Published in final edited form as:

Gynecol Pelvic Med. 2019 October ; 2: . doi:10.21037/gpm.2019.09.04.

Reasons that should prompt a referral to a reproductive urologist: guidelines for the gynecologist and reproductive endocrinologist

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Abstract

Obstetricians and gynecologists, and in particular reproductive endocrinologists (REIs), are typically the gatekeepers and first-line providers for couples initially seeking an infertility evaluation. A timely referral to a reproductive urologist may improve pregnancy outcomes in certain clinical scenarios. This review examines the evidence behind circumstances requiring referral and delivers practice-based recommendations on commonly encountered scenarios in the clinic. Scenarios that should prompt referral to a reproductive urologist include semen analysis (SA) abnormalities (e.g., asthenozoospermia, azoospermia, globozoospermia, leukocytospermia, necrozoospermia, oligospermia), recurrent intrauterine insemination (IUI)/in vitro fertilization (IVF) failure, and idiopathic recurrent pregnancy loss (RPL). Conversely, deferment is appropriate in the cases of isolated teratozoospermia and subclinical varicocele. Men with infertility are also at higher risk for other comorbid conditions and should have at least a baseline evaluation by a primary care physician. Coordination of care between a REI and reproductive urologist is critical in several clinical scenarios and expedient referral can improve reproductive outcomes.

Keywords

Recurrent pregnancy loss (RPL); azoospermia; intrauterine insemination failure (IUI failure); in vitro fertilization failure (IVF failure); sperm aneuploidy; sperm DNA fragmentation; male infertility

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Contributions: (I) Conception and design: NJ Farber, P Patel, R Ramasamy; (II) Administrative support: All authors; (III) Provision of study materials or patients: NJ Farber, P Patel, R Ramasamy; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Introduction

Infertility affects approximately 12% of all couples, with a male factor contributing to up to 60% of these cases (1). Further, recent trends suggest that one of the most common reason for visiting an *in vitro* fertilization (IVF) center is male fertility concerns (37% of visits) (2). Most couples seek initial consultation with a reproductive endocrinologist (REI), who performs both the initial male and female evaluations. The decision to subsequently refer a patient to a reproductive urologist is not always clear-cut, with no current guidelines or evidenced-based literature outlining the scenarios that necessitate such a referral. Achieving a pregnancy is often a time-sensitive endeavor (3), and so an expedient referral to a reproductive urologist, given the right circumstances, may improve pregnancy outcomes. Conversely, certain abnormal findings in the male patient do not always warrant a referral and could unnecessarily burden the couple with additional lost time and cost. Therefore, we sought to outline a set of common clinical scenarios for which referral to a reproductive urologist is recommended.

Semen analysis (SA) abnormalities

The SA is the cornerstone of the male infertility workup. A workup for the male patient in an infertile couple should always include a minimum of two semen analyses. The variation between SAs may be substantial, with a recent report demonstrating that in men with a normal first SA, a sizable number (27%) had pathologic findings in their second SA (4). Patients with abnormalities on one or both SAs should be referred to a reproductive urologist (Table 1). Additionally, those patients with a borderline-low/normal SA results may benefit from a referral, as the World Health Organization (WHO) recently lowered the reference limits for the SA. One effect of this change is an inclusion of a greater percentage of patients that may have sub-fertility in the “normal” reference range. For instance, oligospermia was previously defined as a sperm concentration of $<20\times10^6$ sperm/mL, but is now defined as $<15\times10^6$ sperm/mL. This is an important example of how inclusion in the 95% confidence interval for “normal” semen parameters does not guarantee fertility, especially if the parameters are near the lower limit of normal; this concept guides our recommendation for referral for borderline-normal SA results.

Azoospermia

The most important SA finding that should prompt a referral to a reproductive urologist is azoospermia. These patients may have an obstructive or non-obstructive etiology for azoospermia, and the treatment algorithm will vary dramatically depending on additional testing. Treatment for non-obstructive azoospermia (NOA) patients may include microdissection testicular sperm extraction (mTESE) and/or correction of any palpable varicoceles. Alternatively, for those patients unable to afford these treatment options, donor sperm and IUI may provide a fiscally obtainable treatment plan. In addition, karyotype abnormalities are especially common in men with NOA (14–19% of the time), and these men should undergo a detailed genetic evaluation (5). The most common genetic cause of NOA is Klinefelter’s Syndrome (KS) (most commonly 47, XXY), a potentially occult condition that underscores the need for a full-workup in men with azoospermia. This

syndrome is characterized by testicular failure and derangements in endocrine function, leading to not only impaired spermatogenesis but also hypogonadism. A testosterone deficient state creates more global health implications than just infertility, including poor muscular development, osteopenia in up to 40% of KS men, gynecomastia, and potential cognitive or developmental delays (5,6). Many of these men require sperm retrieval via mTESE, with potential aromatase inhibitor augmentation and close monitoring of gonadotropin levels. Medical therapy for the comorbid conditions should be individualized based on patient-specific problems.

