Is IVM Safe?
Is IVM Effective?

It depends…

Penelope Nayudu,
Olena Tkachenko, Johanna Bernhard,
Stefka Delimitreva

German Primate Center, Goettingen
pnayudu@googlemail.com

There are many factors involved and our knowledge is incomplete

For matched patients pregnancy rates for IVM even after stimulation are around half of the IVF rates.

Why?

Both in vivo and in vitro factors are important.

In vivo factors that affect IVM and IVF

Ovary function → Oocyte Quality

- PCOS and the associated metabolic changes can have major effects on oocyte quality.
- Drugs and environmental toxins can affect reproductive function

Ovary Quality; marmoset monkey as model species

A pretty good ovary

Bernhard, Nayudu

What is important to know about the healthy ovary?

– **Which follicle population for IVF?**

Follicles with “dominant” characteristics
(good response to hCG – high embryo production rate)

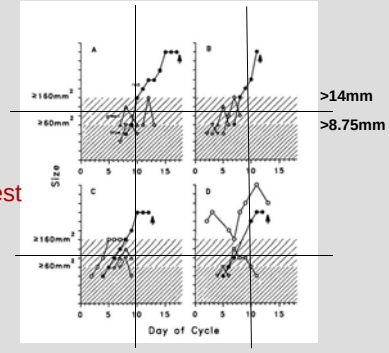
– **Which follicle population for IVM?**

Which are healthy enough?
Which have developed far enough to respond to hCG?

Follicle populations and threshold stages in healthy human ovaries

Natural cycles

When to harvest for IVM?



>14mm

>8.75mm

Gore et al., HR,1995

Follicle populations and timing as factors in success

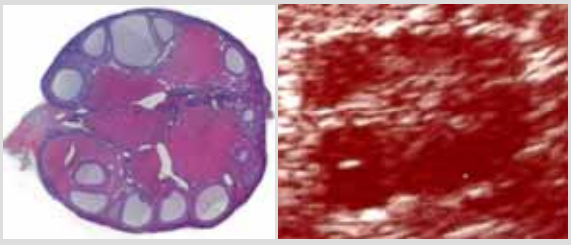
- If collecting follicles 10 mm and above, then the chance of aspirating an oocyte from a non-viable follicle is ¾.
- This fits with existing data about success rates in natural cycle IVM.
  - And if timing is not exactly right or ovary health not optimal– the chance goes down.

But what happens when the ovary is polycystic?

- The normal control mechanisms are disturbed and the structure and follicle dynamics of the ovary are changed.

The marmoset polycystic-like ovary

How many of these follicles contain healthy oocytes?



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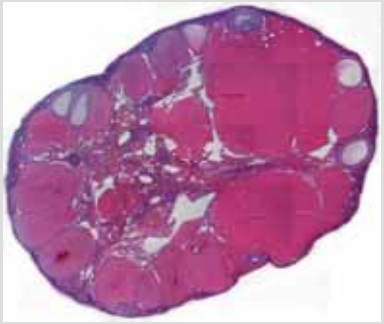
The marmoset polycystic-like ovary

- ↑ Increased ovary size
- ↑ Increased number of antral follicles
  - Increased ovulation rate in early stages
  - But later ovulation ceases
- ↑ Increased amount of luteal tissue
- ↑ Increased preantral follicle atresia
- ↓ Rapid depletion of the primordial follicle pool.

But when it goes to far-

The ovary is emptied



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What goes together with marmoset PCO

- Elevated androgen
- Elevated estrogens
- Shortened follicular phase, eventually permanent luteal phase.

- Overweight
- Glucose intolerance
- Elevated insulin
- Metabolic syndrome

The same as for human.

Everybody knows that not all antral follicle ooctes are developmentally competent

What kind of things can go wrong with the oocyte—in the follicle?

Healthy ovary	High proportion of all small follicles are in some degree atretic	→ Abnormal cytoskeleton ⇧
PCO ovary	More of the preantral and antral follicles are atretic or abnormal	→ The frequency of abnormal oocytes is higher and more extreme but total number of antral follicles is higher. ⇧⇧

Cytoskeleton as a major source of aneuploidy in IVM oocytes

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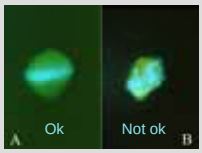

