Oocyte in vitro maturation(IVM) in clinical practice?

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IVM - introduction

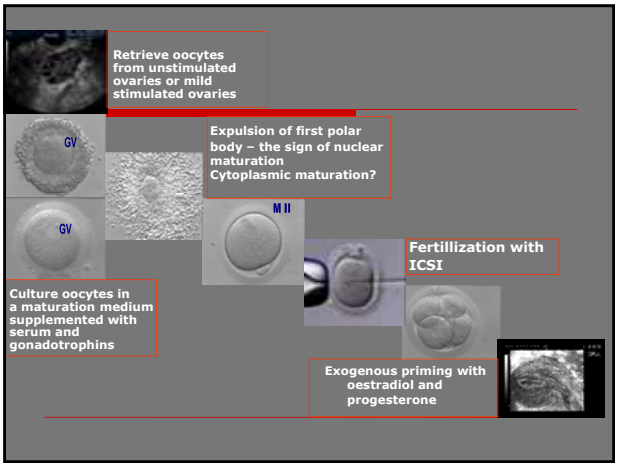
- Is a "new" method of ART
- The basis of IVM is the maturing *in vitro* of oocytes from germinal vesicle (GV) stage to metaphase II stage, fertilization of mature oocytes and transfer of embryos into uterus

IVM history

- **Pincus G and Enzmann EV**. The comparative behaviour of mammalian eggs in vivo and in vitro. J EXP Med **1935**;62:666-75.
- **Edwards RG**. Maturation in vitro of human ovarian oocytes. Lancet **1965a**;II:926-9.
- **Edwards RG, Bavister BD, Streptoe PC**. Early stages of fertilisation in vitro of human oocytes matured in vitro. Nature **1969;**221:632-5.

First pregnancies

- **1983; Veeck at al.** Two pregnancies from ET of immature oocytes from stimulated cycles.
- **1991; Cha et al.** First pregnancy from immature oocytes from unstimulated ovaries
- **1994; Trounson et al.** First pregnancy from immature oocytes from PCOS patient



The main **difference** between IVM and IVF/ICSI methods

- IVM patients don't receive medications for conventional COH!

Advantages of IVM

- **Avoid the side effects of aGnRH and gonadotrophins**
- **Avoid the risks of ovarian hyperstimulation syndrome - OHSS**
- **Safe treatment for PCOS patients**

- Costs are reduced compared with conventional IVF
- Easy for the woman, less invasive treatment

Application of human oocyte maturation in vitro

- Patients with PCOS
- Patients with high risk of OHSS

- Regular cycling patients

- Maturation of GV oocytes recovered from superovulation cycles
- Oocyte donation
- In vitro culture of follicles
- Possibility to rescue cancer patients‘ fertility

Different Priming in IVM

- No priming
  (Mikkelsen et al. HR 1999)
- Priming with low dose **FSH**
  (Mikkelsen and Lindenberg HR 2001)
  (Lin et al. HR 2003)
- Priming with **hCG**
  (Chian et al. FS 1999)
- Priming with **FSH+hCG**
  (Lin et al. HR 2003)

Different Priming in IVM

- **PCOS/PCO**

FSH PRIMING (Mikkelsen et al, 1999)
- •Improved MR
- •Improved PR

hCG PRIMING (Chian et.al, 2000)
- •Maturation was hastened
- •Improved clinical pregnancy rate

- **NORMAL OVARIES**

NO PRIMING

FSH PRIMING

Success of IVM

- In last years PR was improved according to early studies!

	No. of cycles	PR/ET (%)
Chian '99	25	32,0
Cha '00	94	24,5
Chian '00	24	25,0
Child '01	121	26,0
Child '02	107	21,5
Lin '03	68	33,9
Le Du '05	45	20,0
Södeström A '05	48	23,8 IVF 17,1 ICSI
Mikkelsen '01	36	29,0

McGill Reproductive Centre, Montreal, Canada	254	11.1	24.0 (61)
Maria Infertility Hospital, Seoul, Korea			
Day 3 transfer	419	11.6	32.7 (137)
Day 5 transfer	80	27.2	53.8 (43)
Infertility Medical Centre, CHA General Hospital[1] Seoul Korea	94	6.9	27.1 (23)
Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan	68	10.5	33.8 (23)
Hospital Antoine Béclère[2], Clamart, France	45	10.9	20.0 (9)

[1] Cha et al., 2000.
[2] Le Du et al., 2005.

(Papanikolaou et al. RBM Online 2005)

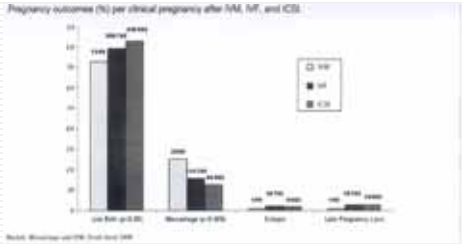
- Cha et al., Fertil Steril 2000
- Cha et al., Fertil Steril 2005
- Mu et al., Early Human Development 2006
- Mikkelsen, RBM Online 2005
- Södeström – Anttila, Hum Reprod 2006
- Buckett et al., Obstet Gynecol 2007
- Buckett et al., Fertil Steril 2008

Perinatal outcome and IVM
Congenital abnormalities

	OR	95% CI
IVM	1.42	0.52 – 3.91
IVF	1.21	0.63 – 2.62
ICSI	1.69	0.88 – 3.26

(Buckett et al. Obstet Gynecol 2007)

Perinatal outcome and IVM
Pregnancy outcomes after IVM, IVF and ICSI



(Buckett et al. Fertil Steril 2008)

Numerous factors have been identified which influence the maturation of human oocytes:

- nature of women – age, PCOS or non PCOS women,
- length of menstrual cycle,
- follicle size and atresia,
- treatment with gonadotrophins and ovarian steroids,
- cumulus cell and granulose cell function (Trounson, 2003)
- endogenous endocrine background?

