Appendix 11
Section 11 – Male infertility

Genetic counselling for AZF deletions
After conception, any Y-deletions are transmitted to the male offspring, and genetic counselling is therefore mandatory. In most cases, father and son will have the same microdeletion [1], but occasionally the son may have a more extensive deletion [2]. The extent of spermatogenic failure (still in the range of azoo-/-oligo-zoospermia) cannot be predicted entirely in the son, due to the different genetic background and the presence or absence of environmental factors with potential toxicity on reproductive function. A significant proportion of spermatozoa from men with complete AZFc deletion are nullisomic for sex chromosomes [3, 4], indicating a potential risk for any offspring to develop 45,X0 Turner’s syndrome and other phenotypic anomalies associated with sex chromosome mosaicism, including ambiguous genitalia [5]. Despite this theoretical risk, babies born from fathers affected by Yq microdeletions are phenotypically normal [1, 6]. This could be due to the reduced implantation rate and a likely higher risk of spontaneous abortion of embryos bearing a 45,X0 karyotype.

Y-chromosome: ‘gr/gr’ deletion
A new type of Yq deletion, known as the gr/gr deletion, has been described in the AZFc region [7]. This deletion removes half of the gene content of the AZFc region, affecting the dosage of multicopy genes mapping inside this region. This type of deletion confers a 2.5 to 8-fold increased risk for oligozoospermia [1, 8-10]. The frequency of gr/gr deletion in oligozoospermic patients is ~5% [11].

According to four meta-analyses, gr/gr deletion is a significant risk factor for impaired sperm production [9-11]. It is worth noting that both the frequency of gr/gr deletion and its phenotypic expression vary among different ethnic groups, depending on the Y-chromosome background. For example, in some Y haplo-groups, the deletion is fixed and appears to have no negative effect on spermatogenesis. Consequently, the routine screening for gr/gr deletion is still a debated issue, especially in those laboratories serving diverse ethnic and geographic populations. A large multi-centre study has shown that gr/gr deletion is a potential risk factor for testicular germ cell tumours [12]. However, these data need confirmation in an ethnically and geographically matched case-control study setting. For genetic counselling it is worth noting that partial AZFc deletions, gr/gr and b2/b3, may predispose to complete AZFc deletion in the next generation [13].

Autosomal defects with severe phenotypic abnormalities and infertility
Several inherited disorders are associated with severe or considerable generalised abnormalities and infertility (e.g., Prader-Willi syndrome [14], Bardet-Biedl syndrome [15], Noonan’s syndrome, Myotonic dystrophy, dominant polycystic kidney disease [16, 17], and 5 α-reductase deficiency [18-21], etc.) Pre-implantation genetic screening may be necessary in order to improve the ART outcomes among men with autosomal chromosomal defects [22, 23].

Sperm chromosomal abnormalities
Sperm can be examined for their chromosomal constitution using FISH both in men with normal karyotype and with anomalies. Aneuploidy in sperm, particularly sex chromosome aneuploidy, is associated with severe damage to spermatogenesis [24-27] and with translocations and may lead to recurrent pregnancy loss (RPL) or recurrent implantation failure [28]. In a large retrospective series, couples with normal sperm FISH had similar outcomes from IVF and ICSI on pre-implantation genetic screening (PGS). However, couples with abnormal FISH had better clinical outcomes after PGS, suggesting a potential contribution of sperm to aneuploidic abnormalities in the embryo [29]. In men with sperm aneuploidy, PGS combined with IVF and ICSI can increase chances of live births [30].

Measurement of Oxidative Stress
Oxidative stress is considered to be central in male infertility by affecting sperm quality, function, as well as the integrity of sperm [31]. Oxidative stress may lead to sperm DNA damage and poorer DNA integrity, which are associated with poor embryo development, miscarriage and infertility [32, 33]. Spermatozoa are vulnerable to oxidative stress and have limited capacity to repair damaged DNA. Oxidative stress is generally associated with poor lifestyle (e.g., smoking) and environmental exposure, and therefore antioxidant regimens and lifestyle interventions may reduce the risk of DNA fragmentation and improve sperm quality [34]. However, these data have not been supported by RCTs. Furthermore, there are no standardised testing methods for ROS and the
duration of antioxidant treatments. Although ROS can be measured by various assays (e.g., chemiluminescence), routine measurement of ROS testing should remain experimental until these tests are validated in RCTs [35].

**Outcomes from assisted reproductive technology and long-term health implications to the male and offspring**

It is estimated that > 4 million babies have been born with ART since the first baby was conceived by IVF in 1978 [36]. As the number of couples undergoing ART has increased [37, 38], safety concerns related to ART have been raised. Assisted reproductive technology-conceived offspring have poorer prenatal outcomes, such as lower birth weight, lower gestational age, premature delivery, and higher hospital admissions compared with naturally conceived offspring [39, 40]. However, the exact mechanisms resulting in these complications remain obscure. Birth defects have also been associated with children conceived via ART [41-43]. Meta-analyses have shown a 30-40% increase in major malformations linked with ART [44-46]. However, debate continues as to whether the increased risk of birth defects are related to parental age, ART or the intrinsic defects in spermatogenesis in infertile men [47-52].

As for the long-term outcomes, post-natal growth patterns are mostly not associated with ART [41, 53, 54]. However, a number of studies have shown that ART children are taller [55, 56]. This may be important as there is evidence showing that rapid weight gain during early childhood is linked with higher blood pressure levels in children conceived via ART [57]. It is also suggested that ART-conceived children have similar childhood illnesses and hospital services rates as compared with naturally conceived children [58-60]. Some studies have shown an increased risk of retinoblastoma [61] and hepatoblastoma in children after ART. However, these studies have been challenged with other studies that have not supported these findings [62]. The current evidence for cancer risk in children conceived with ART is inadequate and further studies are warranted [63, 64]. Finally, several epigenetic alterations seem to be caused by ART, which might be the molecular basis to some complex traits and diseases [65].
References


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