Male subfertility and assisted reproduction: the quest for the ultimate treatment strategy
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Introduction and outline of the thesis

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In about one third of couples with subfertility, the problem seems to be related to the male partner because of the presence of poor semen quality. First line treatment would ideally focus on the semen impairments, but only a few causes of male subfertility are known, and even fewer can be dealt with.

The efficacy of existing causal treatments of male subfertility depends on the underlying pathophysiological processes. The surgical treatment of obstructions of the male genital tract (mainly post-infectious, like gonorrhea) has been practiced for over a hundred years, but is still moderately successful. The successes of ICSI with surgically retrieved spermatozoa have bypassed microsurgery of the male genital tract.

The efficacy of surgical treatment of varicoceles has also been under debate over the last decennia. Evidence now suggests that it does not improve fertility outcome in male subfertility.

On the other hand, the hormonal correction of rare pituitary disorders, like Kallmann’s syndrome and hyperprolactinemia, does lead in most cases to recovery of spermatogenesis and should be first choice treatment. Finally, the administration of gonadotrophines, androgens, anti-estrogens, antibiotics, corticosteroids or anti-oxidants for the treatment of unexplained male subfertility has had varying results on semen characteristics and pregnancy rates. Overall, there is too little evidence of efficacy to advocate the widespread use of these substances.

Unfortunately, clinical breakthroughs in this field are not expected in the near future and the mainstay in the treatment of male subfertility is not causal treatment, but assisted reproductive techniques (ART) in the female partner. In this introduction we will outline the history of ART for male subfertility emphasizing ethics, safety and efficacy.

History

After the microscopic visualisation of spermatozoa by Antoni van Leeuwenhoek in 1677, it took some decennia for scientists to accept male sterility as a cause of infertility. In all probability the first treatment of the female partner dates from as early as the seventeen hundreds when intrauterine insemination with homologous sperm was first described. The first publications on intrauterine insemination (IUI) were from animal scientists who performed IUI on life stock, especially on horses. French gynaecologists who had been experimenting with artificial inseminations in women referred to the promising
results of these stables to strengthen their plea for this treatment. The first scientific record was published in 1799 when Everard Home reported that John Hunter in England had, in 1785, inseminated a woman with her husband's semen. The man ejaculated into a jar and Hunter successfully inseminated the wife with the use of a quill. In 1866 James Marion Sims performed fifty-five inseminations in six women, but was successful in only one. He diverted his attention to donor inseminations, and it was William Pencoast who was reported to have been the first to perform a successful donor insemination in 1884. The woman in question was sedated and the witnesses to this procedure were sworn to secrecy. It has been suggested that it was the donor himself, a medical student, who came forward with a letter to a medical journal.

These first steps into assisted reproduction were made with trial and error. The insemination of the full ejaculate into the uterine cavity lead to pain, discomfort and sometimes even to severe pelvic infections. E.J. Iwanoff, a Russian scientist and the director of the Central Experimental Breeding Station for Domestic Animals in Moscow, developed in the early 1900's a technique for collection, dilution and subsequent insemination of equine semen. In the following decennia, these techniques were developed further for application in humans.

In the 1970s it was still customary to inseminate the full ejaculate, albeit in a concentrated volume of 0.3 ml, into the uterine cavity with cramping and the need for prophylactic antibiotics as a result. In 1973 it was discovered in the context of attempts to separate X- and Y-bearing human sperm- that semen that advanced through columns of liquid albumin was free of the extraneous cells that are often found in the ejaculate. Soon thereafter, the suggestion was put forward that this technique could perhaps help in processing semen specimens to contain less of the material that was irritating to the uterus. In 1978 Ronald Ericsson and Robert Glass for the first time applied albumin columns to isolate spermatozoa from the semen and achieved pregnancies after intrauterine insemination. In the following years this isolation technique was further improved, with the addition of swim-up and/or density gradient centrifugation to isolate the progressively motile and morphologically normal spermatozoa.

In the 1970's, the results from clinical trials using these semen-processing techniques became available. The pregnancy rates per cycle varied from 5-30%, most likely due to the heterogeneous populations described, with different semen defects and different female factors. Even as late as 1982...
a review paper on management of male subfertility concluded that timed intercourse, IUI and in vitro fertilisation (IVF) were not very effective and that artificial insemination with donor semen was still the mainstay of management. IUI with homologous sperm was mainly advised to couples with ejaculation disorders, cervical hostility or unexplained subfertility.

