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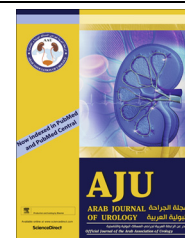
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# Chromosomal abnormalities in infertile men with azoospermia and severe oligozoospermia in Qatar and their association with sperm retrieval intracytoplasmic sperm injection outcomes

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## KEYWORDS

Genetics;  
Male infertility;  
Azoospermia;  
Oligozoospermia;  
Karyotype

## ABBREVIATIONS

AZF, azoospermia factor;  
ICSI, intracytoplasmic sperm injection;

**Abstract Objective:** To study the types and incidence of chromosomal abnormalities in infertile men with azoospermia and severe oligozoospermia in Qatar, and to compare the hormonal changes, testicular sperm retrieval rate, and intracytoplasmic sperm injection (ICSI) outcome between patients with chromosomal abnormalities and patients with idiopathic infertility.

**Patients and methods:** This study involved the retrospective chart review of 625 infertile male patients attending an academic tertiary medical centre in Qatar. Retrieved information included data on medical history, family history, clinical examination, semen analysis, initial hormonal profiles, and genetic studies, ICSI, and sperm retrieval results.

**Results:** The incidence of chromosomal abnormalities was 9.59% (10.6% amongst Qatari patients, 9.04% amongst non-Qataris). About 63.6% of the sample had azoospermia, of whom 10.8% had chromosomal abnormalities. Roughly 36.4%

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KS, Klinefelter syndrome;  
 MENA, Middle East and North Africa region;  
 SSR, surgical sperm retrieval;  
 TESE, testicular sperm extraction;  
 YCMD, Y chromosome microdeletions

of the sample had oligozoospermia, of whom 7.5% had chromosomal abnormalities. There were no differences between patients with chromosomal abnormalities and those with idiopathic infertility for demographic and infertility features; but for the hormonal profiles, patients with idiopathic infertility had significantly lower luteinising hormone and follicle-stimulating hormone values. For ICSI outcomes, patients with chromosomal abnormalities had a significantly lower total sperm retrieval rate (47.4% vs 65.8%), surgical sperm retrieval rate (41.2% vs 58.1%), and lower clinical pregnancy rate (16.7% vs 26.6%) when compared to the idiopathic infertility group.

**Conclusion:** The incidence of chromosomal abnormalities in Qatar as a cause of severe male infertility is within a similar range as their prevalence internationally.

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## Introduction

Infertility, defined as the inability to conceive after at least 1 year of regular unprotected intercourse, is a major health challenge affecting > 186 million couples worldwide [1]. In the USA, 10–15% of couples attempting to conceive are infertile, with male factors contributing to ~50% of such cases [2]. Amongst the several causes of male factor infertility, genetic causes play an important role with a reported incidence of 2–8% in infertile men, increasing to ~19% in men with azoospermia [3].

Chromosomal abnormalities are mainly found in cases of severe testicular impairment: azoospermia and severe oligozoospermia. Such abnormalities can be numerical and/or structural. The most common numerical genetic abnormality is Klinefelter syndrome (KS), with 5% and 10% prevalence in men with severe oligozoospermia and azoospermia, respectively [4]. It is characterised by the presence of an extra X chromosome leading to severe testicular dysfunction, failure of spermatogenesis, and hypergonadotrophic hypogonadism. Structural genetic abnormalities include chromosomal translocations (Robertsonian or reciprocal), inversions, and Y chromosome microdeletions (YCMD).

The study of the genetics of male infertility became more important in the past few decades with the advent of intracytoplasmic sperm injection (ICSI) in 1992. Infertile patients with severe oligo/azoospermia became capable of fathering their biological children [5]. However, using ICSI in this group of patients with a high genetic abnormality ratio could lead to increased risk of inheritance of genetic disorders to offspring, or the evolution of novel genetic disorders [5]. In addition, such chromosomal abnormalities may adversely affect the outcome of pregnancy, with a higher incidence of spontaneous abortion than amongst men with normal genetic assays [6]. Patient counselling, together with the possibility of using pre-implantation genetic diagnosis prior to ICSI should be offered to infertile patients with chromosomal abnormalities.

The literature on genetic causes of male factor infertility reveals several gaps, and our understanding of this issue remains limited [7]. Generally, there are few studies with a primary focus on the association of hormonal profile changes in infertile men with chromosomal abnormalities [8]. In addition, there is a noticeable lack of research of the chromosomal abnormalities in male infertility in the Middle East and North Africa region (MENA), with some rare exceptions in some countries of Northern Africa e.g. Morocco, Tunisia, and Jordan [9,10], but with no studies from Arabian Gulf area. This is despite that the MENA exhibits a unique social portfolio characterised by a high prevalence of consanguineous marriages amongst their populations, commonly driven by ethnic or tribal considerations [11]. In some countries, up to two-thirds of marriages are between cousins, causing an increase in the incidence of recessive disorders [12]. Indeed, high consanguinity rates along with their role in the occurrence of genetic diseases are witnessed across the MENA. For instance, amongst Palestinian Arabs, 44.3% of marriages are between relatives (22.6% between first cousins) [13]; in Morocco, the consanguinity prevalence was 15.25% [14]; and, in Jordan about 20–30% of all marriages were between first cousins [15].

