IVM in PCOS patients

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Introduction (1)

- IVM could be a major advance in ART procedures (reduce cost and simplify treatment). Especially in PCO and PCOS patient.
- The target is to avoid OHSS in PCO patient. *(Cha, 2000; Child, 2002; Lin, 2003, Ledu 2005)*

Introduction (2)

- Pincus and Enzman (1935) attempted to mature mammalian oocytes in vitro
- The concept of IVM in human is not recent (*Edwards et al 1965, 1969*).
- The first IVM from ovary *(Cha et al 1991).*
- The first IVM from PCOS *(Trounson, Fertil Steril 1994).*
- About 1000 life births, 100 from PCOS.

(Chian, Tan 2004, RBMOnline 2004)

Indications of IVM

- IVM in normal ovulatory patients
  (*Mikkelsen 1999, 2000, 2001; Child 2001; Yoon 2001; Soderstrom, Antilla 2005)*
- Rescue of oocytes which have failed to mature in stimulated cycles *Liu, Fertil Steril 2003*
- Unexplained primarily poor-quality embryos
  (Tan, J Gynecol Obstet Biol Reprod 2003)
- Oocyte donation *(Tan, International Symposium on IVM, Berlin 2004)*
- Oocyte preservation before sterilization
  (Oktay, The Lancet 2004)
- PCO syndrome *(Chian RBMOline 2004;*
  Le Du & R Frydman, Hum Reprod 2005)
- Risk of *OHSS* *(Schröder, Eur J Obstet Gynecol Reprod Biol 2003)*

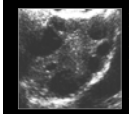
Polycystic Ovary syndrome

- Rotterdam definition: 2 out of 3 of
  1. Oligo and/or amenorrhea
  2. Clinical and/or biochemical signs of hyperandrogenism
  3. Polycystic ovaries: ≥ 12 follicles/ovary measuring 2 to 9 mm and/or increased ovarian volume >10ml

  And exclusion of other ætiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome)
  (Rotterdam ESHRE/ASRM, PCOS Consensus)
- Thessaloniki definition

- 1 in 12 women of reproductive age
- Infertility: about 40%
  (Hart, Best Pract Res Clin Obstet Gynaecol 2004)
- OHSS Risk in IVF-ET: 11.2%
  (T.J.Child, Obstet Gynecol 2002)

ART, PCO and Infertility

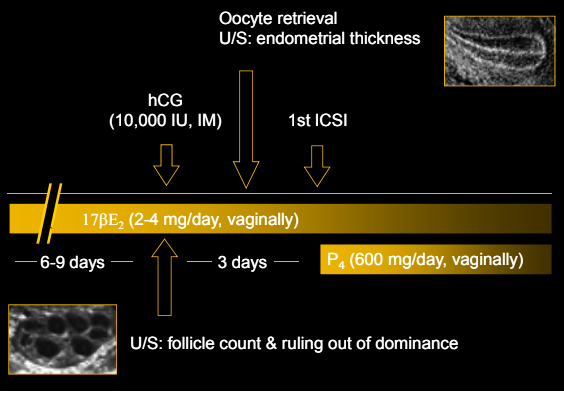


- Weight loss
- Clomiphene citrate *(Homburg, Hum Reprod 2005)*
- Metformin *(Checa, Hum Reprod Update 2005)*
- Ovulation induction using gonadotropins
  (Van Santbrink EJ, Fauser EC. Best Pract Res Clin Endocrinol Metab 2006)
- Ovarian drilling *(Fernandez H, J Am Assoc Gyn Laparosc 2004)*
- IVM *(Chian, RBMonline 2004;*
  Saleh, Khalil. Acta Obstet Gynecol Scand 2004)

