Natural Cycle & Mild stimulation IVF/ICSI in women with Poor Ovarian Response (POR)

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ISMAAR Terminology
Human Reprod –Nargund et al 2007

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*

Modified Natural cycle IVF

- Spontaneous cycle
- Exogenous hormones used

Scenarios:

1. hCG only
2. GnRH antagonist ±FSH add-back & hCG
3. Indomethacin
4. 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

Natural /Modified natural cycle IVF

- Cohort studies
- Cumulative data
- Mainly retrospective
- In selected population

1. Poor responders
2. Failed implantation
3. Older women

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

-Endometrium favourable for implantation

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

Natural/Modified Natural IVF-Protocol

- Counselling ,options & informed decision
- Pre-IVF scan
- Assessment of cycle length & ovulation
- Two monitoring scans
- E2 & LH –if required
- 150 IU FSH & Antagonist from follicle 14mm
- Indomethacin if appropriate
- Egg collection at 16mm+
- Embryo Transfer Day 2-3
- Luteal support –Progesterone

Medication used to prevent LH surge/ ovulation in modified natural cycles

- Indomethacin (50mg TDS)
- Antagonist (2-3 days)
- Indomethacin + Antagonist

Indications for King's study

- Primary infertility & previous poor response

<2 follicles (35%)

- Primary infertility with blocked tubes who could not afford conventional IVF (60%)

- Secondary infertility with blocked tubes who wanted to avoid multiple pregnancy (5%)

