1.7

Natural cycle IVF: Is it effective & cost-effective?

- Yes. For selected groups of patients

For a wider application using public purse:
Well designed, large scale, randomised, controlled trials are required using different methods of stimulation.

- Mild IVF would be an acceptable future strategy for wider application