Monitoring of IVM cycles

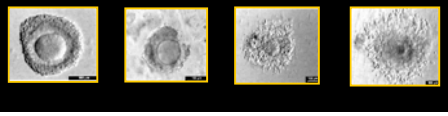
- Oral contraceptive or progesterone if irregular cycles
- D3: U/S scan endometrial thickness measurement and hormonal measurement
- Repeat U/S scan between D6 and D9. If at least 10 follicles became larger than 7mm without any dominant follicle
  - 10000 IU of hCG and oocyte retrieval 36-38 hours later
  - ± 17 ßEstradiol administration

Usual clinical protocol for IVM



Oocyte retrieval

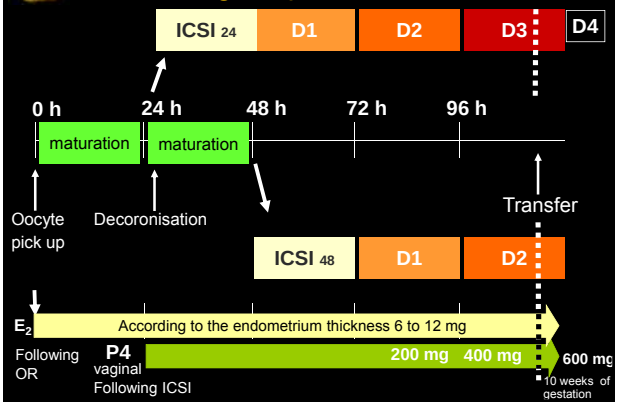
- General anesthesia
- 17 or 19-gauge single lumen aspiration needle
- Half usual aspiration pressure (7.5 kPa)
- 15 ml Nucleon tubes containing 3 ml warm Sodium Heparinate 2 IU/mL in a temperature controlled system
- COC washing in universal IVF medium (Medicult)



IVM and fertilization

- Medium
  - ✓TCM-199 supplemented with pyruvate, FSH, LH and inactivated maternal serum (20%)
  - ✓IVM Medicult medium
  - ✓Retrospective comparison of two media for in vitro maturation of oocytes
    (M. Filali and N. Frydman RBMOnline 2008)
- 24h mature oocytes are fertilized by ICSI
- GV and GVBD are cultured one day more and fertilized by ICSI
- ET at D3 post first ICSI

Usual biological protocol for IVM



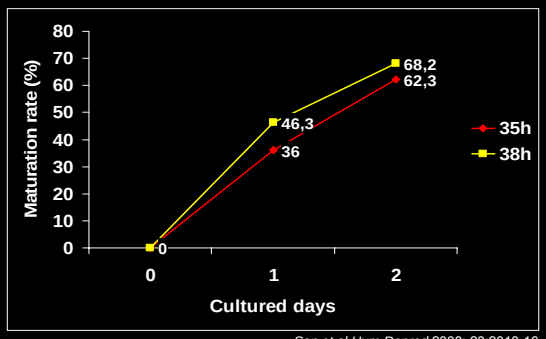
Details still debated

- FSH/hCG priming:
  - Could improve oocyte maturation *(Junk, Theriogenology, 2003)* and implantation rate in PCO
  - But no additional benefit with hCG priming *(Lin, Hum Reprod, 2003)*
- Dominance induced atresia
  - Few pregnancies with immatures oocytes retrieved from ovaries with a dominant follicle *(Chian, Fertil Steril 2004)*
- ICSI commonly used (hardening of the zona pellucida) but pregnancy described without it
  (Suikkari, International Symposium on IVM, Berlin 2004)

Details which can make a difference

- 35 or 38 hours after hCG
  (Son et al, Hum Reprod 2008)
- 17ßE$_2$
  - No early follicle growth nor dominance
    (Lelaidier et al, Hum Reprod, 1992)
  - Vaginal route more effective than oral route
    (Fanchin, Fertil Steril, 2001)
- Temperature ≥ 37°C for COC
  (Yuge, Cryobiology 2003)
- Endometrial thickness ≥ 10 mm predictor of pregnancy *(Child, Fertil Steril 2003)*

