REVIEW PAPER

ANDROLOGY AND SEXUAL UROLOGY

Recurrent miscarriage and male factor infertility: diagnostic and therapeutic implications. A narrative review

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Introduction Recurrent miscarriage is defined as 2 or more failed clinical pregnancies, typically known as repeated pregnancy loss, occurring before 20 gestational weeks, and further categorized into primary and secondary types. It represents a common and distressing condition to deal with in the field of reproductive medicine, usually affecting <5% of couples, with up to 50% of cases lacking a clearly defined aetiology. The epidemiology also varies depending on maternal age. Remarkably, the situation significantly afflicts expecting parents, whereas maternal factors, such as age and previous pregnancy loss rate, are commonly reported as risk factors. Although previously underestimated, existing evidence suggests the male factor is a possible cause of recurrent pregnancy loss.

Material and methods A non-systematic literature review was conducted in the PubMed and Scopus databases for articles written in English investigating the possible association of the male factor in recurrent pregnancy loss. The eligible studies were synthesized in a narrative review format upon discussion and consensus among the authors after being previously independently assessed and selected.

Results Lifestyle, obesity, genetic predisposition, chromosomal anomalies, endocrine dysfunction, anatomical abnormalities, immunological factors, infections, and oxidative stress can result in poor embryo development and recurrent miscarriage. Although professional organizations currently recognize male gender as a possible risk factor, specific recommendations on the diagnostic and therapeutic field are still lacking, and the condition necessitates a high level of suspicion and case-by-case management.

Conclusions In this review, we delve deeper into the contribution of the male factor in the concept of recurrent miscarriage.

Key Words: recurrent miscarriage ‹› recurrent pregnancy loss ‹› infertility ‹› male factor

INTRODUCTION

Miscarriage is an unfortunate loss during the intrauterine stage with significant legal, psychological, spiritual, and health-related aspects for the expecting parents [1]. It may occur in up to 20% of known pregnancies and is considered the most common gynaecological complication, and a frequent cause of at-

tendance in the emergency department, which causes significant distress and warrants interventional strategies [2]. Definitions vary, but recurrent miscarriages are mostly defined as consecutive or non-consecutive, recurrent pregnancy losses (RPL), usually 2 or 3. Gestational infertility can be described as repeated embryo loss after fertilization resulting in the inability to conceive [3]. Maternal age and previous rate of pregnancy losses have been reported to carry predictive significance in terms of the risk of recurrence [4]. Historically, the male factor has also been implicated as a possible cause. The story of Henry VIII, King of England (1491–1547), is a phenotypic example that male infertility can manifest in the form of repeated miscarriages. In 11 documented pregnancies with 3 of his wives, 7 miscarriages or stillbirths were recorded. Overweight by his thirties, Henry's high-energy diet low in vitamins and fibre, and possible genetic predisposition have been speculated as obvious causes [5]. The aetiology concerning the male factor seems complex, and the effect of fine genetic abnormalities may be larger than the conventional quality of the human sperm [6, 7]. Moreover, chromosomal abnormalities have also been reported as a possible cause of gestational infertility in a large population of over 4000 infertile men [3]. Oxidative stress (OS) may also result in poor embryo development and recurrent miscarriages [8]. Recent meta-analytical data report that in couples with RPL semen DNA fragmentation (SDF) is increased in men. However, the subjects were mostly compared with fertile men, and thus SDF may not be considered specific [9]. However, in ART reports, SDF is associated with poor embryo development, lower implantation rate, and higher miscarriage rate in non-male factor infertility and may represent a hidden pathology [10]. Aging, particularly paternal age over 40 years, may also predispose to pregnancy loss, interfering negatively with the anticipated outcomes of Assisted Reproduction Technology (ART), and this warrants special management [11]. The complex aetiology and the rarity may explain why, although expert societies recognize the role of the male factor in RPL, firm recommendations are lacking regarding specific diagnostic and therapeutic aspects [12]. In this review, we discuss the role of male factor infertility in RPL, seeking deep insight into diagnostic and therapeutic implications on the matter relevant to daily urological practice. Figure 1 summarizes the spectrum of causes and risk factors of this clinical entity.

