

# Male-factor infertility: do we really need urologists? A gynaecological view

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The Royal College of Obstetricians and Gynaecologists state that male factor infertility is responsible for up to 25% of all cases of infertility and may contribute in a further 25%. Where the role of the

urologist ends and gynaecologist begins in these couples is a matter of debate. We therefore discuss the management of these couples and the need for a multidisciplinary approach.

## KEYWORDS

azoospermia, gynaecologist, male-factor infertility, sperm retrieval, urologist

## INTRODUCTION

Since the first published study of the epidemiology of infertility in 1886 by Mathews Duncan (Fecundity, Fertility & Sterility), inconsistencies in the definition of infertility, approach to investigation and diagnostic criteria have led to considerable variation in the published prevalence of infertility and the relative contributions of particular causes. Nevertheless, male-factor infertility is consistently shown to be the commonest single diagnostic category in many studies [1]. The Royal College of Obstetricians and Gynaecologists state that male-factor infertility is responsible for up to 25% of all cases of infertility and may contribute in a further 25% [2].

A recent survey of over 1000 couples presenting to four separate units over a year showed that >80% of the male partners were recorded as having abnormal sperm values (personal communication, J. Ramsay, Table 1). To what extent these men were labelled 'infertile' is unknown but the effect of such a conclusion is often significant. There has been much debate about the constitution of 'normal' ejaculated sperm. The acceptable percentage of sperm of normal morphology has recently been reduced from 30% to 15% [3], and when this criterion is applied to the data in Table 1, only half of the male partners would have been deemed subfertile. Clearly, if the sperm is to blame in even half of couples presenting for treatment, an attempt at male factor diagnosis is appropriate.

Data taken from a WHO study of >8500 couples showed that the largest single male

diagnostic category was men with seminal abnormalities of unknown cause [4]. A later WHO report found no demonstrable cause in almost half of couples with male-factor infertility [5]. Beyond this, varicocele was the commonest pathology detected. Despite the increased prevalence of varicocele in men with suboptimal semen values, any causal relation that exists between the distension of the pampiniform plexus and impairment of fertility is unconfirmed. Furthermore, two recent meta-analyses of randomized trials of varicocele ligation [6,7] both show no benefit of intervention on pregnancy rates. Kamischke and Nieschlag [7] also suggested that regular counselling of the infertile couple and optimization of female reproductive functions are as effective as interventionist treatment of the varicocele in achieving pregnancy.

If the results are also considered from further Cochrane reviews suggesting that there is no evidence to support the empirical treatment of idiopathic male infertility with hormonal interventions, e.g. gonadotrophins, GnRH, androgens, bromocriptine, anti-oestrogens and kallikrein, the role of the urologist in male-factor infertility would appear to be limited to treating the azoospermic man.

Azoospermia is found in 1% of males and the incidence in subfertile couples has been reported to be as high as 10–15% [8]. The first method of sperm retrieval for assisted conception that led to a successful pregnancy was microsurgical epididymal sperm aspiration (MESA) [9]. Although offering greater diagnostic accuracy and the opportunity for epididymovasostomy, newer

less invasive techniques requiring minimal training and equipment have become increasingly popular. Percutaneous needle aspiration (PESA) has been shown to be as effective as MESA but with fewer complications [10], repeatable with equally successful results [11] and patient satisfaction [12]. Testicular sperm aspiration (TESA) is similarly easy to perform and well tolerated [12] with high retrieval rates (96% [13]). Although the epididymis is known to be important for sperm maturation and motility, passage through the epididymis is not required for successful fertilization or pregnancy. Even though the most motile sperm are normally found in the cauda epididymis, in obstructive azoospermia this appears not to be the case. The most motile sperm are found in the proximal epididymis with sperm in the cauda senescent, dying or dead. This is confirmed by the outcomes of intracytoplasmic sperm injection (ICSI) cycles in men with obstructive azoospermia. Data from our unit referring to obstructed cases confirm no difference in fertilization rate (49% vs 51%), implantation rate (15% vs 16%), clinical pregnancy rate per embryo transfer (28% vs 29%) or live-birth rate (20% vs 21%) between epididymal and testicular sperm [14]. These findings are confirmed in a meta-analysis of published reports comparing epididymal or testicular sperm [14]. The question therefore arises that if a simple TESA or PESA is as effective in terms of retrieval rates, patient satisfaction and ICSI outcome as an open MESA, and does not necessarily require the expertise of a urological surgeon, why can they not be used routinely within an *in vitro* fertilisation unit by suitably trained gynaecologists or perhaps nursing staff?

**TABLE 1** Abnormalities in seminal analyses from four assisted reproduction units (WHO criteria)

Unit	Number of semen analyses	Abnormalities found (%)
1	631	468 (75)
2	181	87 (48)
3	192	165 (86)
4	783	736 (94)
Total	1787	1456 (81)

Up to 6% of men request a reversal after a vasectomy and this group of patients comprise a large percentage of patients with obstructive azoospermia. The success of vasectomy reversal depends on the skill and experience of the operator, time from vasectomy, and the use of microsurgical techniques and type of reversal required. Although data from the USA suggest that microsurgical reversal gives the highest chance of a delivery for a single intervention in this group of patients, as well as being the most cost-effective [15], this is not a view widely held by most fertility units in the UK, where clinical decisions are less dictated by health management organizations. In our unit the mean time between vasectomy and assisted reproduction is >15 years, with reports showing worsening patency and pregnancy rates with increasing vasectomy-to-reversal interval [16]. Furthermore, we have found that maternal age is the principal determinant of the success of ICSI for azoospermic men after vasectomy, and our findings show no effect on the outcome of ICSI with time since vasectomy [17]. The mean age of women undergoing ICSI in our unit as a consequence of previous vasectomy is 34.3 years, and it is therefore our experience that most couples in the older group are often unwilling to undergo reversal which necessitates surgery and a wait of 6–12 months to see if the ejaculated sperm values have become suitable for natural conception. The risk is that ICSI will still be required but that success rates have worsened because of advancing maternal age. A simple aspiration procedure with assisted reproduction (29% clinical pregnancy rate per embryo transfer after vasectomy in our unit) is therefore often the preferred choice in these couples as first-line management.

