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What did we learn from the review of 1000 natural cycles for IVF/ICSI ?

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Return to the Natural Cycle for in Vitro Fertilization (Alleluia! Alleluia!)[1]

JAIRO GARCIA[2]

Journal of in Vitro Fertilization and Embryo Transfer, Vol. 6, No. 1,1991

New definition of success, which is different from the past (number of oocytes and embryos, implantation or pregnancy rates)

Efficacy of natural cycle IVF

- Systematic literature review (**20 selected studies**)

Pelinck et al. Hum Reprduction Update 2002;8:129-139.

1800 natural cycles embryotransfer rate 45.5 %
pregnancy rate per cycle 7.2 %
pregnancy rate per transfer 15.8%

Cancellation of OPU
Ovulation triggering with HCG: rate of oocyte retrieval per cycle 67.3%
Timing of spontaneous LH surge: rate of oocyte retrieval per cycle 80.6 %

Oocyte recovery rate: 88.6 %
Fertilization rate
Cycles with IVF : 44.2 to 100 %
Cycles with ICSI: 56.3 to 62.5%

- **Natural cycle as substitute for stimulated IVF / ICSI cycle**
- **Natural cycle in menagement of poor responders on COH**

16.6% pregnancy rate per OPU in 35 cycles — Lindheim et al. 1997
18.6% pregnancy rate per OPU in 16 cycles — Bassil et al. 1999
20.0 % pregnancy rate per OPU in 44 cycles — Feldman et al.2001
9.8% pregnancy rate per OPU in 500 cycles — Schimberni et al. 2008

- **Natural cycle IVF combined with IVM**

40.4% pregnancy rate per OPU in 151 cycles — Lim et al.2008

Factors affecting pregnancy success of IVF in natural cycles

- Patient age
- Indications for IVF
- Previous IVF treatment
- Baseline value of FSH, LH, PRL
- Embryo, oocyte and semen quality
- Endometrial thickness
- Day of ET
- Serum E_2 level on day of hCG administration
- etc.

Natural cycle

- **Accurate monitoring**
- **Selection of patients**
- **Method : IVF or ICSI ?**
- **Embyotransfer : day 2 or day 5 ?**
- **Influence of patient s age**
- **Luteal supplementation**
- **Efficacy**

Factors affecting pregnancy success of IVF in natural cycles

Accurate timing of hCG administration

Criteria:

- Serum estradiol level E_2 *(0,4-1,1 nmol/L)*
- Follicle size *(15-20 mm)*
- Endometrial thickness (7 mm)
- Negative LH test
- Day of menstrual cycle *(17-18 before anticipated menstruation)*

When is the correct moment to induce final oocyte maturation ?

Protocol 1

- Follicle diameter: >17mm
- Endometrial thickness >7mm
- E2 not measured !

When is the correct moment to induce final oocyte maturation ?

Protocol 2
(Paulson et al.1993)

When the dominant follicle allained 16-20 mm.

or

Estradiol levels were indicating satisfactory follicular development (>1.1 – 0.73 nmol/L).

Follicular diameter	Estradiol level
16 mm	1.1 nmol/L
18 mm	0.91 nmol/L
20 mm	0.73 nmol/L

When is the correct moment to induce final oocyte maturation ?

Protocol 3
(Maribor IVF)

When the dominant follicle allained >15 mm.

and

Estradiol levels were indicating satisfactory follicular development
> 0.49 nmol/L

Comparisson between the cycles with pregnancy and cycles without pregnancy

Variable	Cycles with pregnancy	Cycles without pregnancy	P value
Duration of infertility (years)	5,75 ± 4,22	6,78 ± 4,37	NS
Baseline value of FSH (IE)	6,44 ± 3,09	6,95 ± 1,53	NS
Baseline value of LH (IE)	4,55 ± 1,97	4,40 ± 1,58	NS
E_2 level on day of HCG i. (nmol/L)	0,825 ± 0,231	0,725 ± 0,233	**0,018**
Average follicular diameter (mm)	**15,59 ± 1,34**	**15,53 ± 1,32**	**NS**
Max. follicular diameter (mm)	16,90 ± 1,57	16,66 ± 1,57	NS
Endometrial thickness (mm)	**8,24 ± 1,70**	**8,16 ± 1,62**	**NS**
Day of HCG injection	11,54 ± 2,81	10,54 ± 2,32	**0,014**

Estradiol pattern predicts natural IVF/ICSI outcome

Prospective study; 305 natural IVF/ICSI cycles

Serum estradiol concentrations were determined :

- on day 2 of menstrual cycle
- every 2 days from day 7 onward
- every day when the follicular diameter was >12 mm and serum E_2 concentration >0.3 nmol/L.
- DAY 0 - on day of hCG inj. (~12 hours before hCG inj.)
- DAY 1 (12-17 hour after hCG inj.)
- DAY 2 - day of oocyte recovery

