REPRODUCTIVE MEDICINE MILESTONES AND FUTURE VISIONS

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- Thanks for the invitation to be part of and lecture at the 175th Anniversary of the Berlin Society for Obstetrics and Gynecology

- I have no competing interest to declare

- My contribution reflects the work of many colleagues of the Centre for Repoductive Medicine and Centre for Medical Genetics of University Hospital and Medical School of the Vrije Universiteit Brussel from 1980 until now

BRUSSELS IVF STORY

- Start of clinical IVF in January 1983, small team guided by Paul Devroey (the clinician) and André Van Steirteghem (reproductive biologist)
- First IVF Workshop Monash University July 1982
- Birth of first IVF child November 1983
- Birth of first “ICSI child” January 1992

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EUREKA MOMENT OF ICSI

Historical overview on ICSI

- Attempt to answer the following questions:
  - Why did we start?
  - What did we do?
  - What did we find?
  - What does it mean?

Why did we start?

- Louise Brown was born 25 July 1978 (Oldham UK), followed by births in Australia, USA, France, Germany, The Netherlands and also in Belgium (1983)
- Conventional IVF (cIVF), successful for tubal and idiopathic infertility
- Pour outcome of cIVF for male infertility

Why did we start?

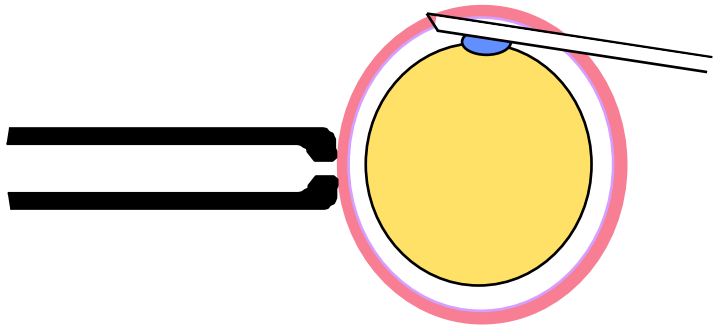
- Chances of fertilization and embryo transfer reduced if impaired semen parameters
- Artificial Insemination with Donor sperm (AID) is only alternative treatment

ASSISTED FERTILIZATION

- End of eighties research projects to assist fertilization process
- Zona drilling: success in mice but not in human
- Partial zona dissection: mechanical slit in oocytes, which were then incubated in sperm suspension. Fertilization was observed but monospermic and polyspermic fertilization occurred. Inconsistent clinical results

ASSISTED FERTILIZATION

(a) PZD

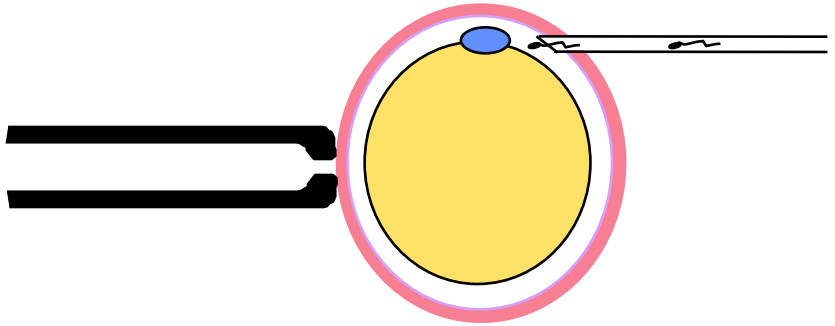


Subzonal insemination = SUZI

- Case reports by Ng (Singapore) and Fishel (Rome): Fertilisation and embryo development and a few births
- At VUB decision to invest in SUZI
- But first experimental and preclinical research before clinical application

