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5

Management of male-factor infertility

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For many years, the management of male-factor infertility has been empirical rather than evidence-based. In current clinical practice, assisted reproductive techniques are the most successful methods of alleviating male-factor infertility. To date, it remains unclear what adjuvant actions can be taken to improve the outcome of assisted reproductive techniques for male-factor infertility. Evidence shows that smoking adversely affects sperm quality to some extent, and the genetic make-up of sperm to a greater extent; however, because of the scarcity and heterogeneity of studies, its effect on in-vitro fertilisation outcome remains largely unknown. Although smoking cessation should be part of the assisted reproductive techniques treatment plan, the benefit of antioxidant treatment in either smokers or non-smokers undergoing assisted reproductive techniques is still under scrutiny. Other lifestyle modifications in subfertile men, such as refraining from moderate alcohol and caffeine consumption, are even more controversial. When embarking on assisted reproductive techniques to alleviate male-factor infertility, intrauterine insemination may be considered as a first-line treatment for couples in whom the female partner has a normal fertility status, and at least 0.8×10^6 progressively motile spermatozoa are recovered after sperm preparation. If no pregnancy is achieved after three to six cycles of intrauterine insemination, in-vitro fertilisation can be proposed. When too few progressively motile spermatozoa are obtained after sperm processing for in-vitro fertilisation, or when surgically retrieved sperm are to be used, intracytoplasmic sperm injection is preferable. Although the outcome of no other assisted reproductive techniques has been scrutinised so much, and no large-scale 'macro-problems' have yet been observed after intracytoplasmic sperm injection, malformation rates are reported to be higher compared with the general population. Therefore, candidates

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for intracytoplasmic sperm injection should be rigorously screened before embarking on in-vitro fertilisation or intracytoplasmic sperm injection, and thoroughly informed of the limitations of our knowledge on the hereditary aspects of male infertility and the safety aspects of assisted reproductive techniques.

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Introduction

Subfertility is defined as failure to conceive with 1 year of (regular) unprotected sexual intercourse. Subfertility is a major problem worldwide, affecting at least one in six couples.[1] A male factor as the single cause of subfertility is present in at least 30% of couples, and in 39% of cases both a male and female factor is present.[2,3] Because a couple's fecundity is determined by an interaction between both partners, the ability to have children is also influenced by a 'female factor'.

Nowadays, female age has become an important 'female' factor because many couples tend to postpone pregnancy to a later age. This interaction makes it difficult to define what a 'male factor' is, and perhaps clinicians should focus on prognosis rather than diagnosis. Semen analysis is used to investigate the fertility of men but it is known that biological variability and intra- and inter-observer variability make semen analysis inaccurate.

Normozoospermia has been defined by the World Health Organization (WHO) and semen analysis has been standardised.[4] Once a male factor has been 'diagnosed', several treatment options are available that aim to increase the total motile sperm count. Regretfully, only few men have potentially treatable conditions with a rational or effective treatment,[5] and drugs to increase the total motile sperm count in men with unexplained oligozoospermia have been unsuccessful so far.[6,7] Therefore, although assisted reproductive techniques (ART) should not be invariably viewed as primary treatment options, they seem the most effective options in cases of a male factor. Several new techniques have been developed in the past decades, making conception possible in couples that would have never conceived before.

Improving assisted reproductive techniques for male-factor infertility

Although empirical, ART has become the most effective means of coping with male-factor subfertility because treatments with proven efficiency to increase semen parameters and fecundity do not exist. In addition to insemination procedures (intrauterine insemination [IUI], in-vitro fertilisation [IVF] or intracytoplasmic sperm injection [ICSI]), female age, the number of embryos to be transferred, and life-style modifications,[8] can also affect the success rate of ART; the effect of dietary supplements is still under debate.[9] Whether corrective measures from the male side may improve ART outcome is still a matter of debate.

