Male subfertility and assisted reproduction: the quest for the ultimate treatment strategy
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General discussion

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With the introduction of IUI, IVF and ICSI, it became possible for couples with male subfertility, who were traditionally dependent on donor semen, to achieve pregnancies with decreasing numbers of spermatozoa. As is often the case in reproductive medicine, these techniques were introduced very quickly in clinical practice without prior research into the efficacy and safety of these treatments and are now applied on a large scale. A typical example of this is that many clinics offer ICSI in male subfertility regardless of semen quality. Other clinics offer IUI and IVF as an alternative, but base their choice between IUI, IVF and ICSI on authority based cut-off values for semen parameters, usually the post-wash TMC during the fertility workup. Even today there is limited good-quality evidence to support the use of individualized approaches to male subfertility.

Given this lack of reliable evidence, the Third EVAR Workshop Group advocated the use of a sibling oocyte technique (i.e. half of the oocytes are inseminated by conventional IVF and half by ICSI) if the likelihood of spontaneous fertilization is uncertain. This approach does not take into account that the occurrence of pregnancy is a multifactorial process, where female and male factors interact. And again it is suggested that in vitro techniques are superior to IUI in male subfertility while there is no evidence to support this theory.

In this thesis we have shown that prediction models can be of value in the counselling of patients with male subfertility and selecting them for the appropriate type of ART.

Prediction models are more and more introduced in daily practice. There are now three models with good predictive performance in reproductive medicine for the prediction of ongoing pregnancies after IVF, the prediction of pregnancies after IUI and pregnancies after natural conception. None of these have evaluated sperm parameters.

Our prediction models on ongoing pregnancy rates after IUI and IVF in male subfertility and total fertilization after IVF have not been validated externally and are therefore not applicable yet in daily clinical practice. Although definitive proof is thus lacking, it may well be that by using these models, we could be able to distinguish couples suffering from male subfertility who should be advised to undergo ICSI, from those that still have a realistic chance of an ongoing pregnancy with IVF and/or IUI.

The factors we found to have the largest impact on pregnancy chances are not related to semen quality, but to female age and duration of subfertility. The younger the female partner, the better pregnancy rates are, irrespective
of semen quality. Still, all around the world post-wash total motile counts are calculated and based on authority based cut-off values, the choice between IUI, IVF or ICSI is made or ICSI is advised regardless of any cut-off values. The latter is probably based upon the idea that ICSI is the best possible treatment, with the highest pregnancy rates possible. But is that really the case? As we have shown in our IUI and IVF prediction models, IUI and IVF lead to good pregnancy rates, 14 % per cycle and 30 % per cycle, respectively, in 35% and 19% of the original population respectively, selected by the models.

The second main finding of this thesis is that we found no differences in pregnancy rates between IVF and ICSI once there is fertilization. Two other studies in which IVF and ICSI were performed on sibling oocytes in couples with male subfertility are in line with this finding 7,8. The first study was a randomised trial comparing IVF in a standard insemination concentration (0.2x10^6/ml) in one group and a high concentration (0.8x10^6/ml) in another group. In both groups ICSI was performed on sibling oocytes. The high insemination concentration group showed fertilisation and pregnancy rates comparable to ICSI. Also, the same study performed a meta-analysis on the available literature and calculated a number needed to treat of 3.1 ICSI cycles to be performed to prevent one case of total fertilisation failure (TFF) with IVF.

The second study found differences in fertilisation failure and fertilisation rates between IVF and ICSI on sibling oocytes, but no difference in pregnancy rates once fertilisation had occurred. The prediction of TFF is therefore very useful. TFF is mainly dependent on semen characteristics, but once fertilization occurs, pregnancy chances are probably dependent on female factors. In our study the number of oocytes was an important factor in predicting fertilisation failure, while studies on sibling oocytes do not take this factor into account.

It takes less oocytes to achieve fertilisation in ICSI than with IVF, so female age, i.e. the ovarian response to stimulation, should be taken into account when deciding between IVF or ICSI in male subfertility.

In our prediction models for fertilization failure and ongoing pregnancy in IVF, more semen parameters come into the equation than for IUI. This implies that female factors become more important with increasing numbers of spermatozoa. So, when the subfertility problem approaches the diagnosis of unexplained subfertility, semen parameters are of less value in predicting pregnancy after ART. As others have already shown, female age and duration
of subfertility are key in predicting pregnancy after ART. Where they did not address the male factor in detail, we have shown that sperm values are indeed of lesser consequence. Real male subfertility is on the outer side of the spectrum, where sperm counts are very low. In these cases ICSI with ejaculated spermatozoa is the only treatment option left and can even be performed in near azoospermia after an extended sperm preparation.

The findings in this thesis lead us to believe that a change in policy must be made in the approach of the subfertile couple in the outpatient clinic. The emphasis on sperm characteristics in the decision-making should shift to a couples’ approach with the use of prediction models. For daily practice, this means that after the fertility work-up, all patient characteristics should be incorporated in a prediction model to weigh the different predicted probabilities for an ongoing pregnancy after IUI or IVF to make a balanced decision between the various treatment options, IUI, IVF or ICSI. With the use of these predicted probabilities and detailed information on the risks of IUI, IVF or ICSI, the patients can make an informed decision. This interaction between prognosis and patient preferences will lead to more efficient use of assisted reproduction with more motivated patients. So, personalized management strategies based on individual patient characteristics and patient preferences may prove to represent real progress towards improved treatment outcome, also in male subfertility.

Future research

In male subfertility studies on semen characteristics and semen function tests alone should be abandoned. Only multivariable analyses in large populations should be conducted in subfertility research. To gain more insight into the general applicability of our prediction models we propose a randomized controlled trial comparing IUI and IVF as well as IVF and ICSI in good prognosis patients to determine if the prediction models are accurate in predicting ongoing pregnancy rates. If our prediction models are indeed accurate, they should be used in clinical practice and therewith as an inclusion criterion for further studies on the efficacy of treatments in male subfertility.
General discussion

References