MATERIAL AND METHODS

We performed a non-systematic search in September 2022. In Scopus, we used the search string ((TITLE-ABS ('miscarriage' AND 'male infertility'), and in PubMed/Medline, the text terms 'Miscarriage' AND 'Male infertility', the Mesh terms ((('Abortion, Spontaneous'[Mesh]) OR 'Abortion, Threatened'[Mesh]) OR 'Abortion, Habitual'[Mesh]) AND 'Infertility, Male'[Mesh]. We performed an additional search in PubMed with the terms (DNA Fragmentation[Mesh]) AND (((Abortion, Spontaneous[Mesh]) OR Abortion, Threatened[Mesh]) OR Abortion, Habitual[Mesh]). No time limitations were set. Studies reporting the diagnostic and therapeutic implications of male factor infections, chromosomal anomalies (microdeletions, polymorphisms, aneuploidies), and DNA fragmentation in recurrent pregnancy losses were screened by abstract for further full-text evaluation. Non-English studies, case reports, letters to the editor, animal studies, unavailable full-text, and retracted studies were excluded. Original search was preferred over review articles (but review articles not a prior excluded). References in narrative/systematic reviews and meta-analyses were additionally searched for relevancy. Articles were selected for presentation and discussion to the judgment of the authors and according to relevance, merit, and up-to-date content. Overall, 1323 articles were identified for screening and further selection (500 and 823 from Scopus and PubMed/Medline, respectively).

RESULTS

1. Viral infections

Diagnostic implications

In a study of 63 men, adeno-associated virus DNA was seen in up to 50% of men with normospermia in couples with RPL. The prevalence was lower (2 out of 14; $p < 0.05$) in men with normospermia achieving fatherhood and without a history of RPL. However, in the same study, adeno-DNA was detected in up to 60% of men diagnosed with oligo-asthenospermia without RLP [13]. Human papillomatous virus (HPV) has also been reported to affect gestational fertility [14]. In a study of 226 infertile couples for ART, 54 men had HPV semen infection. During the evaluation period, no natural pregnancies occurred (0% vs 8.1% in the HPV-negative group; $p < 0.05$). In contrast, a higher miscarriage rate (62.5% vs 16.7% of noninfected; $p < 0.05$) was observed after intrauterine insemination (IUI) or intracytoplasmic sperm injection (ICSI); all abortions of the infected group happened up to the 6th gestational week. Infection to exfoliated cells was favourable (3 ongoing pregnancies), whereas all 5 cases of miscarriage had infected sperm. Furthermore,