Alongside the development and evaluation of IUI as a tool for assisted conception, another experimental technique was developed in mammals, which tried to fertilise eggs in vitro. The first published attempt at this so-called In vitro fertilisation with mammalian oocytes dates from 1878, when Samuel Schenk, known as the “sex-regulator” in Vienna, isolated ova of rabbits and guinea pigs. He added a drop of epididymal sperm to the eggs that were suspended in follicular fluid together with uterine mucus. He noticed the break-up of the follicular granulose cell mass by the sperm suspension, but did not achieve fertilisation in vitro. Where Schenk failed, M.Onanoff claimed in 1893 that he was successful in fertilizing rabbit and guinea-pig ova in vitro, but the eggs were recovered from the uterus, so the fertilisation probably already occurred in vivo and not in vitro. Around the turn of the twentieth century scientists were philosophizing on using in vitro fertilisation in humans to overcome all sorts of fertility disorders.

"We are still far from mixing together female egg and male spermatozoon in vitro and to bring them to formation. Indeed, we will probably always be far from it. Our vial which we cannot do without, is and will be the uterus and in its dark inside alone and hidden from our eyes generation and development mystically evolve. However, we are on the point of making this process dependent on our intentions, our minds and to master it in those cases in which nature lets us down.”

Gregory Pincus and Ernst Vincenz Enzmann stated in 1934 that they were the first to demonstrate that rabbit eggs could be fertilised in vitro and that pregnancies could occur after transfer to the Fallopian tube. This statement was debated by Min Chueh Chang who claimed that the experiments of Pincus and Enzmann did again not prove fertilisation in vitro but in vivo and that he was the first to achieve real fertilisation of rabbit ova in vitro in 1957. After these mammalian experiments, they started their work on human
ova. Unfortunately, they miscalculated the maturation period of human eggs to be 12 hours. Scientists who used this time frame were not able to achieve fertilisation of human eggs. The ideas and experiments by pioneers like John Rock and Landrum Shettles around the 1950’s were followed by the successes of Robert Edwards and Patrick Steptoe in the 1970’s \(^{32,33}\). Edwards showed that the correct maturation period for human eggs was 37 hours \(^{34}\). Following that breakthrough, IVF in women soon became a reality when in 1978 Steptoe and Edwards sent a letter to the editor of the Lancet to inform the public of the birth of a healthy baby after in vitro fertilisation in a woman with tubal dysfunction \(^{35}\). After a few years of experience with this technique, it appeared that a small percentage of couples with severe male subfertility could also conceive via IVF \(^{36,37}\). In cases of very poor semen quality, poor fertilisation and total fertilisation failure remained a serious problem \(^{38,39}\).

To increase the probability that a sperm capable of fertilisation came in contact with the oocyte, partial zona dissection (PZD) was attempted \(^{40,41}\). Although this method improved the results of conventional IVF, the improvement was only marginal and relatively large numbers of sperm were still required. These drawbacks applied less to the subsequent technique of subzonal microinjection of spermatozoa into the perivitelline space (SUZI) \(^{42}\). However, fertilisation rates remained low, rates of polyspermic fertilisation were increased, and men with a very limited number of spermatozoa in their ejaculate could still not be treated.

The introduction of intra-cytoplasmatic sperm injection (ICSI) in 1992 was the breakthrough in severe male subfertility and almost instantly became common practice \(^{43}\). In ICSI, the spermatozoa are injected directly into the oocyte, which makes fertilisation possible even in cases with just a few spermatozoa. It even became an option to inject non-ejaculated spermatozoa into the oocyte, aspirated from the epididymis (MESA) or harvested from the testicle (TESE) in azoospermic men. Fertilisation rates were lower than with ejaculated sperm, but pregnancy rates per cycle were comparable. They were 40% for ejaculated sperm, 58% for epididymal sperm and 46% for testicular sperm \(^{44}\).
Ethics and concerns

When in 1912 the first publications on IUI in Germany hit the newspapers, great expectations about its effectiveness were met with anxiety about the safety of this new technique. The moral concerns about the conception of a child without intercourse, i.e. an illegitimate child, were avoided by collecting the ejaculate in a condom during intercourse and inseminating the sperm directly after intercourse into the uterine cavity and by limiting IUI to married couples with more than five years of primary subfertility. Even L. Prochownick, who published on his successes with artificial insemination, wrote that it was rather disgusting and that he would only use IUI as an ‘ultimum refugium’ when everything else had failed. Many infertile couples shrank away from artificial insemination, because most women regarded artificial insemination as immodest or rejected it for religious reasons.