Subzonal insemination = SUZI

(b) SUZI



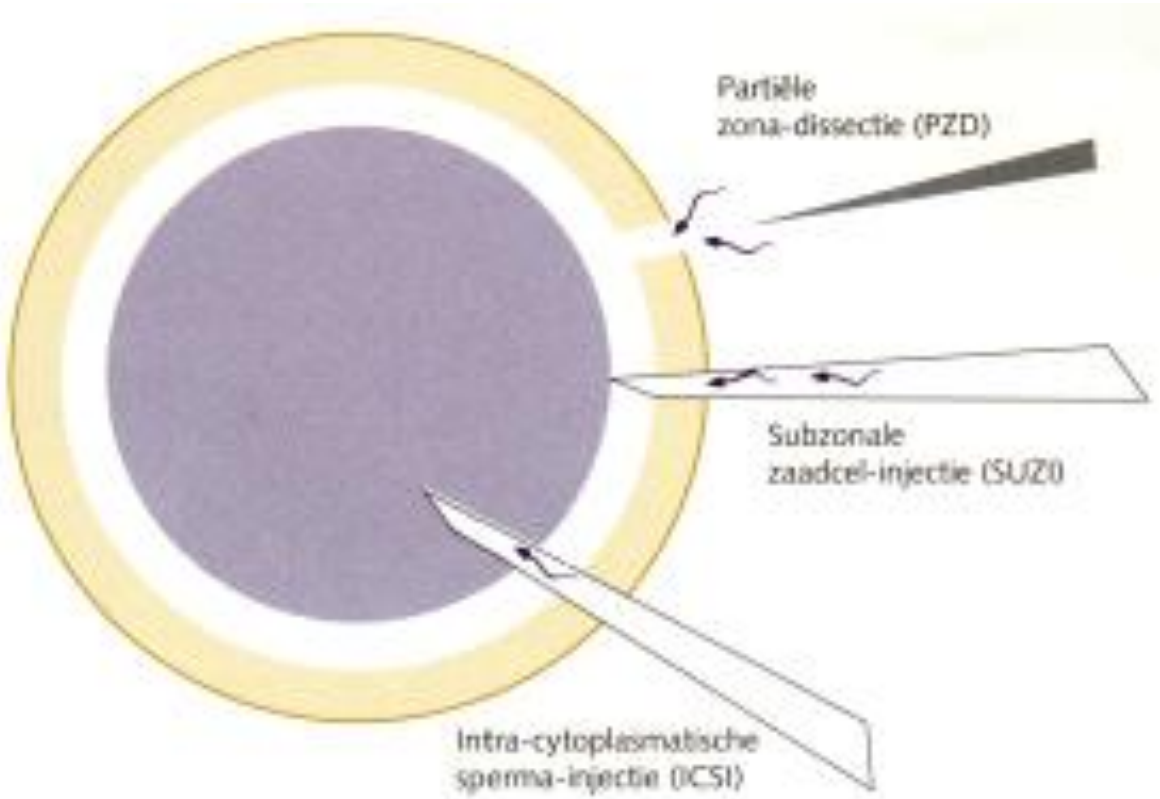
What did we do?

- Project submitted at Fund for Scientific Research – Flanders on experimental SUZI in mice as a model for clinical application in human
- Can the induction of acrosome reaction in mouse sperm (by chemical means or electroporation) result in fertilization and embryo development when one treated sperm cell was injected subzonally?

- Good fertilization and embryo development occurred, normal pups were born after transfer in pseudo pregnant mice and the mice were able to reproduce
- Experimental results made us to consider clinical protocol for patients that had failed several cycles of conventional IVF

- Ethical approval was asked and obtained from Hospital Ethical Committee under certain conditions
- Full information to couples on the new procedure
- Initially in couples with several failed cIVF cycles
- Couples accepted thorough follow-up of pregnancies and children born, including prenatal diagnosis and prospective follow-up of children born (joint project with Centre for Medical Genetics)

- Number of pregnancies and births occurred after SUZI of a few spermatozoa, which had been treated to induce acrosome reaction
- SUZI is technically challenging: “Failed SUZI” sometimes noticed, sperm entered cytoplasm of oocyte and normal fertilization and embryo development occurred after “failed SUZI”



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- In case of only embryos after “failed SUZI” replacement was done and first such pregnancy occurred in 1991 with birth in January 1992
- Initially SUZI was continued as well as ICSI on a few oocytes. It became rapidly clear that more consistent results were obtained after ICSI
- Ethical approval for ICSI under same conditions as SUZI