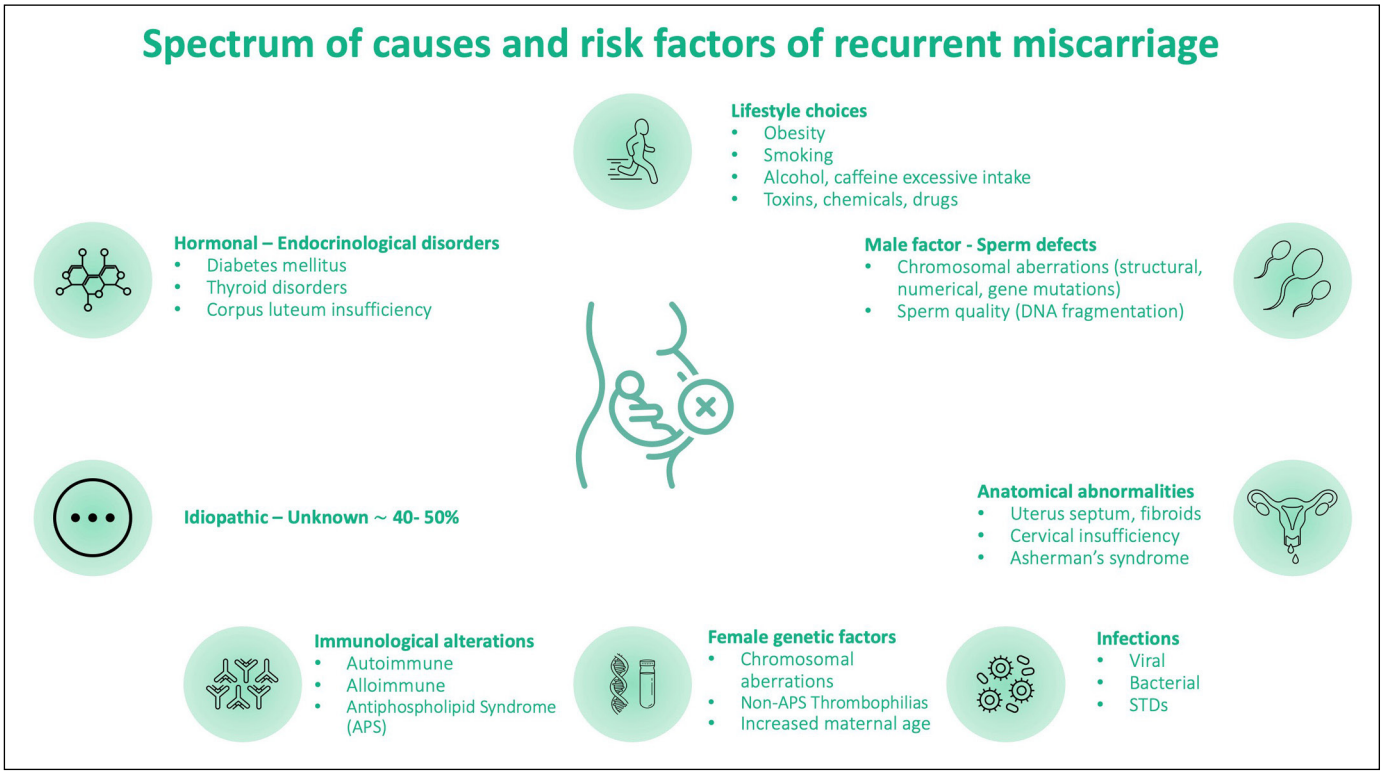

Figure 1. *Spectrum of causes and risk factors of recurrent miscarriage.*

STDs – sexually transmitted diseases; APS – antiphospholipid syndrome.

cumulative pregnancy rates differed significantly in noninfected and infected couples (38.4% vs 14.2%, respectively; p <0.05) [15]. Finally, a recent meta-analysis showed that HPV infection is more frequent in infertile men compared to the healthy population; a significant association with male infertility was noted (OR 3.02, 95% CI = 2.11–4.33). In addition, there was a considerable increase and DNA fragmentation (OR 7.24, 95% CI 4.44–10.03) and miscarriage rate (OR 5.13, 95% CI 2.40–10.94) [16]. Besides the negative effect on sperm quality, HPV semen infection is linked with adverse effects on ART outcomes, reflected by lower pregnancy and higher miscarriage rates [17]. Therefore, if there is suspicion of HPV (e.g. known history or multiple partners) and the couple suffer from otherwise unexplained PRL, a diagnosis of semen HPV infection must be considered.

Therapeutic implications

A study of 151 infertile couples with detection of HPV in semen evaluated the effect of HPV vaccination on pregnancy, delivery, and miscarriage rates. Two groups were formed (a control group of 72 unvaccinated men and a vaccinated group [with 3 vaccine doses] of 79 men). The control group showed a higher miscarriage rate than the vaccine group (7 vs 1 miscarriage, 9.7% vs 1.7%, p <0.05). Once again, losses occurred up to the 7th week of gestation, and the presence of the virus in the exfoliated cells was favourable. Overall, pregnancy was more frequent in the vaccinated group compared to the untreated group (15.3% vs 38.9%, p <0.05) [18]. Therefore, the most appropriate action upon diagnosis seems to be vaccination, because it can increase the chances of fatherhood and reduce the risk of spontaneous abortion [18]. On the other hand, there is limited evidence to recommend screening for other viral causes in couples with RPL.