Directly after the publication on the birth of Louise Brown, clinicians, scientists and politicians discussed the ethical implications of IVF. They raised questions on whether scarce medical resources should be spent on IVF and whether the procedure was “natural”. In addition, they had concerns about the moral status of the embryo and the disposition of excess embryo’s, and on restrictions for access to IVF. The Vatican opposed assisted reproduction, whereas other Christian denominations allowed these techniques within a marriage as long as their own gametes were used. The Jewish population accepted ART under the same conditions. The Islamic countries were very liberal when it comes to ART, since, according to Islam, the embryo has no soul before day 42 of embryonic development.

With the introduction of ICSI the discussion on ethics and safety became more intense. The main argument against ICSI was that it was introduced into clinical practice before extensive research on animals had been completed and safety had been demonstrated. The main concern was that the manipulation of the oocyte and sperm cell would lead to DNA changes and to chromosomal abnormalities in the offspring, especially male offspring. Because of the piercing of the oocyte membrane, ICSI had been branded ‘the ultimate rape of the oocyte’, appearing to bypass all biological and genetic selection.
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Safety

In an attempt to address these concerns about the safety of ART, many studies were undertaken in the last decennium to establish its safety, focusing on the health of ART offspring compared to naturally conceived children. These outcomes can be subdivided into obstetrical outcomes, neurological and behavioral development, metabolic effects, prevalence of congenital malformations, and chromosomal and genetic abnormalities.

As far as obstetric complications are concerned, there seems to be an association between ART and placenta praevia, low birth weight, premature birth and placental abruption. A recent review article concluded that the main risks for the future wellbeing of ART children remain multiple pregnancies and low birth weight. The outcome of singletons born at term following ART was generally reassuring. Although twin pregnancies are associated with worse obstetrical outcomes than singleton pregnancies, it has been suggested that ART twin pregnancies show fewer complications as compared to spontaneous twin pregnancies. Others found increased rates of pre-term birth in ART twins as compared to naturally conceived twins.

The first data on congenital malformations after ART were reassuring, as there was no increase in major congenital malformations, not even in a subgroup of patients where ICSI with testicular sperm was performed. The overall risk of congenital malformations in IVF-related procedures was deemed small. There was an excess of congenital malformations registered in the Medical Birth Registry in Sweden between 1982-1997 for IVF/ICSI children as compared to spontaneously conceived children (n = 516, odds ratio = 1.47), but this excess disappeared when confounders were taken into consideration. The only risk that remained was an excess risk of hypospadias after ICSI. However, there is now accumulating evidence suggestive of an association between ART and birth defects, like cardiac malformations, oesophageal and anal atresia and cleft lip.

Although it is difficult to separate ART-related risks from those secondary to the underlying reproductive pathology, there are some clues that the risks are mainly contributable to this underlying pathology. In an extensive cohort study, pregnancy outcomes were compared in 2546 Norwegian women who had...
singleton pregnancies conceived both naturally and after assisted reproduction. Birth weight, gestational age, and risks of small for gestational age babies, and preterm delivery did not differ among infants of women who had conceived both spontaneously and after assisted fertilisation.

Research into the field of neurological and behavioural development of children born after ART is extensive and reassuring. All studies on this subject show no differences between ART offspring and naturally conceived children. When focusing on male subfertility, there seems to be no indication that growth and cognitive development in ICSI and IVF children differ with regard to paternal sperm concentration.

Regarding chromosomal and genetic abnormalities, no clear differences between ART pregnancies and spontaneous pregnancies have been found after adjustment for confounding factors, most importantly maternal age. A higher incidence of imprinting disorders has been suggested, but this seems to be of no clinical significance. Routine screening for imprinting disorders in children conceived by ART is, therefore, not recommended. There is however concern about the increased risk of metabolic disorders in children born after IVF, mainly expressed in a disturbed body fat composition and greater weight gain in early infancy in IVF children compared to controls. It is speculated that the adverse health outcomes observed in children born after IVF might have an epigenetic origin, but this assumption needs further research to identify the clinical implications.