Paternal life style and art outcome

In women, some lifestyle modifications are known to improve the outcome of ART. Because female smoking affects both oocyte number and quality, refraining from smoking may have a profound effect on ART outcome. Data from meta-analyses show the importance of discouraging cigarette smoking in women undergoing ART: women smoking 10 or more cigarettes a day need about twice as many IVF and ICSI cycles to become pregnant compared with non-smokers.[10] In men, evidence shows that smoking is associated with slight reductions in sperm count and morphology,[11] but evidence of an important adverse effect on fecundity remains inconsistent.[12]

More importantly is the effect of smoking on the genetic make-up of spermatozoa. Smoking may increase the aneuploidy rate in spermatozoa,[13] and may harm the integrity of DNA, which may be associated with an increased incidence of mutations among the offspring of male smokers.[14] Although the effect of smoking on sperm DNA integrity is well established, the effect of DNA damage on IVF outcome is still a matter of debate, and the role of DNA integrity testing on sperm used for ART is under scrutiny.[15] In view of the body of evidence on the adverse effect on sperm DNA integrity, smoking cessation in the male partner too should be part of the ART treatment plan.

The role of oral antioxidant treatment in men is also subject to debate. The Practice Committee of the American Society for Reproductive Medicine (Fertility and Sterility, 2008) concluded that evidence to support the use of antioxidant treatment is insufficient, although antioxidant supplementation reduces sperm DNA damage. This is because good evidence on any beneficial effect on either routine sperm parameters or reproductive outcomes is lacking.[16] Yet, a recent Cochrane review[17] suggested that antioxidant treatment may play a role in the treatment of male subfertility. In this meta-analysis, results of 34 randomised-controlled trials on couples undergoing ART were analysed. On the basis of 15 trials, the pooled odds ratio for establishing a pregnancy was 4.2 (95% CI 2.6 to 6.6) (level of evidence (LOE) 1a). In many studies, a high drop-out rate was reported. Method of randomisation was reported in about one in three studies. Furthermore, only three trials reporting on live birth showed a pooled odds ratio for establishing a live birth of 4.8 (95% CI 1.9 to 12.2). This estimate, however, was based on only 20 live births from a total of 214 couples, and one of the studies included was not powered to detect any improvement in live birth rate.[18] An alpha-error might thus be present, and the wide confidence intervals indicate the need for further trials. Although the investigators point out that no hard conclusions can be drawn and further study is needed, this meta-analysis is now used to promote the indiscriminate use of antioxidant treatment.[19] In the meantime, given the benefit of the doubt, antioxidant supplementation in men can be proposed whenever the agent used is free from (gastro-intestinal) side-effects and inexpensive.

Other modifications in the lifestyle of subfertile men and their effect on ART outcome are even more controversial or remain unidentified. Only one study investigated the effect of alcohol consumption by the male partner on IVF outcome but failed to show an effect.[20] The same investigators assessed the effect of caffeine intake on male fertility status but, again, no effect on either sperm parameters nor IVF outcome could found.[21] The effect of exposure to heat (e.g. sauna, hot baths, type of underwear, sedentary activities), semen quality and fecundity is another unresolved controversial issue.

Varicocelectomy and male reproductive potential

In subfertile men, disorders of the testis or scrotum are often found. Varicocele is presumably found in 25% of subfertile men.[4] The relation between varicocele and subfertility is unknown, as is the mechanism by which varicocele would affect fertility. Discussion is ongoing whether varicocele in subfertile men should be treated. Yet, varicocelectomy is still the most common male infertility surgery. A Cochrane meta-analysis[22] of eight randomised-controlled trials showed a combined Peto odds ratio of 1.10 (95% CI 0.73 to 1.68), indicating no benefit of varicoceles treatment over expectant management in subfertile couples in whom varicoceles in the man is the only abnormal finding (LOE 1a).[22] Unfortunately the included studies were statistically and clinically heterogeneous, and included men with normal semen parameters. Subgroup analysis with studies that included subfertile men only revealed inadequate power to draw firm conclusions. The combined Peto odds ratio of three trials was 1.75 (95% CI 0.97 to 3.14). Whether varicocelectomy may improve IVF and ICSI outcome remains even more indeterminate. Only one recent retrospective study evaluated the effect of this surgery on IVF and ICSI outcome but failed to show any beneficial effect (LOE 3).[23] While awaiting further randomised-controlled trials, the advice is to apply varicocelectomy for treating subfertile semen in randomised-controlled trials only.

What to expect from assisted reproductive techniques for alleviating male-factor subfertility?