Nargund et al Human Reprod 2001

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

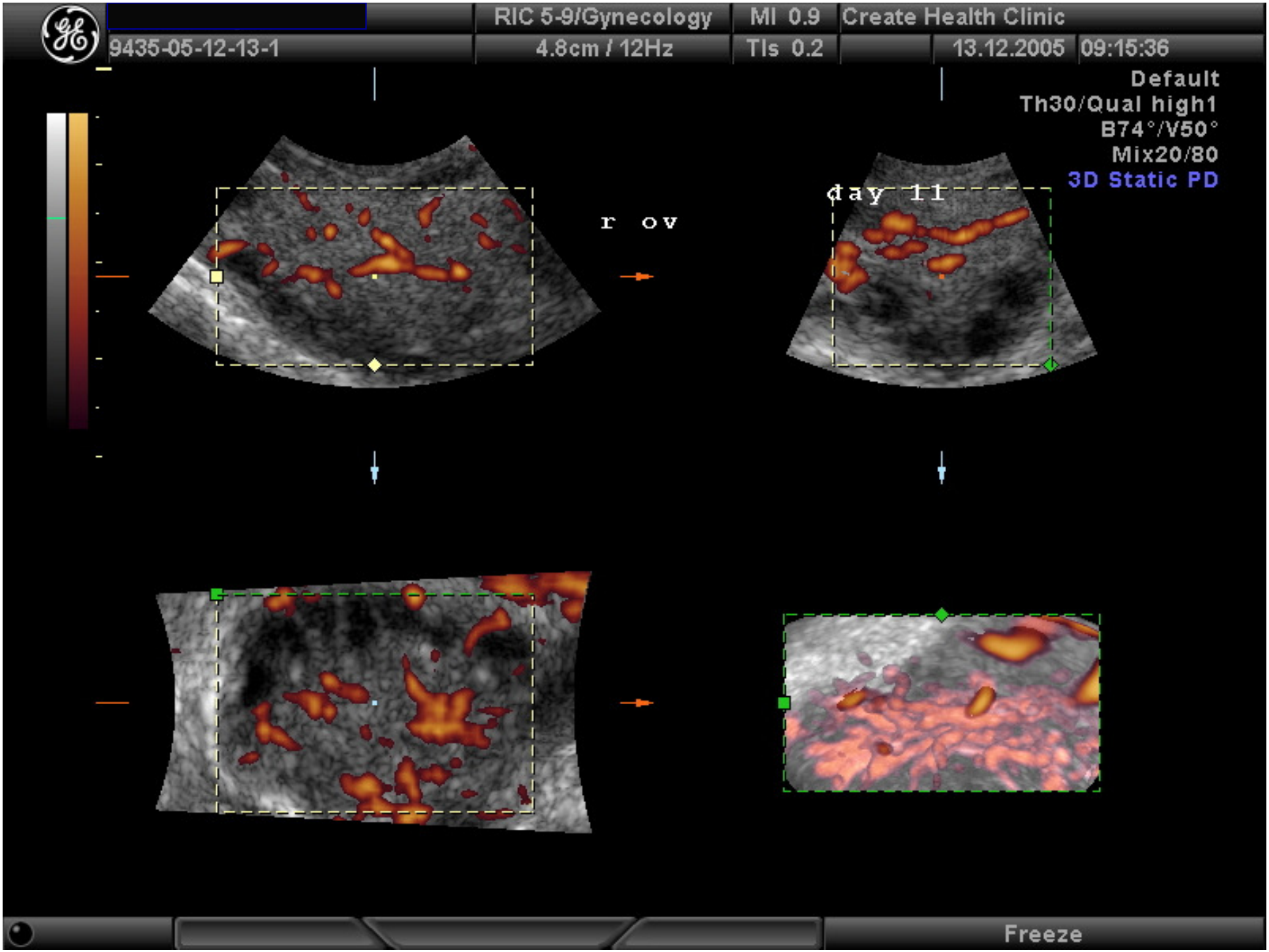
After 4 successive cycles of treatment

Cumulative probability of pregnancy -46%

Cumulative probability of Live birth -32%

Baseline ovarian ultrasound assessment

- Ovarian volume
- Stromal velocity
- AFC (<5mm & 5-9mm)
- R/O cyst/s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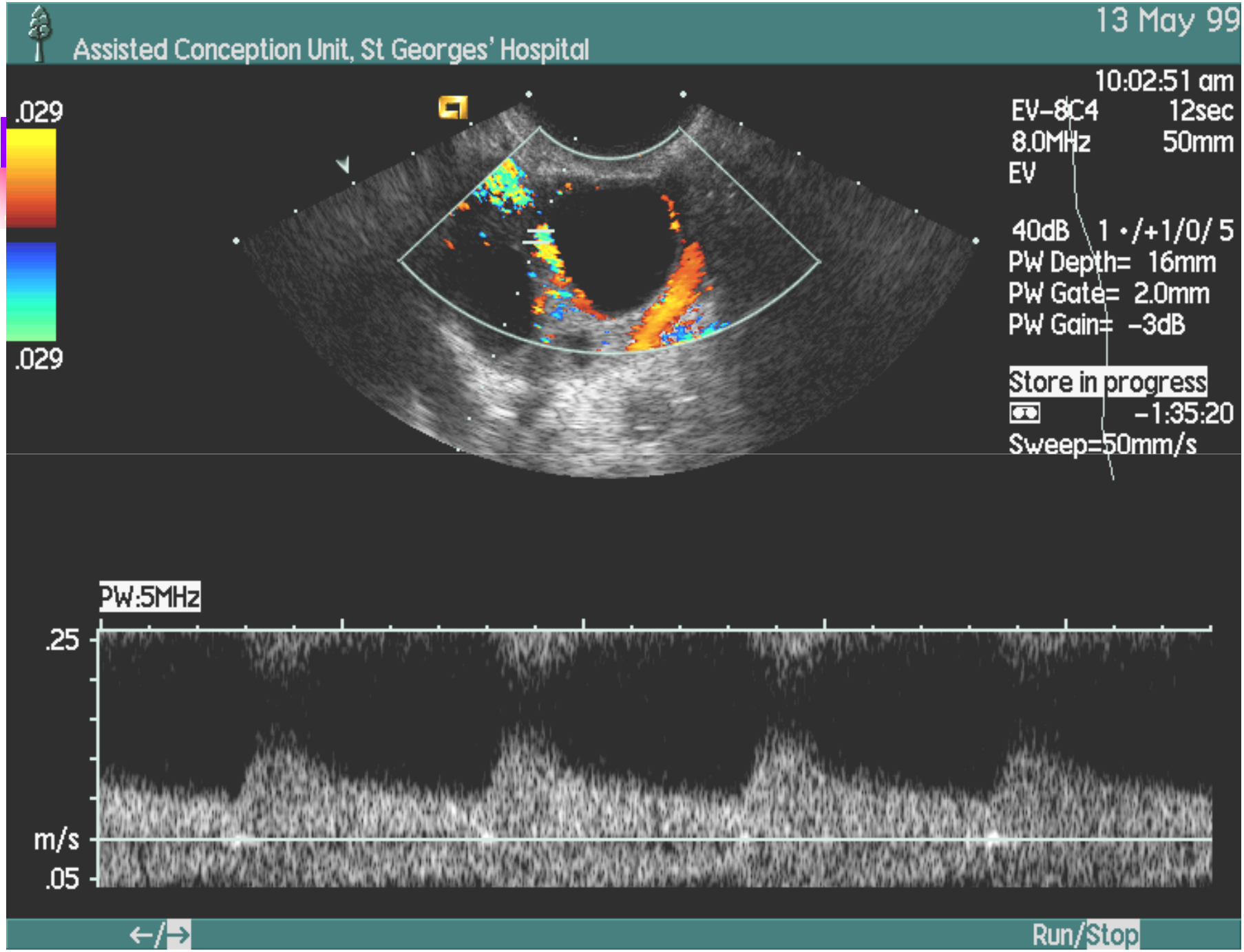
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Treatment protocols-Women>40