PCOS

- Heterogeneous endocrine disorder
- Affect 1 in 15 women worldwide
- The most frequent cause of hyperandrogenism and oligo - anovulation
- Psychological, social, economic consequences

PCOS

- Endocrinological irregularrities:
  - elevated LH in 40% of women
  - insulin resistance in 40% of obese women
  - obesity in ~ 50% women
  - hyperandrogenism
- Follicular endocrine environment is related to oocyte quality!

  (Teissier et al., 2000)

- Hyperinsulinemia and IR play an important role in the pathogenesis of PCOS.

  (Dunaif, 1997)

- Obesity has a synergistic effect, thus increasing hyperinsulinemia and IR.

  (Homburg et al., 2001)

- The consequent hiperandrogenism leads to abnormal folliculogenesis and endometrial development.

  (Stadtmauer et al.,2002)

The prevalence of IR in PCOS women is high!

- Does the developmental potential of immature oocytes obtained from IR-PCOS women differ from non-IR PCOS women?

Material and Methods

- The study included 41 PCOS women undergoing IVM
- IR was assessed by calculating the HOMA index (fasting serum insulin [μU/ml] x fasting serum glucose [mmol/L] / 22.5)
- 36 hours prior to immature oocyte retrieval all women were primed with 10.000 IU of hCG.

Material and Methods

- All immature oocytes were cultured in IVM medium (MediCult) supplemented with 75 mIU/ml FSH + 75 mIU/ml LH (Menogon) and 10 % heat inactivated maternal serum, for 24 to 30 hours.
- ICSI was performed in all matured oocytes and the embryos were transferred on day 2 after ICSI.

Differences in clinical and embryological parameters between HOMA- IR positive and HOMA- IR negative group of PCOS patients undergoing IVM.

	HOMA – IR +	HOMA – IR -	p
	N=17	N=24	
Insulin	21,1 ± 4,4	6,6 ± 3,3	<0,001
BMI	38,83 ± 4,9	24,72 ± 4,9	<0,001
No. of oocytes retrieved	8,35 ± 5,25	13,12 ± 6,98	0,02
No. MII	3,7 ± 2,44	7,25 ± 4,41	0,004
No. 2PN	2,7 ± 1,96	4,75 ± 2,77	0,01
No. embryos	2,58 ± 1,9	4,12 ± 2,62	0,04
Maturation rate (%)	47,01	58,98	0,027
Fertilization rate (%)	73,01	65,51	NS
Cleavage rate (%)	95,65	86,84	NS
PR/cycle (%)	5,88 (1/17)	12,5 (3/24)	

Vlaisavljević V, **Kovač V**, Čižek Sajko M. Impact of insulin resistance on the developmental potential of immature oocytes retrieved from human chorionic gonadotrophin – primed women with polycystic ovary syndrome undergoing in vitro maturation. Fertil & Steril, 2008, in press.

Differences in clinical and embryological parameters between group of PCOS women with BMI ≥ 30kg/m^2 and group of PCOS women with BMI <30 kg/m^2 undergoing IVM.

	BMI ≥ 30	BMI < 30	p
	N=20	N=25	
Insulin	19,65 ± 6,14	6,87 ± 3,53	<0,001
Index HOMA	4,35 ± 1,62	1,31 ± 0,71	<0,001
No. of oocytes retrieved	7,5 ± 4,66	12,4 ± 6,7	<0,05
No. MII	3,6 ± 2,39	7,5 ± 4,49	0,001
No. 2PN	2,65 ± 1,92	5 ± 2,72	<0,05
No. embryos	2,5 ± 1,84	4,2 ± 2,45	<0,05
Maturation rate (%)	48,34	60,64	<0,05
Fertilization rate (%)	67,08	67,2	NS
Cleavage rate (%)	94,3	85,6	NS
PR/cycle (%)	15 (3/20)	8 (2/25)	

PREDICTIVE FACTORS
Multiple Linear Regression Analysis on:
oocyte recovered

	β Univariate analysis	p Univariate analysis	β Multivariate analysis	p Multivariate analysis
FSH 3.d.c	-0,35	0,019*	-0,46	0,001*
age	0,02	0,88		
BMI	-0,3	0,045*	-0,33	0,145
Insulin	-0,31	0,049*	-0,15	0,501
Index HOMA	-0,28	0,08		

*p<0,05

PREDICTIVE FACTORS
Multiple Linear Regression Analysis on:
maturation rate

	β Univariate analysis	p Univariate analysis
age	0,027	0,86
BMI	-0,35	0,017*
Insulin	-0,027	0,08
Index HOMA	-0,22	0,149
Estradiol 3.d.c	-0,15	0,34

*p<0,05

Conclusions

- Our study indicates the importance of evaluating insulin metabolism and BMI prior to infertile PCOS women enter IVM procedure.
- Pretreatment with insulin sentisizers?
- Weight – loss interventions?

Challenges of IVM

- Process of oocyte maturation is still poorly understood!
- Less effective than IVF
- Lower implantation rate!

- Risk of congenital abnormalities?
- Imprinting problems?
- **Long term follow up is needed!**

Summary

- IVM offers elimination of the risk of OHSS!
- So far, there have been no alarming reports on the safety of the IVM procedure or on the normality of the babies born!
- Improvement of **clinical menagement** (endometrium receptivity, embryo quality) and **culture techniques** will lead to improvement in clinical pregnancy!