Intrauterine insemination

In cases of male subfertility, IUI is often the first treatment option. Is IUI effective in these cases? When a male factor is present, the latest Cochrane review clearly states that evidence is insufficient to conclude whether IUI is effective or not (LOE 1a).[3] A previously published study found a significant beneficial effect of IUI.[24] Results, however, were often presented as pregnancy rates per completed cycle, and many trials had a cross-over design. Nowadays, results should be expressed as live birth rates (or at least ongoing pregnancy rates) per couple applying intention-to-treat analysis, and ideally a randomised-controlled trial should have a parallel design. From crossover trials, the results of the first cycle only can be used in meta-analyses. Nevertheless, evidence from older trials do point to a place for

IUI in cases of a moderate male factor. The optimal number of cycles to be offered to couples is unknown. Most clinics carry out three to six cycles of IUI. For each cycle, the insemination should be carried out twice in case of a male factor, but this conclusion seems solely based on one trial, and should be confirmed in other trials (LOE 1a) (six trials, common odds ratio with 95% CIs 1.8, 1.4 to 2.4).[25]

The total number of motile sperm inseminated has the ability to predict failure: in other words, when less than 0.8 to 5 million motile sperm are inseminated, pregnancies hardly occur.[26] This widespread lower cut-off levels indicates that large differences exist between hospitals. It is advised that each clinic defines its own cut-off level of success.

When the total motile sperm count before sperm preparation has an average value above 10 million, almost resembling couples with unexplained subfertility, mild ovarian hyperstimulation might be added (LOE 1b).[27] In cases of immunologic male infertility, semen is often produced in medium to wash out most of the anti-sperm antibodies. In these cases, IUI can be carried out in natural cycles.

When IUI in natural cycles is carried out in cases of a moderate semen defect, pregnancy rates of 5–10% per started cycle are reported. In cases of mild or minimal ovarian stimulation and IUI in couples with a mild male factor, these pregnancy rates rise to 10–15%.

In-vitro fertilisation and intra-cytoplasmic sperm injection

When IUI fails or sperm parameters are too low to carry out IUI at all (often a total motile sperm count after sperm processing below 1 million), IVF of ICSI can be carried out. It is difficult to choose between both treatment options solely based on sperm parameters because prospective studies on this subject are lacking. Most clinics use 1 million motile sperm as cut-off level, but this is not based upon proper randomised-controlled trials. Again, clinics should define their own lower cut-off levels of total number of motile sperm before of after sperm processing, below which ICSI should be the first treatment option of choice. It seems that ICSI has no advantage over IVF in cases of unexplained subfertility, although robust trials are lacking,[28] and it therefore can be assumed that in cases of a mild semen defect only, IVF should be offered.

Originally, IVF was developed as a treatment of infertility for couples in whom the woman had bilateral tubal occlusion. Without proper randomised-controlled trials, IVF was introduced as a treatment option for male subfertility. It was not until 2000 that Goverde et al.[29] showed IVF to be less cost-effective compared with IUI, with or without mild ovarian hyperstimulation, in couples with unexplained infertility as with male subfertility (LOE 1b).[29] This trial supports the opinion that, in cases of moderate-to-mild male subfertility, IUI should precede IVF treatment.

In cases of male subfertility, most women are fertile and healthy. It is, therefore, of the utmost importance that serious complications such as ovarian hyperstimulation syndrome and multiple pregnancies are prevented. To prevent ovarian hyperstimulation syndrome, mild IVF stimulation protocols using gonadotropin-releasing hormone agonists and 150 IU gonadotrophins starting dose is suggested.[30] It is generally accepted that the number of embryos to be transferred should be reduced to prevent (high order) multiple pregnancies. In favourable groups, single-embryo transfer should be the option of first choice.[31]

In couples with severe male-factor subfertility or total fertilisation failure after IVF, ICSI is the treatment option of choice. Again, large randomised-controlled trials are lacking to establish the position of ICSI compared with IVF, IUI, donor insemination or expectative management. Although it can be concluded that ICSI is a great new technique giving opportunities to couples without perspectives before the era of ICSI, proper randomised trials expressing results as cumulative live birth rates in a defined period of time are still needed. Furthermore, a longer period of follow up is needed to establish the role of ICSI in congenital malformations and neonatal outcome of newborns. Up until now, results of follow-up studies seem reassuring, although malformation rates are reported to be 20–30% higher after ICSI compared with the general population (LOE 2).[32,33]