2. Chromosomal anomalies

2a. Translocations

Diagnostic implications

Chromosomal translocations have been linked with RPL. Cytogenetic analysis can detect these anomalies using peripheral blood. Balanced reciprocal translocations were reported in a study of 5235 infertile men in less than 2% of the study population [19]. Although these translocations do not influence the phenotype, they have been involved in inability to conceive and pregnancy loss or stillbirth; the vari-

ability of the breakpoints is responsible. Balanced translocations in various chromosomes have been reported, presenting either with severe semen impairment or normospermia [19–26]. Robertsonian translocations are a specific type of translocations, typically seen between chromosomes with a short p-arm (13, 14, 15, 21, and 22). They have been reported as a possible cause of male infertility [27]. They may result in pre-gestational or gestational infertility. A well-studied example of such an anomaly is the Robertsonian (13;14) translocation, which has been reported to be inheritable, with an unpredictable phenotype ranging from asymptomatic spectrum to mental retardation among family carriers [28]. The prevalence of balanced translocations is regarded as low, and some authors advocate that neither semen parameters nor a history of RPL are reliable for triggering screening [29]. However, translocations should be suspected in unexplained pregnancy loss, particularly if no obvious factor is identified, even in normospermia. They may also be associated with a familial predisposition, and thus, suspicion may be raised if family history is indicative [30].

Therapeutic implications

An expectant management aiming for natural pregnancy may be an option in balanced translocations. The live-birth rate following natural conception ranges from 25% to 71% with significantly lower cost [31]. However, in the case of natural conception and known translocation of the male, the couple should be offered genetic screening up to the 2nd trimester to identify significant chromosomal abnormalities in the embryo [32]. Moreover, although the possibility of conception exists even in complex translocations/chromosome rearrangements, there is a significant risk of abnormal foetal phenotype [33]. In these cases, the ability to conceive should not be the sole determining factor, and the inheritance of the anomalies should be taken into serious consideration [31]. Otherwise, especially in the background of severe semen abnormalities present, ART is preferred. Nuclear volume differences can be used to identify balanced against unbalanced spermatozoa in the translocations carriers [34]. A pre-implantation diagnosis in men with translocations can also improve outcomes. In a study of 120 infertile couples undergoing ART alone due to male factor, there were Robertsonian translocations in 6 oligospermic men. These couples had more than 4 failed ART attempts, in vitro fertilization (IVF), and ICSI [35]. In a study of 111 couples of male and female Robertsonian translocation carriers, using PGD before ART was associated with a take-home-baby rate of 71.4% [36]. Therefore, genetic counselling seems to be the ideal choice in the case of RLP and if the man is a known translocation carrier [32].

2b. Polymorphisms and inversions

Diagnostic implications

Chromosomal polymorphisms mainly refer to variants in the chromosomal heterochromatin region [37]. Y chromosome polymorphisms have been reported as the most prevalent type (more than 60%) in a study of 132 infertile couples in which the men carry a chromosomal polymorphism [38]. Concerning gestational infertility, a study comparing 507 couples with RPL and 465 healthy couples (no miscarriage, at least one pregnancy) showed more frequent Y chromosome polymorphisms in the case group compared to controls (12.0%, 61/507 vs 2.2%, 10/465; $p < 0.05$). The Y polymorphisms were an independent risk factor for RPL along with shorter gestational age, higher frequency of miscarriages, and longer pregnancy interval ($p < 0.05$) [39]. In a study of infertile couples undergoing IVF, Y polymorphisms were absent, and the most common was the polymorphism at chromosome 1 (42/131 male carriers). Among other polymorphisms, the pericentric inversion at chromosome 9 had the higher early miscarriage rate (both in male and female carriers) [37]. Inversions are polymorphisms involving two breaks of the chromosome followed by a rotation of the segment 180 degrees with reinsertion. They may produce abnormal gametes resulting in altered embryonic chromosomes and spontaneous pregnancy loss. They have been reported in infertile men, frequently occurring in severe oligozoospermia [38]. As other anomalies, they can be detected by the karyotype [40]. Pericentric or paracentric inversions have been associated with impaired or normal spermatogenesis resulting in RPL and infertility [41, 42]. Identical inversions have been reported in brothers with a different type of male infertility (pre- or gestational infertility), highlighting the complexity of the events that may finally result in infertility [43]. Therefore, inversions may be inherited until possibly a secondary event results in stillbirth or miscarriage. The racial or geographical contribution may be pivotal because a study reported a likely 'founder' effect of a novel sizeable pericentric inversion of chromosome 9 [44].