- As of July 1992 the only assisted fertilization practiced at VUB was ICSI
- First publication Lancet July 1992 and two large series in Human Reproduction in July 1993
- Articles became “citation classics” and are still among the most cited “Belgian” articles

- Openness to the world showing ICSI in several live & video sessions, hand-on workshops and visitors from overall the world
- Very deliberate attitude following personal experience of 3 years as visiting scientist at NIH and attitude of Monash University and group of Zeilmaker-Alberda in Rotterdam

What did we find?

- ICSI proved to be a consistent treatment for alleviation of severe male infertility including cases of cryptozoospermia
- ICSI can also be applied with epididymal and testicular sperm, resulting in similar results as ICSI with ejaculated sperm and the results of cIVF for female-factor or idiopathic infertility

- Sperm can only be found in half of the patients with non-obstructive azoospermia
- If this is the case, the only alternative for these couples is the use of AID

ARE ART CHILDREN HEALTHY?

- Most important parameter
- Since start of IVF few formal and systematic evaluations of childrens' health
- VUB policy since 1983: prospective follow-up studies of children born after IVF
- Joint venture between Centre for Reproductive Medicine and Centre for Medical Genetics
- ICSI included in studies since the first birth in 1992
- Is ICSI an additional risk factor?

- Procedure more invasive and used sperm is unable to fertilise
- ICSI outcome compared to cIVF and spontaneous conceptions (SC)
- Short- and long-term risks need to be addressed
- Chromosomal abnormalities in prenatal diagnosis: low numbers but in ICSI increase in inherited and de novo abnormalities
- Birthweight similar after IVF and ICSI for singletons, twins and triplets
- Prematurity not higher in singletons
- Major malformation rate slightly higher (around 3%) but no difference between IVF and ICSI

- Similar development at 2 years (Bayley development scales)
- All studies including VUB study report slightly more risks compared to spontaneous conceptions
- Why? Major reason is subfertility status, possible role of use of ovarian stimulation and enveromental factors such as culture conditions in the laboratory

Studies in children and adults

- 5 years: ICSI does not affect psychological well-being or cognitive, development, no difference comparing IVF and ICSI as well as ICSI and SC
- 8-14 years: reassuring results regarding testicular development and hormonal status (inhibin B, AMH and testosterone)
- ICSI men at 18 years: increased risk of elevated FSH, sperm concentration lower but no correlation between sperm concentration fathers and sons
- More work needs to be done, differences may increase or decrease

- Further studies are necessary
- In adults and beyond
- Further generations
- Other ART procedures are currently used: vitrification, in vitro maturation and PGD need also to be addressed