Despite the poor results of surgical treatment of acquired obstruction and the arguments

discussed above, we think that where possible the management of men with obstructive azoospermia should be multidisciplinary. Although, treating such couples can be offered in the absence of urological input, a proper diagnosis, that usually involves exploratory surgery, cannot.

Scrotal exploration will always produce a diagnosis and copious sperm for either synchronous use or freezing, as well as offering the possibility of reconstruction. The choice should not be between reconstruction or sperm retrieval (PESA or TESA) and assisted reproduction, but one should be an adjunct to the other, with sperm retrieval (MESA) always offered at the time of scrotal exploration and reconstruction. Furthermore, if live-birth rates are used to judge the outcome of assisted reproduction, our data and the statistics from the meta-analysis indicate that in obstructive azoospermia a careful epididymal aspirate is as effective when fresh as frozen-thawed [18]. It is thus sensible to always plan aspiration and storage from all patients who undergo scrotal exploration. We have neither statistical nor scientific evidence to recommend the synchronous retrieval of fresh epididymal gametes, except under specific circumstances. Based on our data, synchronous sperm retrieval is limited to cases in which reconstruction may be possible and in which delay is inadvisable (e.g. advancing maternal age).

There is therefore a clear role for the urologist in obstructive azoospermia, which involves surgical exploration in men where there is a suspected acquired cause. Epididymovasostomy can be attempted and importantly, sperm can be retrieved. This enables the couple to proceed with ICSI at a time-scale to be decided in conjunction with the clinicians, and several ICSI cycles can result from a single surgical procedure. In cases where the obstruction is not amenable to surgery (e.g. vasal aplasia and ejaculatory dysfunction), the case for diagnostic urological input is strong, but PESA or TESA may in these cases be adequate means of gamete retrieval.

Perhaps the most difficult question facing fertility units relates to the use of sperm (often immotile) retrieved from testicular aspiration or biopsy in cases of unobstructive azoospermia, often with some elevation of FSH and with accompanying histological evidence of reduced Johnsen score and

'patchy' spermatogenesis. First, the evidence comparing the use of fresh and frozen-thawed testicular sperm is controversial. Most studies that analyse testicular sperm use a combination of men with obstructive and unobstructive causes without comparing the effect of cryopreservation by aetiology of infertility. The two papers that have compared fresh and frozen-thawed testicular sperm from only men with unobstructive azoospermia [19,20] showed no significant differences in either fertilization or pregnancy outcome. Despite this, it is difficult to conclude, as we have with epididymal sperm, that the role of synchronous retrieval is minimal. This is because testicular retrieval in men with an unobstructive cause commonly yields few spermatozoa, often of poor motility and morphology, and the technical difficulty associated with frozen-thawed testicular samples. The decision is further confounded by the apparent paradox seen in a recent meta-analysis that live-birth rates are unaffected by cryopreservation but implantation is significantly impaired by the use of frozen-thawed testicular sperm [18]. Therefore, the decision between the use of synchronous retrieval (using donor or previously cryopreserved sperm as a back-up) or retrieval followed by a planned cycle using frozen-thawed testicular sperm should be made for each patient jointly by the clinical staff (urologist and gynaecologist) and embryologists. Furthermore, in patients with impaired spermatogenesis, retrieval rates of up to 50% can be achieved with TESE, compared with only 12.5% with TESA [21]. Therefore exploration, diagnosis and biopsy by a urologist is the only correct option. If a synchronous ICSI cycle is to be applied at the time of exploration and retrieval, a realistic estimate of the chances of successful retrieval needs to be discussed, the couple counselled and donor back-up (or sperm cryopreserved at a previous retrieval) provided to minimize the unnecessary risks of a stimulation cycle to the female partner should retrieval be unsuccessful. We also need urologists to take an interest in these cases to maximize the supply of biopsy material not only for diagnosis but also research.

From the above discussion the role of urologist in the diagnosis and treatment of the azoospermic man is clear. However, if half of presentations are associated with male factors there must also be a role in diagnosis and research of 'non-azoospermic' male infertility. The diagnosis, investigation,

treatment and ongoing research of male factor infertility needs to become a strictly multi-speciality undertaking, ideally within an assisted reproductive setting, with dedicated gynaecological, urological and embryological staff supported by suitable counselling (both fertility and genetic) where needed. Above all, we should be taking shared responsibility for the correct diagnosis of male infertility and further effects of that diagnosis on men.

## CONFLICT OF INTEREST

None declared.

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**Abbreviations:** MESA, microsurgical epididymal sperm aspiration; PESA, percutaneous needle aspiration; TESA, testicular sperm aspiration; ICSI, intracytoplasmic sperm injection.