Obstructive azoospermia patients typically will require either vasal reconstruction or sperm extraction. There is concern that patients with female partners of age greater than 35 should be counseled toward assisted reproductive technology (ART), however it may often be cost-effective for patients with history of prior vasectomy to first undergo vasal reconstruction rather than sperm extraction/ART. Moreover, in a cohort of 136 men who underwent vasectomy reversal, Kapadia *et al.* demonstrated comparable pregnancy and live birth rates per IVF cycle, for paired female age groups (35–37, 38–40, >40 years), based on IVF data from the 2015 annual ART national summary report (7). Therefore, the various pros and cons of these options should be discussed with the patients by the reproductive urologist.

Further, patients with obstructive azoospermia and congenital bilateral absence of the vas deferens may have or be carriers of cystic fibrosis and warrant additional genetic testing of their female partner.

Finally, less common but potentially correctable causes of azoospermia should be ruled out. These include retrograde ejaculation or ejaculatory duct obstruction, which may require a post-ejaculatory urinalysis or surgical correction of the ejaculatory ducts, respectively. In short, patients with azoospermia always require additional evaluation by a reproductive urologist to help elucidate the cause of the azoospermia and determine the appropriate course of management.

Oligospermia

Oligospermia may be categorized as mild (10–20 million sperm/mL), moderate (5–10 million sperm/mL), or severe (<5 million sperm/mL). With mild abnormalities in sperm count, intrauterine insemination (IUI) is a viable option if natural conception fails. However, moderate or severe oligospermia—especially in conjunction with an elevated FSH and small, atrophic testicles—may be reflective of testicular failure. A genetic evaluation should also be performed in these cases, as karyotype abnormalities are found in 3–5% of men with severe oligospermia (5). Like azoospermia, all cases of oligospermia should be referred to a reproductive urologist to ascertain the underlying etiology and, thereafter, help determine the proper course of treatment.

Leukocytospermia

Leukocytospermia (i.e., >1 million leukocytes/1 mL of semen) is a condition that may be associated with inflammation or infection in the genital tract. Interestingly, the link between leukocytospermia and infection/inflammation has been questioned, but even in the definitive absence of infection, this condition is adversely correlated with fertility outcomes (8).

Specifically, the presence of leukocytes may generate reactive oxygen species, which negatively affects sperm parameters (8). With respect to therapies, antibiotics, anti-oxidants, and frequent ejaculation are all potential options recommended by various guidelines and the results of a systematic-review (8,9). In short, given that this condition is ill-defined yet affects up to 30% of men with infertility, a diagnosis of leukocytospermia should prompt referral to a reproductive urologist for a discussion of its significance and the various treatment options.

Abnormal sperm morphology

Recently, the diagnostic value of sperm morphology (i.e., teratozoospermia) has been challenged. Kohn *et al.* performed a systematic review and meta-analysis analyzing the effect of sperm morphology on pregnancy success via IUI (10). They found that when comparing sperm morphology at the <4% *vs.* ≥4% thresholds, there was no significant difference in clinical pregnancy rate (14.2% *vs.* 12.1%, P=0.06) with a small 3.0% risk difference (95% CI: 1.4–4.6). Similarly, when men with sperm morphology of <1% *vs.* ≥1% were compared, no significant difference was found in clinical pregnancy rate (14.0% *vs.* 13.9%, P=0.97) or risk difference (1.6%, 95% CI: −4.5 to 7.6). Recent data by Patel *et al.* further confirmed these findings, with sperm morphology (4% normal forms threshold) having no significant effect on clinical pregnancy rate (12.3% *vs.* 13.6%, P=0.59) or live birth rates in 501 couples undergoing 984 IUI cycles (11). Even patients with the most severe forms of isolated teratozoospermia (0% normal forms) have approximately a 30% chance of a natural conception and do not require IVF or ICSI upfront (12).

Other previous reports fail to demonstrate a significant link between sperm morphology and pregnancy outcomes following IVF or ICSI (13–16). Overall, sperm morphology in isolation with an otherwise normal SA is likely a scenario that does not require referral to a reproductive urologist. The potential caveats to this recommendation are: (I) a significant portion of these patients, if not thoroughly evaluated by history and physical exam, may have a concomitant, unrecognized cause of male infertility (e.g., varicocele) and (II) the presence of globozoospermia is a separate, severe sperm morphology issue and requires ICSI (17).