In men with poor semen quality, the situation is more complicated. About 5% of men with severe oligozoospermia and azoospermia have chromosomal abnormalities, and oligozoospermic men with a normal somatic karyotype have increased frequencies of sperm chromosome abnormalities. Especially in severe oligozoospermia, a significantly higher frequency of sex chromosome aneuploidy has been observed in spermatozoa. It is still unclear if these abnormalities contribute to an increased risk of sex chromosomal abnormalities in ICSI offspring. What we do know is that boys conceived with ICSI whose fathers have certain Y-chromosome abnormalities will inevitably inherit these defects, with different expressions. Although the Dutch guideline for prenatal invasive testing in 1999 listed ICSI as an indication for invasive testing, in a new concept guideline this indication has been deleted.
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press at the time of this thesis). The risks of invasive prenatal testing do not seem to outweigh the added risk of minor (sex) chromosomal abnormalities.

In summary, after ART there is a possible increased risk of obstetrical complications, a higher incidence of congenital malformations, metabolic changes and sex chromosomal abnormalities in the offspring. These adverse outcomes are mostly not attributable to the procedure itself, but to the fertility status of the couple, especially to the underlying severe sperm defects.

Efficacy

There are two reviews in the Cochrane Library on male subfertility and IUI. One review on IUI and male subfertility concluded that there is no evidence to support that IUI with or without controlled ovarian hyperstimulation (COH) is superior to timed intercourse with or without COH. The other review investigated whether pregnancy outcomes differ between fallopian tube sperm perfusion (FSP) and IUI in the treatment of non-tubal subfertility, including male subfertility. The results indicate no clear benefit for FSP over IUI, but a subgroup analysis for male subfertility could not be performed. Both reviews conclude that there is a clear need for large (randomized controlled) trials and that couples suffering from male subfertility should be analyzed separately. There are no (Cochrane) reviews on the efficacy of IUI relative to IVF in male subfertility, but there are cost-effectiveness studies on IUI and IVF in male subfertility. In 2000 the results of such a study implied that IUI was more cost-effective than IVF in mild male subfertility. The pregnancy rates for IVF in this study were much lower than the average pregnancy rates today, which make the conclusions of this study not applicable to current daily practice. In 2001 it was argued that the total motile sperm count (TMC) determined whether IUI or IVF was the most cost-effective intervention. Studies on the total motile sperm count as a predictor of pregnancy after IUI have been abundant, but have not lead to a cut-off value for the TMC. In another more recent study two strategies were compared for unexplained and mild male subfertility: first six cycles of IUI followed by IVF or direct IVF. This comparison was based on a mathematical model for a hypothetical cohort of subfertile patients, and no definition of mild male subfertility was given.

There are no Cochrane reviews on male subfertility and IVF/ICSI, but there are some studies comparing IVF with ICSI in male subfertility. These studies show a higher incidence of total fertilisation failure (TFF) in IVF as compared to
ICSI, but no differences in embryo quality and pregnancy rates in cycles with fertilisation. However, these studies do not provide a tool to identify those couples with male subfertility that are at risk for TFF. There is so far, no study that has identified which couples with male subfertility should be treated with IUI and which couples with IVF or ICSI. As a consequence, evidence-based guidelines in the field of male subfertility are limited and clinical practice is dominated by authority-based interpretations of the scarce literature.

**Background of the research described in this thesis**

For the whole spectrum of male subfertility, ranging from mild subfertility, i.e. semen analyses just below the WHO criteria, to severe subfertility, i.e. just a few spermatozoa in the ejaculate, there is a clear need for evidence to aid in the decision to advise expectant management or to perform IUI, IVF or ICSI with ejaculated or surgically retrieved spermatozoa. Which patient characteristics and which readily available (sperm) tests are of value in this decision-making? At the time of starting this thesis there was no prediction model after completion of the fertility work-up to distinguish couples with male subfertility that will benefit from IUI, IVF or ICSI. Therefore, we investigated the factors influencing IUI and IVF outcome in male subfertility, constructing a prognostic model for both treatment options. In addition, we investigated if TFF in IVF can be predicted based on the semen characteristics during the fertility work-up and at the time of ovum pick-up.

As in the daily routine of deciding which treatment path to follow, patients’ preferences are also a factor of increasing importance; we present data from a study on patients’ preferences for either IUI or IVF. Finally, on the far side of the male subfertility spectrum, i.e. when only a few spermatozoa can be found in the entire ejaculate, we examined the risk of cancellation and the success rates of ICSI with ejaculated spermatozoa.
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