Male subfertility and assisted reproduction: the quest for the ultimate treatment strategy
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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. In most cases there is no clear cause attributable to the poor semen quality, and treatment options are rare. In most cases of male subfertility, it is the female partner that undergoes assisted reproductive techniques (ART) to achieve a pregnancy. The irony is that, although ART is presently the only available technique, so far, no studies have addressed the issue of which couples with male subfertility should be treated with intrauterine inseminations (IUI) and which couples with in vitro fertilisation (IVF) or intracytoplasmic sperm injection (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.

Because of this lack of evidence, we initiated several studies on male subfertility and ART to try and find the optimal form of ART in these patients. We developed prediction models for ongoing pregnancy in IUI and IVF, as well as a prediction model for total fertilisation failure in IVF. We also looked into patients’ preferences concerning IUI and IVF. Finally, we explored the performance of ICSI in severe male subfertility, i.e. near azoospermia on the day of follicle aspiration.

CHAPTER 1 outlines the history of ART in male subfertility with emphasis on ethics, safety and efficacy.

CHAPTER 2 shows the results of a meta-analysis on the performance of the total motile count after preparation (post-wash TMC) as a predictor of ongoing pregnancy in IUI.

We detected 16 studies that reported on post-wash TMC at insemination and IUI outcome. Summary receiver-operating-characteristics-curves indicated a reasonable predictive performance towards IUI outcome. At cut-off levels between 0.8 to 5 million motile spermatozoa, the post-wash TMC provided a substantial discriminative performance. At these cut-off levels, the specificity of the post-wash TMC, defined as the ability to predict non-pregnancy, was as high as 100%, while the sensitivity of the test, defined as the ability to predict pregnancy, was limited.

In conclusion, the post-wash TMC at insemination could potentially be used in counseling patients for either IUI or IVF. However, further studies are needed to establish the accuracy of a post-wash TMC during the fertility work-up, rather than at insemination to enable patient counseling before the start of treatment.
CHAPTER 3 presents a prediction model for ongoing pregnancy in IUI in male subfertility.

We evaluated the predictive capacity of baseline (female) characteristics, semen parameters (both pre- and post-wash) and anti-sperm antibodies (ASA) obtained during the fertility work-up on IUI outcome in couples with male subfertility in a retrospective cohort study. We included 290 couples, who underwent a total of 722 IUI cycles. The overall ongoing pregnancy rate was 9% per cycle. Model I with female age, duration of subfertility, secondary subfertility, the presence of anovulation, cervical hostility and cycle number had an AUC of 0.59. Addition of the presence of ASA to this model improved the AUC to 0.65 (model II). Further addition of the post-wash TMC to the model with ASA (model III) improved the AUC to 0.67. When the models would have been used to exclude couples from IUI due to low expected pregnancy rates, this would increase the pregnancy rate to 11% per cycle with model I and to 14% per cycle for model II and for model III.

From this study we concluded that the combined use of female baseline characteristics and ASA could prevent unnecessary IUI in 65% of the couples with male subfertility, causing an increase in the pregnancy rate from 9% to 14% per cycle. A post-wash TMC during the fertility work-up will have very limited additional value.

CHAPTER 4 explores patients’ preferences for either IUI or IVF.

It is generally acknowledged that patients’ preferences should also be incorporated into medical decision making as patients’ perspectives on the burden and benefits of therapy can differ from those of health professionals. To gain more insight into this issue we conducted trade-off interviews with couples undergoing IUI.

Seventy-three couples undergoing IUI, with a total of 111 interviews at different stages in the IUI treatment, were included. We offered these couples scenarios in which pregnancy chances after IUI with COH was varied against a fixed pregnancy rate after IVF. The probability of an ongoing pregnancy after one year of IUI was reduced or increased until the couple switched their preference. We also investigated the impact of the risk on a multiple pregnancy on the couple’s preference. The interviews were held before the start of IUI (baseline-group), after three or four IUI cycles (mid-group) and after six IUI cycles (end-group). With a decreasing probability of an ongoing pregnancy after IUI with COH, an increasing number of couples switched their preference from IUI to IVF.
This switch occurred in the end-group at a statistically significant higher mean cumulative pregnancy rate (53%) as compared to the baseline- and mid-group (31%). With an increasing risk on a multiple pregnancy the preference for IUI declined only slightly in the baseline- and mid-group, with a mean risk of 73% and 78% on a multiple pregnancy, respectively. This percentage was statistically significantly higher in the end-group (83%).

In summary, at the start of IUI with COH and after three to four cycles the majority of our patients wanted to continue this treatment. After six cycles most couples demanded such high cumulative pregnancy rates with IUI that continuation of IUI became unrealistic and IVF would be preferred. The risk on a multiple pregnancy hardly affected the preference for IUI with COH in relation to IVF. These data could be incorporated into clinical guidelines on IUI and IVF.

**CHAPTER 5** proposes a prediction model on fertilisation failure in IVF in case of male subfertility.

The chances that none of the oocytes will fertilise in an IVF cycle, i.e. that total fertilisation failure (TFF) will occur, are high in case of severe male factor subfertility. It is therefore essential to be able to predict fertilization failure in IVF and to make a justified trade-off between IVF and ICSI. However, it is still not clear which (semen) characteristics of the couple have the best predictive value for the risk of TFF.