Although ICSI has been a real breakthrough in the treatment of severe male-factor infertility, men presenting with azoospermia can also benefit from this technique. The first successful pregnancies using either spermatozoa extracted directly from the testes of a man with azoospermia or the epididymis were reported in 1993[34] and 1994, respectively.[35] At present, men with obstructive azoospermia who need surgical sperm recovery for ICSI can select different surgical approaches. When

cryopreservation is required, percutaneous epididymal sperm aspiration (PESA) is the method of choice, followed by testicular sperm extraction (TESE) whenever the former approach fails. Both techniques yield high numbers of sperm necessary for cryopreservation. When a minimally invasive technique is preferred (i.e. a 'no-scar technique'), then fine-needle aspiration (FNA) is the technique to be used whenever PESA fails to recover motile spermatozoa.[36]

For men with non-obstructive azoospermia (i.e. azoospermia because of primary testicular failure), TESE is the most frequently used technique for non-obstructive azoospermia with an average sperm retrieval rate of 50%.[37]

Obtaining testicular spermatozoa in men with azoospermia does not infer that eventually offspring will also be obtained. In men with obstructive azoospermia, 35% of couples will obtain a live birth, whereas, in men with non-obstructive azoospermia, this figure will be limited to 17%.[38] Assuming that all couples would continue treatment (i.e. no drop-outs), after three ICSI cycles, these figures would be 48% and 31%, respectively.[38]

In a prognostically more optimal subpopulation of men with non-obstructive azoospermia in whom testicular spermatozoa were harvested and successfully frozen and thawed, the crude clinical pregnancy rate was reported to be 32% after three ICSI cycles with, an expected cumulative pregnancy rate of 55.7%.[39] Another study reporting on a similar subpopulation reported a cumulative delivery rate of 57% after four cycles.[40] Unfortunately, all these are fragmentary data reporting on the outcome of ICSI once testicular spermatozoa had been obtained in a subset of men embarking on TESH. Therefore, to date, it still remains difficult to provide candidate patients with accurate data about their chances to eventually father their genetically own child.

Conclusion

In subfertile couples, a male factor is often present. To define male subfertility, the WHO standards for semen analysis are often used, but these standards are limited by the biological variability of sperm parameters and intra- and inter-observer variability of semen analysis, making semen analysis inaccurate. Perhaps clinicians should focus on prognosis of the couple instead of their desirable need to find a diagnosis. Up until now, no effective treatment or drug has been identified to improve sperm parameters of the spontaneous chance of conception. There may be a place for antioxidant supplementation, but this need to be confirmed in large prospective cost-effectiveness trials. Also, the role of lifestyle modifications needs to be investigated further. In the meantime, empirical treatment options such as IUI, IVF or ICSI (with or without FNA, PESA or TESE) remain the first treatment options of choice. One needs to remember that these treatments were introduced without proper randomised-controlled trials and that these trials are still mandatory to define their place in the armamentarium of treatment options. Finally, the safety of all techniques, especially those in men with azoospermia and their offspring, needs to be established.

Practice points

- Some subfertile men have potentially treatable conditions. A rational or effective treatment can increase their total motile count.
- Although not to be viewed as a primary treatment option, ART are the most effective options for alleviating male-factor infertility.
- Smoking cessation in the male partner should be included in the ART treatment plan.
- Given the benefit of the doubt, antioxidant supplementation in men can be proposed whenever the agent used is free from side-effects and inexpensive.
- In cases of moderate-to-mild male-factor subfertility, IUI should precede IVF treatment.
- In cases of azoospermia, a distinction should be made between non-obstructive and obstructive azoospermia.
- Non-obstructive azoospermia can be treated with TESE, whereas obstructive azoospermia can be treated by FNA of PESA.

Research agenda

- Large randomised-controlled trials reporting results as cumulative live birth rates in a defined subpopulation, and in a defined period of time, are needed to establish the position of IUI, IVF, ICSI compared with expectant management.
- The role of IVF and ICSI in congenital malformations and neonatal outcome of the newborns needs to be studied with a longer follow-up period.
- Data reporting on the outcome of ICSI are needed in an unselected population of men with azoospermia embarking for testicular sperm retrieval.

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