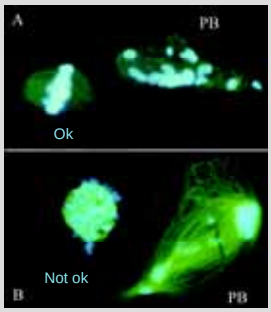

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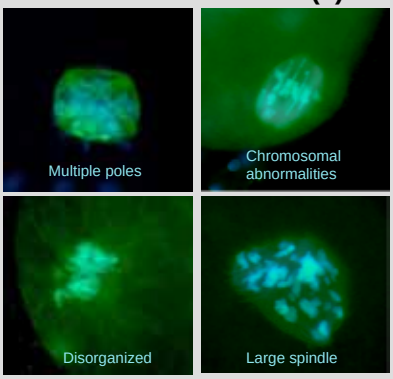
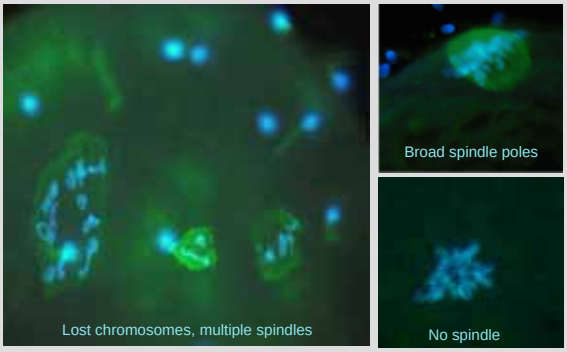
More extreme abnormalities from PCO animals (1)



More extreme abnormalities from PCO animals (2)



Is there something we can do to maximize oocyte quality?

- Reduce PCO related symptoms through patient management
- Light stimulation *in vivo*?
- Oocytes from smaller antral follicles may need different maturation conditions
  - 2 phase medium with first phase maintaining cumulus oolema connections to allow completion of “cytoplasmic” maturation and to stabilize the cytoskeleten.

Avoiding shock during collection may be an important additional factor

Immature oocytes are more sensitive to stress than are mature.

- The collection method can be stressful through puncture and vacuum.
- Oocytes may be dramatically cooled while in the aspriation tube– causing major cytoskeletal disorganization

The optimal *in vitro* environment is also critical

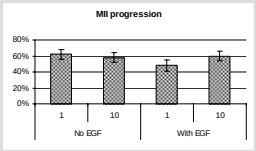
- **What medium compositon and combination?**
- **What hormones and growth factors?**

An example from marmoset

Effects of low and high FSH/hCG - /+ EGF
During oocyte maturation----

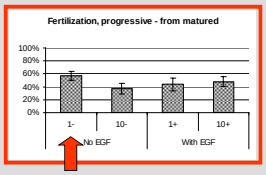
- **On rates of maturation, fertilization and embryo development**

Rate of in vitro maturation not affected by hormone level or by presence of EGF during maturation.

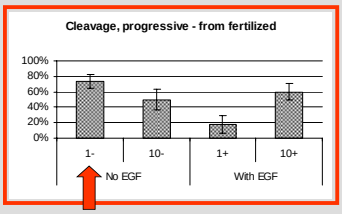


But later

Rate of fertilization is affected! by the hormones and EGF present during maturation.

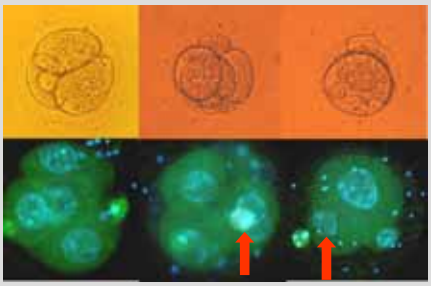


- Embryo cleavage is dramatically affected! by composition of in vitro maturation medium.



Why? Is this also a problem of cytoskeletal organization and aneuploidy?

Is aneuploidy and uneven cleavage more common in IVM?



What are the possible consequences associated with abnormal embryos?

- Low pregnancy rate.
- Is the risk of producing an aneuploid child higher with IVM?
- Are the epigenetic effects greater with IVM?

Are the reasons strong enough for doing IVM?

Are there alternative strategies which may provide a better result?

- Low stimulation or natural cycle IVF with aspiration of larger follicles only.
- More careful stimulation strategies with more finely graded doses of FSH to avoid overstimulation.

What would be necessary for improving IVM as a patient friendly treatment?

1. Improved ovary health through preventative management.
2. Critical experiments on key animals species.
3. Development of better culture systems.

What would be necessary for improving IVM as a patient friendly treatment?

4. Selective follicle aspiration to reduce ovary damage and improve efficiency.
5. Check embryos for aneuploidy before transfer.
6. Long term studies on children produced by IVM, incl. reproductive health.