Therapeutic implications

Polymorphisms with increased miscarriage rate can be managed with genetic counselling and preimplantation diagnosis [37]. Inversions have been

reported to run asymptomatically, transferred from generation to generation, and most likely represent a part of a complex process that may result in different types of infertility [43]. Due to the events in the meiotic process, stable gametes may be formed, and they can proceed to the normal offspring [43]. Therefore, natural conception may occur in specific circumstances (short inverted segment; paracentric inversions; no crossing-over during meiosis), which may allow expectant management in men with inversions but with reported unpredictable results without a biopsy of the embryo [43]. If the male partner has a known inversion, the foetus can be screened up to the second trimester through amniocentesis, ultrasound, chorionic villus sampling, or a combination to detect anomalies and further consultation [45]. RPL in inversion cases can be managed with ART as in other chromosomal and structural abnormalities. Reimplantation genetic testing is the method of choice to reduce the miscarriage rate and optimize the outcome [32, 46].

2c. Y chromosome microdeletions

Diagnostic implications

Although most RPL are unexplained, Y chromosome microdeletions have been reported as a possible cause. Karaer et al. evaluated 43 men from couples with RPL and reported a 16% prevalence of azoospermia factor (AZF) b microdeletions (7/43 men). Age did not differ significantly between men in the RPL population carrying microdeletions and men without microdeletions (35 vs 31.6 years, respectively, $p > 0.05$) [47]. Another study reported a significant presence of Yq microdeletion in males of infertile couples experiencing 3 or more miscarriages compared to 20 fertile controls. In a group of 59 men (8 men with abnormal semen analysis and 51 men with normospermia), deletion in the AZF zone was found in 13 cases (3 and 10 cases, respectively); the control group had none. A Total Motile Sperm Count (TMSC) of less than 20 million/ml was seen in 3 out of 13 cases, all in AZFc. Eight cases carried AZFc microdeletions, 4 had AZFa, and only one had AZFb [48]. Another study of 48 men in couples with RPL showed no AZF microdeletions in the population. However, one man with otherwise normal semen parameters (sperm count >100 million/ml, progressive motility >32%, and normal morphology) and no environmental risk factors (non-smoker, non-alcoholic, no drugs or infection for the past 3 months) had a 46, XY (1qh–) chromosomal complement [49]. Whether the screening for AZF microdeletions in couples with RPL is effective is difficult to identify. Some studies failed to demonstrate any effect on RPL [50–52], possibly due to rarity or racial differences; high prevalence may also be 'skewed', e.g. reports originating from high-volume centres [53, 54]. Nonetheless, AZF in normospermic men is surprising and rare, because AZF microdeletions have been notoriously associated with severe impairment [46]. Therefore, although the aetiology or RPL may be multifactorial, evaluation for AZF microdeletions in patients with otherwise unexplained RPL may be exceptional but meaningful [48].

Therapeutic implications

Because normospermia is reported in cases with Y microdeletions, natural pregnancy is possible but usually results in embryo failure [48]. Otherwise, management of gestational infertility by Y microdeletions can follow the management applied in pre-gestational infertility. Upon diagnosis and if finally proceeding with ART, microdeletions seem not to be a formidable obstacle (upon proper selection). A meta-analysis of 12 studies in men with oligoasthenospermia showed that the fertilization rate with ART (mostly ICSI) in men with AZF microdeletions decreased significantly compared to that in normal men (odds ratio 0.75, 0.63–0.88 CI 95%; $p < 0.05$), but with no significant difference in the good embryo, clinical pregnancy, miscarriage, and baby boy rates ($p > 0.05$) [55]. A preimplantation genetic diagnosis can be used to tackle refractory cases and eliminate the risk of inheritance to offspring [56]. If the couples are not selective regarding the gender of the child, assisted reproduction techniques for AZFc deletions, and especially ICSI, can provide comparable clinical outcomes to men with normal Y chromosomes; consideration of the transmission of the microdeletion is important albeit not determinant on the outcome [57].