Idiopathic recurrent pregnancy loss (RPL)

RPL affects 2–5% of couples and is attributed to an idiopathic etiology in up to 50% of all cases (18). Emerging evidence suggests that the integrity of sperm DNA—a male factor—may be linked to recurrent miscarriage outcomes. While oocytes are able to repair sperm DNA fragmentation (SDF) upon insemination, a high degree of fragmentation may be irreparable and incompatible with embryonic development especially in females of advanced reproductive age.

Multiple recent systematic reviews and meta-analyses have demonstrated that male partners of women with RPL have significantly higher rates of SDF compared to fertile control groups (18,19). The therapeutic benefit of diagnosing this male factor in RPL is that the degree of SDF may guide treatment. For instance, a high SDF level is a poor prognostic factor for couples attempting IUI after RPL, and therefore may influence the decision to

proceed directly to IVF rather than IUI. Men may be advised to implement lifestyle changes and initiate anti-oxidant therapy in attempt to reduce SDF levels. A recent meta-analysis of 7 small randomized controlled trials showed that antioxidant therapy improved both live birth rates (OR 1.79, 95% CI: 1.20–2.67) and clinical pregnancy rates (OR 2.97, 95% CI: 1.91–4.63) (20).

Additional male factors associated with RPL are sperm aneuploidy or chromosomal structural abnormalities. Some couples with RPL have a male partner with essentially normal SA parameters but sperm aneuploidy or chromosomal abnormalities. Thus, couples with ≥2 spontaneous abortions should have the male partner screened for these conditions via a sperm fluorescence *in situ* hybridization (FISH) assay. This assay tests for aneuploidies of chromosomes 13, 18, 21, X, and Y (21). The results of this assay may significantly inform treatment and counseling decisions. For example, couples with a FISH assay positive for sperm aneuploidy may elect to undergo preimplantation genetic testing for monogenic/single gene defects (PGT-M) with IVF or use donor sperm. At the very least, patients with aneuploidy on sperm FISH assay should undergo genetic counseling.

Overall, a male factor (e.g., SDF) should be included in the differential when a couple is faced with RPL in the absence of female factors. A reproductive urologist can aid the couple in the assessment of SDF or sperm aneuploidy via various assays, which may ultimately influence the choice of future treatment (e.g., IUI *vs.* IVF *vs.* ICSI).

Recurrent ART failure

Like RPL, IUI failure may be attributable to elevated SDF levels (22). Bungum *et al.* analyzed 387 IUI cycles and found that couples with a DNA fragmentation index (DFI) >30% on the SCSA assay had higher biochemical pregnancy, and lower clinical pregnancy and delivery rates compared to couples with <30% DFI (23). Other SDF assays, including terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL), have been shown to predict IUI outcomes; that is, high levels of SDF portend poor IUI outcomes and the couple may be advised to proceed directly to IVF rather than undergoing IUI with a low success rate (24). Chen *et al.* recently performed a meta-analysis of 10 studies and concluded that higher levels of SDF were adversely associated with lower pregnancy rates following IUI (25).

Conversely, other SDF assays [i.e., sperm chromatin dispersion (SCD)] have shown no correlation with pregnancy outcomes in IUI (26). Therefore, referral to a reproductive urologist familiar with these various assays may help guide the appropriate selection of SDF assays in the IUI setting and, in a joint effort with the REI provider, help determine when to advance to IVF rather than repeat IUI.

For IVF failure, genetic causes such as chromosomal aneuploidy and structural abnormalities are of significant interest. In a study of 140 patients with RPL (defined as either history of recurrent miscarriage or IVF failure), Ramasamy *et al.* found 45% of men with normal sperm density and motility to have abnormal FISH results, indicating this subpopulation of men may require sperm aneuploidy testing (27). Another study evaluating

IVF/ICSI failure in non-male factor infertility separated patients into cohorts based on SDF rate, using 30% as the cutoff for the two groups (<30% *vs.* ≥30% SDF). Despite similar pregnancy rates, the cohort with higher SDF rates were found to have higher miscarriage rates (42.8% *vs.* 16.8%) as well as lower implantation rates and poor embryo development (28). Despite these poor outcomes, patients with post-ART failures and high DFI (>30%) levels may derive some clinical benefit by the choice of the source sperm. Pabuccu *et al.* recently showed that for normozoospermic men with ART failure, the use of testicular spermatozoa (TESA) via aspiration had superior outcomes (41.9% clinical pregnancy rate) compared to ejaculated spermatozoa (20% clinical pregnancy rate) (29).