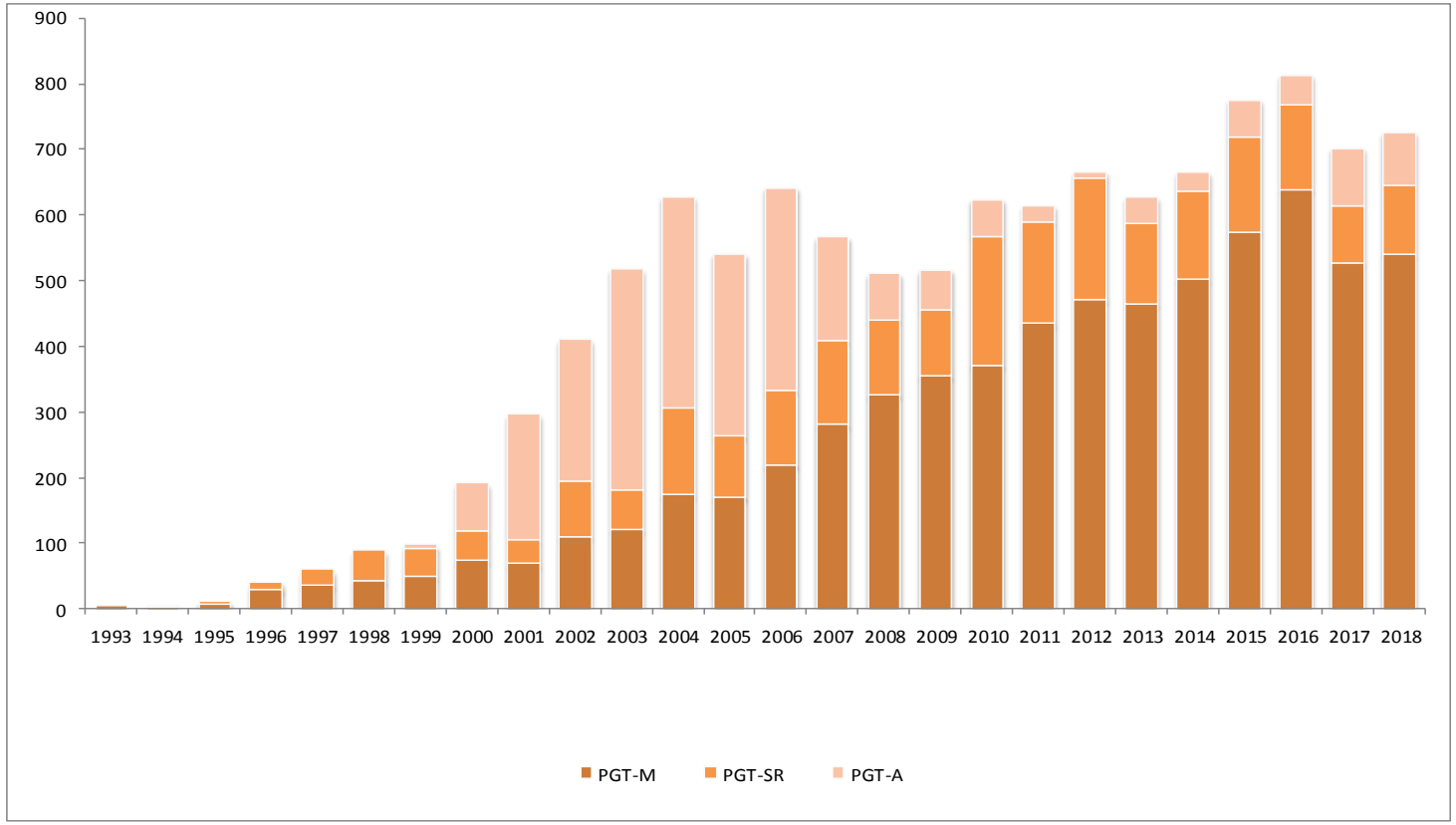
PREIMPLANTATION GENETIC DIAGNOSIS PGD

- 1985 Polymerase chain reaction allows single cell genetics
- 1990 first PGD (Handyside and Winston)
- 1992 VUB PGD for CF
- Before 1990 only genetic counselling and prenatal diagnosis available for couples at risk
- Since 1990 PGD can be offered and includes ART, embryo biopsy and genetic diagnosis
- Case history VUB: 2 births in family at risk for DMD; 20-year old daughter came with her mother for counselling around carriership