Oocyte maturation rate 35 or 38 hours after hCG



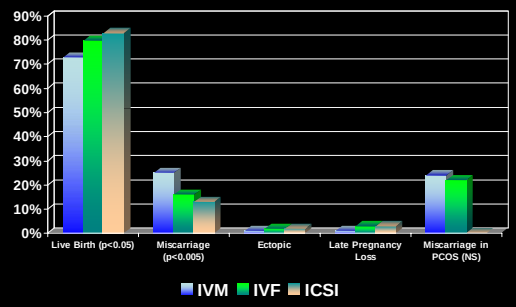
Son et al Hum Reprod 2008; 23:2010-16

Relative risk for any congenital abnormality compared with controls

	RR	95% CI
IVM	1.19	0.35 – 3.25
IVF	1.01	0.52 – 1.90
ICSI	1.41	0.72 – 2.68

Buckett et al., Obstet Gynecol 2007; 110:885-91

Pregnancy outcomes after IVM, IVF and ICSI



Buckett et al Obstet Gynecol 2007; 110:885-91

IVM (PCO patients) Clamart Results 2003-2008

IVM	Cycles	nb punct.	nb transf.	Nb emb.	Clin. Pregn per puncture (%)	Impl. rate	Delivery per puncture (%)
2003	48	36	31	2.48	8 (22.2)	12.9	5 (13.9)
2004	44	38	34	2.55	10 (26.3)	13.8	4 (10.5)
2005	44	40	35	2.34	9 (22.5)	10.9	8 (20)
2006	39	36	30	2.4	7 (19.4)	11.1	6 (17)
2007	54	50	45	2.08	13 (26)	15.9	8 (16)
2008	37	34	31	2,09	8 (23.5%)	12.3	
Total	266	234	206	2.31	55 (23.5%)	12.4%	31 (13.2%)

IVM outcomes (A. Béclère 2003-2008)

	No of oocyte retrievals	No of embryo transfers (Nb Transf Emb)	No of clinical Pregn.	No of miscarriages	No of ectopic pregn.	No of deliveries/ ongoing pregnancies
< 35 yo	166	149 (337)	40 (24.1)	13 (32.5)	1 (2)	26 (15.6)
35-37 yo	52	36 (89)	7 (13.4)	1 (14.2)	0	6 (11.5)
≥ 38 yo	12	9 (23)	2 (16.7)	1 (50)	0	1 (8.3)

IVM (2003-2008): Frozen embryo cycles

No IVM cycles with embryo cryopreservation	No of frozen-thawed cycles	No of frozen-thawed embryo transfers	No of clinical pregn / transfer	No of deliv / ongoing pregnancies	No of miscarriages	Outcomes after previous fresh embryo transfer
20/234	14	11	6 (55%)	3 (27%) / 2 (18%)	1 (9%)	Delivery 2 Miscarriage 1 Failure 8

Summary

- IVM is potentially a major advance in ART procedure (reduce cost and simplify treatment)
- Major advantage is to avoid OHSS (n=0) in the PCOS
- Implantation rate is lower in IVM (12.4%) than in our general IVF-ET program (27%) but implantation rate in IVF for moderate PCOS (24-34 follicles) are higher (43% n=85), but with 3-5% of OHSS

Future: Defining possible causes for low IR in IVM

Endometrium receptivity

Embryo quality

Inadequate hormonal priming

Intrinsic drawback of the selected PCOS population

Related to culture conditions

Chromosomes: IVM limit?

- Experimental abnormalities of chromosome segregation during IVM of horse, pig oocytes have been shown
  (Sosnowski, Theriogenology 2003)
- But obstetric outcomes of pregnancy from IVM in PCOS patient are comparable with those from IVF-ET
  (Cha, Fertil Steril 2005)

IVM: Conclusions

1. Implantation rates in IVM remain to be optimized:
   - ✓Improvement of biological conditions
   - ✓Improvement of endometrial receptivity
2. Administration of E_2 throughout the follicular phase:
   - ✓Adequate endometrial estrogenization
   - ✓Prevention of follicle dominance (ovulatory women?)
3. Vigilance over chromosome abnormalities must be continued
4. IVM is still considered experimental by the ASRM Practice Committee but world experience is increasing