We performed a retrospective cohort study in eight hundred ninety-two couples with a total of 1,569 consecutive IVF cycles. Baseline characteristics were obtained and pre-wash and post-wash TMC were calculated during fertility workup and at the time of ovum pickup (OPU). The area under the curve (AUC) for pre-wash TMC during fertility workup was 0.72, similar to a combination of pre- and post-wash TMC. At the time of OPU, both pre- and post-wash TMC had an AUC of 0.73. A model based on selected baseline characteristics (male age, number of IVF cycles, indication for IVF, and pre-wash TMC during fertility workup) had an AUC of 0.75. A model at the time of OPU, including the number of oocytes, had an AUC of 0.80. Pregnancy rates increased from 20% to 26% with increasing values of post-wash TMC when cycles with TFF were included. In contrast, if cycles with TFF were excluded, pregnancy rates remained constant around 30%.

This study showed that if fertilization occurs with IVF, pregnancy rates are comparable for all couples, even for couples suffering from severe male factor subfertility. We propose that the choice between IVF and ICSI...
can be made before the start of the IVF cycle by using a model of baseline characteristics including pre-wash TMC or, when the model is inconclusive, by postponing the choice of treatment to the day of OPU when the number of oocytes is known.

In **CHAPTER 6** we developed a prediction model for ongoing pregnancy with IVF in male subfertility that can be applied during the fertility work-up.

We performed a retrospective cohort study including all couples with male subfertility undergoing IVF. The main outcome measure was ongoing pregnancy after IVF. The baseline characteristics of couples including parameters of the semen-analysis pre-wash were included in a univariate and multivariable analysis to construct a prediction model (model I). The addition of antisperm antibodies (ASA) and post-wash total motile count (TMC), model II and III respectively, were analyzed comparing the predicted and observed pregnancy rates in couples selected for IVF with these models.

We included 275 couples with male subfertility, who underwent 473 IVF cycles with an ongoing pregnancy rate of 19% per cycle. A prediction model containing female age, secondary subfertility, percentage of progressively motile sperm, percentage of sperm with normal morphology, pre-wash total motile sperm count, bilateral tubal pathology, history of IUI and cycle number was constructed (model I).

If no prediction model was applied, i.e. selection of couples was based on our inclusion criteria for this study (post-wash TMC); the ongoing pregnancy rate was 19% per cycle and 33% per couple with a TFF rate of 12% per cycle. The number of cycles needed to perform for one ongoing pregnancy (CNP) was 5.3 cycles. Using Model I, these data were 28%, 58% and 10% respectively, with a CNP of 3.6 cycles. With Model II (Model I with the addition of ASA) the same number of pregnancies was achieved as with Model I but with less cycles needed to perform, leading to higher pregnancy rates per cycle and per couple.

In this scenario 71% of couples would have been advised to undergo ICSI before the start of treatment. The selective use of Model III (with the addition of the post-wash TMC) in cases that model II would have advised IVF would lead to the exclusion of more couples (73%) with no real improvement in the chance on an ongoing pregnancy. More than 50% of couples that would normally have undergone IVF in our center would have been advised to undergo ICSI on the basis of all models.

In conclusion, in couples with male subfertility, the current method of
deciding for either IVF or ICSI on one semen parameter alone is not efficient. A prediction model with baseline characteristics and semen parameters can improve the selection efficiency for IVF. Addition of ASA to the model improves the efficiency of IVF, whereas addition of the post-wash TMC does not. This information should be used in the counseling of couples for IVF or ICSI.

CHAPTER 7 gives insight in the results of ICSI in severe cases of male subfertility, i.e. men with near azoospermia, on the day of follicle aspiration.

Occasionally, no motile spermatozoa are found in the ejaculate before regular semen analysis or after preparation on the day of follicle aspiration in an ICSI cycle, i.e. near azoospermia. To examine the chances of pregnancy and the risk of cancellation of these ICSI cycles because of the absence of injectable spermatozoa, we analyzed all ICSI cycles in the Center for Reproductive Medicine in the Academic Medical Centre from 1999-2009. We compared three groups: in group A (men with near azoospermia) there were no motile spermatozoa after conventional semen analysis and subsequent semen preparation at the time of follicle aspiration; in these men an extended sperm preparation was performed in which droplets of ejaculate sediment were extensively investigated for the presence of spermatozoa. In group B no motile spermatozoa were found after conventional semen analysis at the time of follicle aspiration but motile spermatozoa were found at subsequent semen preparation. In group C motile spermatozoa were found after conventional semen analysis at the time of follicle aspiration. Outcome measures in the three groups were number of cycles without injectable spermatozoa, number of oocytes injected, fertilization rate, rate of total fertilization failure, number of embryos transferred and ongoing pregnancy rates.

A total of 6499 ICSI cycles were started, of which 6412 cycles resulted in follicle aspiration: 102 cycles were in group A, 145 cycles in group B and 6170 cycles in group C. In group A seven cycles (7%) were cancelled due to the complete absence of injectable spermatozoa. This did not happen in groups B and C. The mean number of oocytes injected and the overall fertilization rate were statistically significantly lower in group A, 7.1 and 40% respectively, compared to 8.5 and 60% for group B and 9.5 and 60% for group C (p=0.03 and p<0.001). There were 19 ongoing pregnancies (19% per cycle) in group A versus 28 and 1253 for groups B and C (20% per cycle for both groups) (p=0.43 and p = 0.38, respectively).

In conclusion, in ICSI cycles with near azoospermia there is a small
Summary

The chance of cancellation due to complete absence of spermatozoa in the ejaculate. Ongoing pregnancy rates are comparable to overall ICSI pregnancy rates, so ICSI with spermatozoa from the ejaculate is still a feasible option in near azoospermia.

In **CHAPTER 8**, general discussion, our main conclusion is that prognostic modeling and personalized management strategies based on individual patient characteristics may prove to represent real progress towards improved treatment, also in male subfertility.