Natural /Modified natural cycle only

- AFC <3 /spontaneous ovulatory cycle
- Stromal PSV <5cm/sec
- Those with single oocyte/embryo with stimulated cycle

Stimulated (Agonist flare)

- AFC>3 (3-8)
- Stromal PSV>5cm/sec (5-10cm/sec)

Stimulated (Antagonist)

- AFC>8 & normal/high AMH
- Stromal PSV>10cm/sec

Women over 40 –Natural & Stimulated cycles – 2009-10

Protocol	Age Group	Total	Pregnancy per cycle	Pregnancy per ET
Stimulated	40-42	121	11.6%	13.7%
	43-44	36	8.3%	9.7%
	45	3*		
Natural	40-42	100	9.0%	20.0%
	43-44	57	7.0%	15.4%
	45	14	0.0%	0.0%
Total		331		

*Low number of cycles

Clinical pregnancy rates based on FSH & AFC - NATURAL CYCLES (2009-10)

Baseline FSH	Total AFC	Total	Pregnancy per Cycle	Pregnancy Per ET
<10	<=6	44	6.8%	11.1%
	>=7	50	10.0%	26.3%
10-13	<=6	19	15.7%	30.0%
	>=7	9*	0.0%*	0.0%*
>=14	<=6	45	6.6%	15.8%
	>=7	7	14.2%	20.0%
Total		174		

*Low number of cycles

Clinical pregnancy rates based on FSH –AFC levels (2009-10) Stimulated cycles

Baseline FSH	Total AFC	Total	Pregnancy Rate per Cycle	Pregnancy Rate per ET
<10	<=6	44	18.2%	19.0%
	>=7	228	30.3%	33.8%
10-13	<=6	15	6.7%	10.0%
	>=7	14	21.4%	21.4%
>=14	<=6	6*		
	>=7	8*		
Total		315		

*Low number of cycles

Clinical pregnancy rates based on FSH levels (2009-2010)

This table includes pregnancy rates for completed cycles by women of all ages with various baseline FSH levels, having a stimulated or natural IVF/ICSI cycle.

Protocol	Baseline FSH	Total	Pregnancy rate per cycle	Pregnancy rate per ET
Stimulated	<10	305	26.8%	29.8%
	10-13	31	19.3%	23.1%
	>=14	15*		
Natural/ Modified natural	<10	105	7.6%	16.6%
	10-13	29	10.3%	21.4%
	>=14	53	7.5%	16.6%
Total		538		

*Low number of cycles

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 at least 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

Controlled natural vs. micro dose GnRH flare cycles in poor responders

- 129 women with previous POR
- 59 women with 114 natural cycles
- 70 women with 101 flare protocol
- Similar pregnancy rates in both groups
- 14.9% implantation rate in natural cycles
- 5.5% implantation rate in flare cycles

Morgia F et al Fertility & Sterility 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 as first approach in older women undergoing ICSI: Pilot study

- 18 women
- Mean age -40.2± 0.7 years
- All had ↑ FSH & ↓ AMH
- 26 natural cycles with ICSI & single ET
- 11.5% clinical pregnancy/cycle
- 20% clinical pregnancy/ET

Papaleo E at al Gynaecol Endocrinol 2006

Embryo implantation rates in poor responders

- 304 women with previous POR
- Retrospective analysis
- Natural cycles -6/30 (20%)
- Gonadotrophin only-3/54 (5.6%)
- Long GnRH protocol 02/52 (3.8%)
- Co-flare protocol 1/52 (1.9%)
- Micro-flare 4/26 (15.4%)
- GnRH antagonists 13/90 (14.4%)

There was a trend towards higher implantation rates with natural cycles

Ata B,Yakin K,Balaban B,Urman B;RBM Online 2008

Natural cycles in poor responders

- 500 consecutive cycles
- Retrospective analysis
- 294 women with previous POR
- 391 oocytes collected (78.1%)
- 285 embryos suitable for transfer (57%)
- 49 pregnancies (9.8%/patient)

Schimberni M et al;Fertility & Sterility Oct 2009

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 2009

Conclusions

- Counselling regarding success rates with own/donor oocytes is essential in older women & those with POR
- Most women would like to try with their own oocytes before opting for donor oocytes
- Time frame for closure for treatment must be established
- Natural & modified natural cycle can be effective in older women and those with poor ovarian response & failure of implantation
- Further prospective ,well designed studies are needed