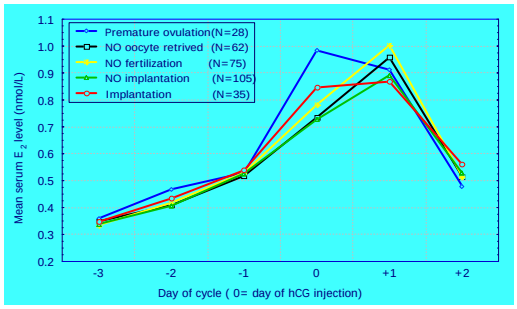
A comparison of serum E_2 levels on day 0, day 1 and their ratio between cycle groups

E2 level (nmol/L)	Conception cycles	Nonconception cycles	p value
Day 0	0.82 ± 0.23	0.72 ± 0.23	0.018
Day 1	0.85 ± 0.28	0.91 ± 0.31	NS
Day 1/Day 0	1.06 ± 0.35	1.30 ± 0.36	<0.001

Multiple logistic regression: E_2 level on day 0, B=1.60, p= NS

E_2 day 1/day 0 ratio, B=-2.21, p=0.007

Preovulatory serum estradiol pattern in 305 natural IVF/ICSI cycles



Reljic M & Vlaisavljevic V JARG 1999

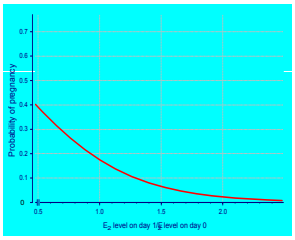
Outcome of natural IVF/ICSI cycles according to 1.1 E_2 on day 1 / E_2 on day 0 ratio

	E_2 on day 1/ E_2 on day0 ≥1.1	E_2 on day 1/ E_2 on day0 <1,1	
	182	123	
Premature ovulation rate	3.3 (6/182)	17.9 (22/123)	<0.001
Oocyte recovery rate	74.4(131/176)	83.2 (84/101)	
Fertilization rate	70.2 (92/131)	70.2 (59/84)	
Implantation rate	12.8 (11/86)	44.4 (24/54)	<0.001
Pregnancy rate per cycle	6.0 (11/182)	19.5 (24/123)	<0.001

Reljic M et al.. Fertil Steril 2001

Probability of pregnancy in relation to E2 ratio in cycles without premature ovulation

- A higher pregnancy rate and lower cancellation rate was obtained when hCG was applied in lower values of serum E2 and smaller follicle diameter.
- In predicting the outcome of natural IVF/ICSI cycles, the importance lies not in E2 levels on the day of hCG administration or on the day after, but rather in the E2 ratio.



Interval in which spontaneous LH rise can be expected calculated from duration of menstrual cycle (mean and standard deviation of 6 menstrual cycles)

SD	26	26.5	27	27.5	28	28.5	29	29.5	30	30.5
0.2	11-14	11-14	12-15	12-15	12-15	13-16	13-16	14-17	14-17	14-17
0.5	**11-14**	**11-15**	**11-15**	**12-15**	**12-16**	**12-16**	**13-16**	**13-17**	**14-17**	**14-18**
0.7	10-14	11-15	11-15	12-15	12-16	12-16	13-17	13-17	13-17	14-18
1.0	10-15	11-15	11-15	11-16	12-16	12-16	12-16	12-17	13-18	14-18
1.3	10-15	10-15	11-16	11-16	11-16	12-17	12-17	13-17	13-18	13-18
1.7	10-15	10-16	10-16	11-16	11-17	11-17	12-17	12-18	13-18	13-19
2.0	**9-15**	**10-16**	**10-16**	**10-17**	**11-17**	**11-17**	**12-18**	**12-18**	**12-18**	**13-19**
2.5	9-16	9-16	10-17	10-17	10-17	11-18	11-18	12-19	12-19	12-19

Characteristics of 583 natural IVF/ICSI cycles monitored with three different protocols

	Protocol A	Protocol B	Protocol C
Started cycles	101	151	335
IVF/ICSI	1.0	2.1	1.9
Mean follicle diameter	18.5 mm	17.5 mm	15.6 mm
Mean estradiol on day of hCG (nmol/L)	Not analysed	0.93	0.75
Cancellation rate Spontaneous ovulation or LH surge (%)	41.5	27.1	9.5

Outcome of 583 natural IVF/ICSI cycles monitored with three different protocols

	Protocol A	Protocol B	Protocol C
Oocyte recovery rate (%)	90.0	88.9	78.9
Fertilization rate (%)	77.7	75.2	73.2
ET rate per oocyte pick-up (%)	60.0	55.0	52.1
Pregnancy rate per ET (%)	16.6	10.0	24.6
Pregnancy rate per puncture (%)	10.0	5.5	12.8
Delivery rate per puncture (%)	5.0	4.6	8.2