2d. Aneuploidies

Diagnostic implications

Aneuploidies in women, with some variation concerning their incidence, have been associated with the occurrence of RPL [58]. Aneuploidies in male gametes should be suspected in otherwise unexplained recurrent pregnancy losses. A study showed that the mean aneuploidy rate in the male partners of couples with RPL was significantly higher than in the general population or fertile men. Interestingly, the percentage of aneuploid sperm is correlated to the percentage of apoptotic sperm and associated with worse morphology [59]. As an adverse feature, aneuploidy will result in failed meiosis and abnormal foetal development, which can explain failure in the ART

level [60]. Levels of aneuploidies correlate with pregnancy and miscarriage rates, and useful conclusions are drawn from ART studies. A sperm aneuploidy rate >1.55% is associated with worse outcomes for pregnancy rates (biochemical, clinical, implantation rates), deliveries (72.7% vs 30.4%; p <0.05), and overall miscarriage rate (11.1% vs 38.9%, p <0.05) compared to a lower rate in couples undergoing ICSI for male factor including azoospermia [61]. A study in 2008 infertile couples showed that high sperm aneuploidy levels were associated with a 2.6-fold decrease (p <0.0001) in the probability of achieving pregnancy, a 0.4-fold increase (p <0.05) in the probability of miscarriage, and 3.7-fold decrease (p <0.0001) in the probability of live birth [62]. Previous abnormal FISH, teratozoospermia, and azoospermia (obstructive and non-obstructive) had a significantly higher percentages of aneuploid embryos compared to control couples with sex-linked diseases undergoing preimplantation genetic diagnosis (PGD) (over 50% vs 33%; p <0.05) [63]. The populations with increased incidence of aneuploidies are men with impaired spermatogenesis (oligospermia, azoospermia, and teratozoospermia), couples experiencing RPL or recurrent implantation failure (RIF) in ART cycles, known previous aneuploid pregnancy, and males undergoing oncological treatments [60].

Therapeutic implications

Pre-implantation diagnosis can increase the chances of achieving pregnancy by reducing the aneuploidy rate and optimizing the selection of healthy embryos [63–65]. The implantation rate has been reported to be significantly higher (43.62% vs 27.88%; p <0.05) and the miscarriage rate significantly lower (17.07% vs 37.93%; p <0.05) when the selection is made with pre-implantation biopsy in comparison with a conventional morphology-based selection [65]. In a recent study, adjusting for several parameters (age of both sexes, levels of anti-Müllerian hormone, type of male infertility, and the number of transferrable blastocysts), PGD for aneuploidy was significantly associated with lower early miscarriage rate (adjusted OR 0.17, 95% CI 0.05–0.55). This retrospective study included 206 couples who underwent ICSI due to severe male factor infertility (non-obstructive and obstructive azoospermia and severe oligoasthenoteratozoospermia), 102 having PGD for aneuploidy and 104 proceeding without [66]. PGD can extinguish the differences between the severity grades of male factor because, although fertilization rates may differ among grades, the euploid rate and implantation potential of the obtained blastocysts are independent of sperm quality [67].