Therefore, for IVF failure as well, referral to a male infertility expert could prompt consideration of sperm aneuploidy testing and SDF assays, allowing collaborative decision-making in helping guide further management.

Varicocele

A varicocele, or dilated pampiniform plexus in the spermatic cord, negatively affects testicular function and is present in approximately 40% of infertile males. A reproductive urologist can diagnose and grade varicoceles on physical exam, as well as counsel the patient appropriately regarding the benefits of varicocele repair. In select patients, especially in those with grade 3 varicoceles or patients with abnormal SA parameters, the benefits may be substantial.

While the effect of repairing a clinical varicocele in men with abnormal semen parameters is well documented, recent meta-analyses have also demonstrated that varicocele repair may improve reproductive outcomes in patients with the most severe forms of male infertility. Kirby *et al.* performed meta-analysis of 1,241 patients with azoospermia or oligospermia and a concomitant clinical varicocele (30). Patients that underwent varicocelectomy prior to ART had significantly higher pregnancy rates (OR: 1.760) and live birth rates (OR: 1.761) than men with varicoceles who did not. Additionally, varicocelectomy improved sperm retrieval rates (i.e., testicular sperm extraction; OR: 2.509) in men with persistent azoospermia. Another benefit of varicocelectomy is that, in some cases, it may obviate the need for assisted-reproductive technology in azoospermic men with a clinical varicocele and allow for other modes of treatment including IUI or timed intercourse. Esteves *et al.* performed a meta-analysis showing that 43.9% of previously azoospermic men with a clinical varicocele had return of sperm to the ejaculate (mean sperm count 1.82×10^6) after varicocelectomy (31). Overall, varicoceles are a common contributing cause in men with infertility and correction of this male factor may improve reproductive outcomes and in certain scenarios allow for unassisted pregnancy.

Various studies have demonstrated the effectiveness of varicocele correction in improving outcomes. A systematic review evaluating the benefit of repairing clinical varicoceles in infertile men with NOA showed sperm retrieval rate (SRR) increased in patients who underwent varicocelectomy, compared to that in patients who did not (OR: 2.65) (31). Moreover, a meta-analysis studying varicocele repair in patients with NOA demonstrated return of sperm in the ejaculate for 39.1% of patients who underwent repair. This study also

found success rates to be significantly higher for men with maturation arrest or hypospermatogenesis on histopathology, in comparison to those with Sertoli-cell-only, indicating the importance of histopathological analysis (32).

Association of male infertility with comorbid conditions

Male factor infertility is often not just an isolated condition but may be a barometer for general health. Particularly in cases of idiopathic infertility, an underlying comorbid condition may be responsible for impaired spermatogenesis. For instance, hypertension and hyperlipidemia are known to be more prevalent in infertile versus fertile men, and should be part of every male infertility evaluation (33,34). A literature review by Choy and Eisenberg even posits a link between male infertility and various other oncologic, metabolic, and auto-immune processes (35).

Recently, a notable study by Shiraishi and Matsuyama found overall rates of comorbidities were significantly higher in 3,328 infertile men (21.7%) compared to 452 fertile men (9.1%) (34). Interestingly, they observed that treatment of comorbid conditions resulted in an increase in total motile sperm count, and that treatment of medical comorbidities remained an independent predictor of total motile sperm count increase on multivariate analysis (OR: 2.06). This suggests that referral of patients with male infertility to a primary care physician may not only assist in the diagnosis of potentially unrecognized comorbidities, but also may help restore reproductive function after treatment of these conditions.

Conclusions

Obstetricians and gynecologists, and in particular REIs, are typically the gatekeepers and first-line providers for couples initially seeking an infertility evaluation. A timely referral to a reproductive urologist may improve pregnancy outcomes in certain clinical scenarios. Circumstances which should prompt referral to a reproductive urologist include SA abnormalities, IUI failure, IVF failure, a palpable varicocele, and idiopathic RPL. Conversely, deferment is appropriate in the cases of isolated teratozoospermia and subclinical varicocele. Men with infertility are also at higher risk for other comorbid conditions and should have at least a baseline evaluation by a primary care physician.

Acknowledgments

Funding: This work was supported in part by grant UL1TR002736.

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Table 1

SA abnormalities

Requires referral
Azoospermia
Asthenozoospermia (abnormal motility)
Oligospermia
Necrozoospermia (sperm death)
Leukocytospermia
No referral
Isolated teratozoospermia (abnormal morphology)
Globozoospermia

SA, semen analysis.