Vlaisavljevic V., et al. J Reprod Med 2001

Natural cycle

- Accurate monitoring
- **Selection of patients**

Pregnancy rates depending on indication for IVF/ICSI procedures in 308 natural cycles

Indications for IVF procedure	PR/ puncture (%)	PR/embryo transfer (%)
Female infertility only	12,28 (14/114)	21,21 (14/66)
- Tuboperitoneal cause (without hydrosalpinx)	13.04 (9/69)	22,50 (9/40)
- Tuboperitoneal cause (with hydrosalpinx)	11,90 (5/42)	21,74 (5/23)
Unexplained infertility	17,91 (12/67)	30,30 (12/35)
Male infertility	5,00 (1/20)	16,66 (1/6)
Indications for ICSI procedure		
Male inferility only	12,67 (9/71)	27,27 (9/33)
Male and female infertility	11,11 (3/20)	23,07 (3/13)
Others	18,75 (3/16)	33,33 (3/9)
TOTAL (IVF and ICSI procedures)	13,31(41/308)	25,31 (41/162)

Natural cycle

- Accurate monitoring
- Selection of patients
- **Method : IVF or ICSI ?**

The comparison of IVF and ICSI cycles outcome in natural cycles

	ICSI cycles	IVF cycles	P
Number	135	151	
Oocyte recovery rate	80.1 (105/135)	77.5 (117/151)	NS
Normal fertilization rate (2PN)	63.8 (67/105)	65.8 (77/117)	NS
Pregnancy rate per embryo transfer	25.4 (17/67)	23.4 (18/77)	NS
Pregnancy rate per oocyte recovery	12.6 (17/135)	11.9 (18/151)	NS

Reljic M., et al. Monduzzi Editore, IFFS 2001.

Journal of Assisted Reproduction and Genetics, Vol. 19, No. 3, March 2002 (© 2002)

Clinical Assisted Reproduction

Results of Intracytoplasmic Sperm Injection of Single Oocyte in 362 Unstimulated Cycles

Veljko Vlaisavljević,[1,2] Borut Kovačič,[1] Milan Reljič,[1] Vida Gavrić Lovrec,[1] and Mojca Čižek Sajko[1]

Cycles	362
Positive OPU (%)	84,6 (269/318)
Fertilization (%)	68,8 (185/269)
Pregnancy per cycle (%)	10,2 (37/362)
Delivery per cycle (%)	6,9 (25/362)
Pregnancy rate per OPU , age > 36	4,8 (5/105)
Pregnancy per OPU, age < 36	9,4 (20/213)

Conclusions: Unstimulated cycles monitored by serum estradiol, urinary LH, and ultrasound can produce an acceptable pregnancy rate after ICSI procedure only in patients younger than 36.

Natural cycle

- Accurate monitoring
- Selection of patients
- Method : IVF or ICSI ?
- **Embryotransfer: day 2 or day 5 ?**

Is there any benefit from the culture of a single oocyte to a blastocyst-stage embryo in unstimulated cycles?

Veljko Vlaisavljević[1,2], Borut Kovačič[1], Milan Reljič[1], Vida Gavrić Lovrec[1] and Mojca Čižek Sajko[1]

[1]Department of Reproductive Medicine and Gynaecologic Endocrinology, Maribor Teaching Hospital, Ljubljanska 5, SI-2000 Maribor, Slovenia

	ET on day 2 (204)	ET on day 5 (187)	p-value
Oocyte recovery rate	79.4(162/204)	82.3 (154/187)	NS
Fertilization rate	73.8 (113/153)	77.7 (115/148)	NS
ET rate per aspiration	51.5 (105/204)	29.4 (55/187)	<0.05
Pregnancy rate per ET	23.8 (25/105)	40.0 (22/55)	<0.05
PR calculated /day 2 ET	23.8 (25/105)	22.2 (22/99)	NS
PR/ aspirated oocyte	15.4 (25/162)	14.3 (22/154)	NS

Natural cycle

- Accurate monitoring
- Selection of patients
- Method : IVF or ICSI ?
- Embryotransfer : day 2 or day 5 ?
- **Influence of patient s age**

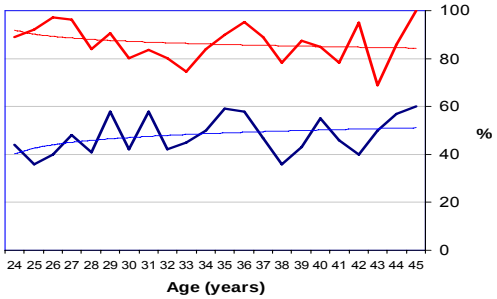
Prevalence of numerical chromosomal anomalies in unstimulated cycle IVF embryos

Verpoest et al. Hum Reprod 2008;23:2369-71.