2e. DNA Fragmentation

Diagnostic implications

DNA fragmentation has been linked with miscarriage risk because damaged DNA transmission into the embryo may impair early development and potentially increase pregnancy loss [68]. Measurement by Comet assay showed that men from couples with RPL had higher sperm DNA damage (average score 33.32 vs 14.87; p <0.001) in a study comparing 76 fertile donors with 217 men whose partners had recently experienced miscarriage (variety in presentation, e.g. first or 2 or more miscarriages after natural conception, first miscarriage or 2 or more miscarriages after ART conception, or miscarriage after biochemical pregnancy) [69]. Other authors argued that although DNA integrity has been linked with the miscarriage risk, it cannot reliably differentiate gestational and pregestational infertility risk [70]. Carlini et al. compared SDFi (TUNEL assay) among 112 men with RPL (2 or more losses), 114 infertile men, and 114 fertile men with normospermia. There was no statistically significant difference in SDFi between RPL and infertile men (18.8% vs 20.8%; p >0.05), but both groups had higher fragmentation than that observed among fertile men with normal semen analysis (12.8%, p <0.001). An inverse correlation of DNA fragmentation with progressive motility ($r = -0.41$, p <0.001) was seen but not with other semen parameters. However, SDFi showed a positive correlation in the RPL group with paternal age (positive correlation, $r = 0.28$; p <0.01) and the number of miscarriages ($r = 0.20$, p <0.05). Also, stratifying the RPL according to DNA fragmentation (TUNEL assay, >30% and <30%) in a study of 140 male partners of couples who presented with RPL, there was no difference in the presence of aneuploidies between the groups [71]. Similarly, a study of 154 embryos from 38 couples undergoing PGD due to RPL or repeated implantation failure showed that there was no correlation between DNA fragmentation and the embryo aneuploidy rate ($R^2 = 0.0215$, p >0.05; $R^2 = 0.0373$, p >0.05, for fresh and processed sperm samples respectively) [72]. Thus, fragmentation may be involved but not directly associated with the miscarriage event, while other gross anomalies may be more critical.

Therapeutic implications

Antioxidant treatment can result in DNA remodeling in the men of couples with RPL, which may be an indirect sign that improvement of the fragmentation could reduce the miscarriage risk [73]. Miscar-

riage risk has been chiefly evaluated as an adverse event, not an infertility endpoint. Although that risk is not increased, further studies are needed to investigate the effect on couples presenting with RPL [74]. When ART is decided for severe male infertility, SDFi is unlikely to impact the cumulative live birth rate. In a study of 1339 couples undergoing ICSI/IVF, an SDFi cut-off of 15% based on TUNEL showed no difference in the miscarriage rate (5.1% vs 6.6% for <15% and >15%, respectively; p >0.05) and live birth rate (36.5% vs 40%; p >0.05) [75]. Similar results may also be expected in the extreme rates of DNA damage. In a study reporting ICSI outcomes in 97 men with excessive DNA fragmentation assessed by flow cytometry, the miscarriage rate was higher in the extreme SDFi group (24.5% vs 36.8%, for SDFi <15% vs SDFi >50%, respectively; p >0.05) but the cumulative pregnancy rate did not differ between the groups (46.5% vs 48.7%; p >0.05) [76]. Following delicate techniques for the selection of highly motile sperm with low levels of fragmentation before ART may not provide any benefit in terms of embryonal formation and clinical miscarriage, or live birth rates [77]. In the same concept, early reports of antioxidant treatment in men undergoing ART have not shown a significant impact on the miscarriage rate, although a favourable effect is seen on the viable pregnancy rate [78].

DISCUSSION

The scope of our review was to evaluate the importance of RPL from the urological perspective. Involvement of the male factor may be rare, but it should not be underappreciated. In the coming years, advancements in the field, e.g. concerning the role of DNA fragmentation, could change our diagnostic and therapeutic standpoint. Furthermore, with roughly half of the cases of RPL being idiopathic, future research should investigate the role of ROS, because the mechanisms by which increased OS induces RPL are yet to be fully understood. Thus far, mounting evidence suggests structural and functional DNA damage through multiple mechanisms, which need further exploration [79]. Another aspect to consider would be using antioxidants to counteract the elevated ROS, thus minimizing sperm DNA impairment [80].

