Since Klinefelter syndrome is associated with several general health problems, appropriate medical follow-up is therefore advised [13, 1605, 1606]. Testosterone therapy may be considered if testosterone levels are in the hypogonadal range when fertility issues have been addressed [15]. Moreover, men with Klinefelter syndrome are at higher risk of metabolic and cardiovascular diseases (CVD), including venous thromboembolism (VTE) and diabetes, particularly when starting testosterone therapy [1607]. In addition, a higher risk of haematological malignancies has been reported in men with Klinefelter syndrome [13].

Testicular sperm extraction in peri-pubertal or pre-pubertal boys with Klinefelter syndrome aiming at cryopreservation of testicular spermatogonial stem cells is still considered experimental and should only be performed within a research setting [1608]. The same applies to sperm retrieval in older boys who have not considered their fertility potential [1609]. Although the data are not unique [1603], there is growing evidence that TESE or mTESE yields higher sperm recovery rates when performed at a younger age [1595, 1604].

11.3.5.1.2 Autosomal abnormalities

Genetic counselling should be offered to all couples seeking fertility treatment (including IVF/ICSI) when the male partner has an autosomal karyotype abnormality. The most common autosomal karyotype abnormalities are Robertsonian translocations, reciprocal translocations, paracentric inversions, and marker chromosomes. It is important to look for these structural chromosomal anomalies because there is an increased associated risk of aneuploidy or unbalanced chromosomal complements in the foetus. When IVF/ICSI is carried out for men with translocations, PGT or amniocentesis should be performed [1610, 1611].

11.3.5.2 Cystic fibrosis gene mutations

Cystic fibrosis (CF) is an autosomal-recessive disorder [1612]. It is the most common genetic disease of Caucasians; 4% are carriers of gene mutations involving the CF transmembrane conductance regulator (CFTR) gene located on chromosome 7p. It encodes a membrane protein that functions as an ion channel and influences the formation of the ejaculatory duct, seminal vesicle, vas deferens and distal two-thirds of the epididymis. Approximately 2,000 CFTR mutations have been identified and any CFTR alteration may lead to congenital bilateral absence of the vas deferens (CBAVD). However, only those with homozygous mutations exhibit CF disease [1613]. Congenital bilateral absence of the vas deferens is a rare reason of male factor infertility, which is found 1% of infertile men and in up to 6% of men with obstructive azoospermia [1614]. Clinical diagnosis of absent vasa is easy to miss and all men with azoospermia should be carefully examined to exclude CBAVD, particularly those semen volume < 1.0 mL and acidic pH < 7.0 [1615-1617]. In patients with CBAVD-only or CF, epididymal sperm aspiration (micro or percutaneous; MESA and PESA respectively), TESA, or TESE in combination with ICSI, can be used to achieve pregnancy. However, higher sperm quality, easier sperm retrieval and better ICSI outcomes are associated with CBAVD-only patients as compared with CF patients [1613].

The most frequently found mutations are F508, R117H and W1282X (according to their traditional definitions), but their frequency and the presence of other mutations largely depend on the ethnicity of the patient [1618, 1619]. Given the functional relevance of a DNA variant (the 5T allele) in a non-coding region of CFTR [1620], it is now considered a mild CFTR mutation rather than a polymorphism and it should be analysed in each CBAVD patient. Men with CBAVD often have mild clinical stigmata of CF (e.g., history of chest infections). When a man has CBAVD, it is important to test his partner for CF mutations. If the female partner is found to be a carrier of CFTR mutations, the couple must consider carefully whether to proceed with ICSI, as the risk of having a child with CF or CBAVD will be 50%, depending on the type of mutations carried by the parents. If the female partner is negative for known mutations, the risk of being a carrier of unknown mutations is ~0.4% [1621].

11.3.5.2.1 Unilateral or bilateral absence/abnormality of the vas and renal anomalies

Congenital unilateral absence of the vas deferens (CUAVD) is usually associated with ipsilateral absence of the kidney and probably has a different genetic causation [1622]. Cystic fibrosis transmembrane conductance regulator gene mutation screening is indicated in men with unilateral absence of the vas deferens with normal kidneys. The prevalence of renal anomalies is rare for patients who have CBAVD and CFTR mutations [1623]. Abdominal US should be undertaken both in unilateral and bilateral absence of vas deferens without CFTR mutations. Findings may range from CUAVD with ipsilateral absence of the kidney, to bilateral vessel and renal abnormalities, such as pelvic kidney [1624].