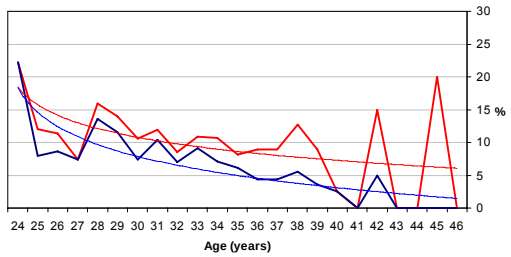
- PGS in 30 cycles
- Chromosomes X,Y,13,16,18,21,22
- Aneuploid embryos : 4/11 (36.4%; 95%CI : 10.9-69.2%)

Positive oocyte pick-up rate(red) and embryotransfer rate per OPU(blue) in 1024 natural cycles for IVF/ICSI (Maribor IVF)

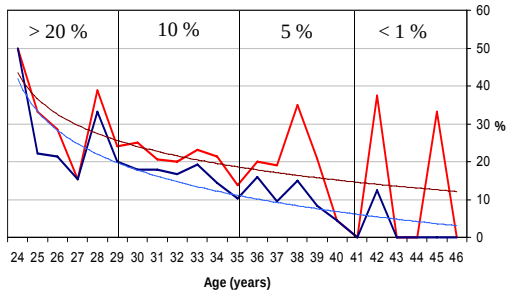
Vlaisavljevic V. RBM Online 2007



Pregnancy rate and delivery rate per oocyte pick-up in 1024 natural cycles for IVF/ICSI (Maribor IVF)



Influence of patients age on pregnancy rate (RED) and **delivery rate** (BLUE) per embryotransfer in 1024 natural IVF/ICSI cycles (Maribor IVF)



Natural cycle

- Accurate monitoring
- Selection of patients
- Method : IVF or ICSI ?
- Embyotransfer : day 2 or day 5 ?
- Influence of patient s age
- **Luteal supplementation**

Luteal phase support

It is not clear whether luteal phase support is necessary in natural cycles.

Luteal support was given after embryotransfer :
(Faulot et al.,1992 ; Paulson et al.,1992 ; Claman et al.,1993 ; Abdulghar et al.,1995; Daya et al.,1995 ; Kim et al.,1996 ; Tomaževič et al.,1996 ; Zayed et al.,1997; Basil et al.,1999; Ng et al.,2001)

535 ET 14.8% pregnancy rate

No luteal support was given after embryotransfer :
Jahnssens et al.,2000; Ingerslev et al.,2001

70 ET 17.1 % pregnancy rate

Luteal supplementation

Didrogesteron (Dabroston 30 mg, Duphare):

96 embryos 12 (13.0%) implantations
8 (8.0 %) deliveries

hCG (1500 IU, Pregnyl, Organon) on day 3 and day 7:

158 embryos 37 (23.0%) implantations
25 (16.0 %) deliveries

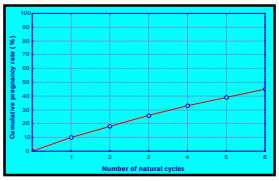
Vlaisavljević et al., J Reprod Med 2001;46:892-8.

Natural cycle

- Accurate monitoring
- Selection of patients
- Method : IVF or ICSI ?
- Embyotransfer : day 2 or day 5 ?
- Influence of patient s age
- Luteal supplementation
- **Efficacy ?**

Cumulative pregnancy rate in natural IVF cycles

- After 3 cycles : 43.0 %
  Paulson et al.1992
- After 5 cycles : 41.7 %
  Aboulghar et al. 1995
- After 4 cycles 46.0 %
  Nargund et al. 2001
- Probability of live birth after 4 cycles : 32.0 %
  Nargund et al. 2001
- Modified natural cycle IVF in 9 cycles : 51.5%
  Pelinck et al. 2008



Maribor data, 2003

Conclusions I

- Satisfactory results are obtained with the natural IVF/ICSI cycles regardless of the cause of infertility and day of embryo transfer.
- A higher pregnancy rate is expected with closer cycle monitoring and proper timing for hCG administration in women under 38 years.

Conclusions II

- Satisfactory results are obtained with the natural IVF/ICSI cycles independent from the cause of infertility and day of embryo transfer.
- A higher pregnancy rate is expected with closer cycle monitoring and proper timing for hCG application in women below the age of 38 years.

Conclusions III

- The cumulative pregnancy rate in 3-4 natural cycles is comparable with the pregnancy rate in selective one embryo transfer in stimulated IVF/ICSI cycle in a selected group of patients.
- The natural cycle is an option for patients where only one or two oocytes are obtained in a stimulated cycle (poor responders).

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