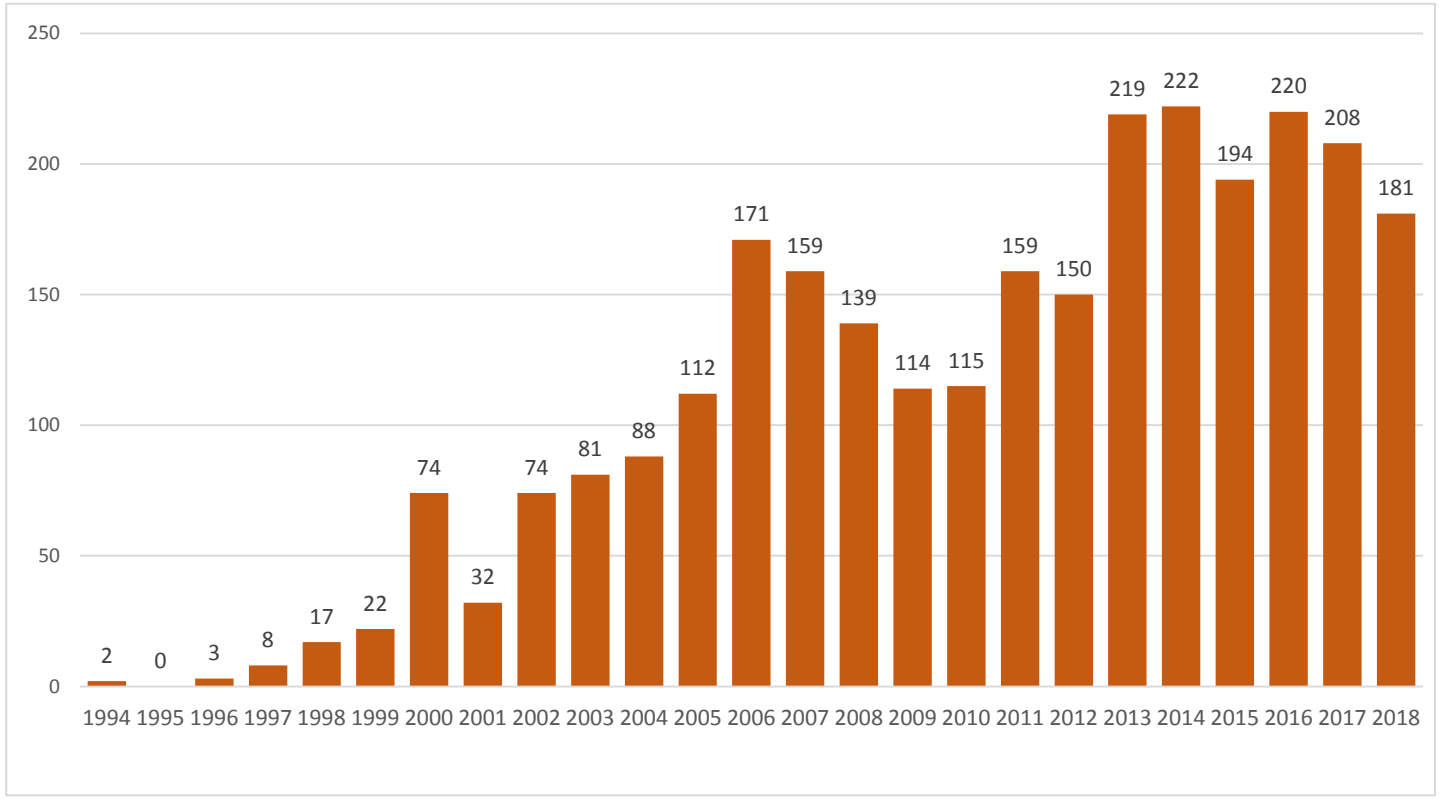
- Technology evolved: initially PCR – FISH – linked markers, now SNP and NGS
- Embryo biopsy: initially at 8-cell stage on day 3, now also trophectoderm biopsy on day 5
- New nomenclature: PGT = preimplantation genetic testing
- PGT-M for monogenic disorders
- PGT-SR for structural rearrangements
- PGT- A for aneuploidy

- Informed consent very detailed, sometimes difficult cases involving ethical issues
- « Parents decide but well-being of child is very important

Cycles DPI VUB 1993 - 2018



Enfants DPI VUB 1094-2017



- Health of PGD children
- PGD compared to ICSI and SC gave similar results in VUB data and literature
- At birth
- At 2 years
- At 5-6 years

HLA typing in view of saviour babies

- With or without monogenic disorders
- Results VUB in the period 1998 – 2016
- 234 requests but 72 couples discontinued
- 25% just HLA, 75 % with monogenic diseases (sickle cell anemia, Beta-thalassemia and Fanconi)
- 162 couples treated in 414 cycles: 67 pregnancies, 64 births and 73 children of which 60 HLA compatible
- 25 transplantations

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