Nevertheless, considering that no clear-cut recommendations and evidence-based knowledge in the form of clinical guidelines currently exist for the exact use of antioxidant compounds, future research should focus on elucidating their impact on RPL as well [81, 82]. Currently, the European Society of Human Reproduction and Embryology (ESHRE) acknowledges the significance of the male factor in the pathogenesis of RPL. Still, any recommendations are limited to lifestyle and possible association with OS and the role of DNA fragmentation (loss of weight, cessation of smoking, physical exercise, and balanced way of life). Sperm selection is not suggested, and routine antioxidant treatment has not proven to be helpful concerning live birth rates [83]. The European Association of Urology also advises the linkage between DNA fragmentation and miscarriage rate, but no particular diagnostic or therapeutic suggestions have been made [84]. Therefore, interpretation needs to be performed cautiously concerning the usefulness of DNA fragmentation tests. Moreover, not all these assays (sperm chromatin assay, sperm chromatin dispersion, TUNEL, Comet assay) demonstrate correlations. In contrast, the tests carry different sensitivity, specificity, and cut-off values to diagnose male infertility [85]. The latter needs to be appreciated by clinicians when an attempt is made to reproduce conclusions. Regarding the therapeutic part, the management of RPL probably needs to be modified according to the clinical concept. A frequent clinical example is that of varicocele; a meta-analysis by Birowo et al. suggested that varicocelectomy may improve sperm quality and reduce DNA fragmentation [86]. Although further investigation is needed, RPL in the concept of a clinical varicocele and altered DNA fragmentation may represent an additional indication for treatment. Close collaboration between fertility specialists and urologists can help identify the most appropriate candidates to optimize the chances of successful pregnancy in affected couples [87].

From the current review, the role of semen HPV infection must also be commented on. This seems to be a treatable, male factor cause of RPL, whereas the infection is easily identified, and vaccination has been shown to improve the natural conception [18]. The cost-effectiveness has to be clarified, but screening for the virus may be of benefit in cases of a previous, known HPV infection in the female partner, an increasing number of lifetime sexual partners, or a history of non-monogamous partners [88]. Another interesting finding in the existing literature is the fact that normospermia does not exclude underlying gross or less severe DNA abnormalities, and screening for underlying causative factors may be pivotal when RPL is unexplained, especially when high total motile sperm count (TMSC) is considered to carry the best prognostic significance for natural conception and ART outcomes [89]. However, translocations and microdeletions have been reported to be present despite normal semen parameters, and they may result in abnormal meiosis and

embryonal development [48]. Furthermore, carriers may transmit these anomalies with various manifestations [28, 31]. Therefore, in cases of an already known abnormality, RPL without apparent cause and normospermia, and family history of recurrent miscarriages, couples could be advised to undergo advanced diagnostics. Although natural conception cannot be excluded, couples may be directed towards ART, where a preimplantation diagnosis can improve the outcomes [46]. Blunting legislation and regional funding discrepancies would enhance the access of infertile couples to PGD and increase their chances for successful pregnancy [90].

The limitations of our work should be highlighted. We performed a comprehensive review using a subjective approach to include relevant studies. This may result in an incomplete representation of the available evidence. Furthermore, the selection had a mixture of randomized, observational, and small case-series studies, leading to heterogeneity. Additionally, because we did not follow a protocol for a systematic review, we did not assess the quality of the involved studies or perform statistical analysis. Consequently, readers should be mindful of the methodology of the included studies when drawing conclusions. Despite these limitations, this review provides a valuable synthesis of the available evidence on the role of male partners in RPL, offering insights and informing future research and practice in the field.

CONCLUSIONS

Recurrent miscarriages negatively affect the experience of a couple trying to achieve pregnancy. Although large-scale studies are lacking, the male factor should not be underestimated as a possible cause, even without impaired spermatogenesis. In circumstances where RPL appears unexplained or idiopathic, advanced diagnostics may be of value and may alter the management. HPV infections represent a treatable cause, and gross DNA anomalies can be treated with ART and preimplantation diagnosis. Finally, although a linkage between DNA fragmentation and RPL has been demonstrated, treatment of OS needs further research concerning the reduction of miscarriages. Future studies may enhance our collective understanding of this heterogeneous medical condition, further improving clinical counselling and reproductive decision-making.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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