Moreover, the young age of consanguineous marriage seen in these countries increases the risk of chromosomal disorders [1–3]. The State of Qatar, in many aspects, is characteristic of the MENA in terms of the high preference for consanguineous unions (51%), and first-cousin marriages comprise 26.7% of all marriages [16]. Such high ‘inbreeding’ could ultimately lead to an increase in homozygous recessive disorders, both known and novel, affecting some reproductive and developmental health parameters, and consequently resulting in infertility related disorders [17].

Therefore, to bridge this knowledge gap, the present study of infertile male patients attending an academic tertiary medical centre in Qatar, assessed:

- (i) the types and incidence of chromosomal abnormalities (across patients with azoospermia and severe oligozoospermia, and by nationality);
- (ii) a range of demographic (age, spouse age), infertility (type, duration), and hormonal (oestradiol, LH, FSH, prolactin, testosterone) profiles of infertile patients in association with chromosomal abnormalities compared with those with idiopathic infertility;
- (iii) Sperm retrieval rate (across whole sample and by genetic abnormality); and
- (iv) ICSI outcomes amongst patients with chromosomal abnormalities and those with idiopathic infertility

To the best of our knowledge, this is the first study in Qatar and across the Arabian Gulf region, and one of the very few in the MENA to conduct such a detailed genetic, hormonal, sperm retrieval and ICSI outcomes undertaking.

## Patients and methods

### *Ethics, sample and procedures*

This retrospective chart review was undertaken at the Male Infertility Unit of the largest tertiary hospital in Qatar, where we searched, retrieved and reviewed the medical records of all patients attending the Unit between January 2008 and January 2012. The study was approved by the Institutional Review Board (Protocol #11,251/11). Inclusion criteria included male infertile patients who had semen analysis showing azoospermia or severe oligozoospermia ( $< 5 \times 10^6$  sperm/mL), and who had performed genetic studies (karyotyping and YCMD assay). Out of the 625 records reviewed, 511 patients met the inclusion criteria. The clinical data collected from the medical records included medical history, family history, and clinical examination. In addition, semen analysis information, initial hormonal profiles, findings of the genetic studies, ICSI data, and sperm retrieval results were also noted.

### *Semen analysis and hormonal profile*

Semen analysis was undertaken according to fifth edition of WHO manual for examination and processing of human semen 2010 [18]. Each patient's baseline hormonal profile (i.e. before receiving any treatment) was documented, including FSH (1–19 IU/L), LH (1–9 IU/L), prolactin (73–407 mIU/L), total testosterone (10.4–35 nmol/L), and oestradiol (73–275 pmol/L).

### *Genetic investigations*

Cytogenetic investigations were performed on the patient's chromosomes obtained from peripheral blood lymphocytes, which were cultured in Roswell Park Memorial Institute (RPMI) medium 1640 (Gibco, Invit-

rogen Carlsbad, CA, USA), phytohemagglutinin (Shanghai Yihua Medical Technology Co., Ltd., Shanghai, China), and foetal bovine serum (Beijing Dingguo Biotechnology, Beijing, China) for 72 h, followed by treatment with 50 µg/mL colcemid. Metaphase chromosome spreads were studied by standard GTG and CBG banding procedures, which included using trypsin and Giemsa for G-banding and barium hydroxide for C-banding. FISH was performed on 30 metaphase chromosome spreads using a mixture of probes specific for X centromere  $\alpha$ -satellite (DXZ1) and Y centromere  $\alpha$ -satellite (DYZ3; CSP X spectrum green and CSP Y spectrum red; Beijing GP Medical Technologies, Beijing, China), and a chromosome-specific probe for core-binding factor  $\beta$  subunit (CBFB, GLP 16 banding at 16q22, spectrum red; Beijing GP Medical Technologies). Multiplex PCR amplification of nine sequence-tagged site markers was used to detect azoospermia factor (AZF) region for YCMD [19].

### *Statistical analysis*

Statistical analyses were undertaken using the Statistical Package for the Social Sciences (SPSS® version 19.0; IBM Corp., Armonk, NY, USA), with significance set at  $P < 0.05$ . Descriptive statistics (frequencies and percentages) were used to summarise the patients' demographic and clinical characteristics. The paired *t*-test compared means of all quantitative variables measured between the two studied groups (patients with idiopathic infertility and patients with chromosomal abnormalities). For categorical variables, the chi-squared test examined the associations between the different parameters with the outcome. In cases where the assumptions of the parametric test were not fulfilled, then either suitable data transformation or the corresponding non-parametric test was used to assess the impact of different factors on outcome.

## Results

The sample comprised 511 patients, of which 179 (35.03%) patients were Qatari nationals, and the remaining 332 (64.97%) patients were of other nationalities (Arab and non-Arab countries). Azoospermia was diagnosed in 325 patients (63.6%), and severe oligozoospermia in 186 patients (36.4%). Based on the genetic findings, patients were categorised into two groups: those with chromosomal abnormalities and those with idiopathic infertility.

Across the whole sample, the incidence of chromosomal abnormalities was 9.59% (49/511 patients). Of the 179 Qatari patients, the incidence of chromosomal abnormalities was 10.6% (19/179 patients), whilst the incidence of chromosomal abnormalities amongst non-Qatari patients was 9.04% (30/332 patients). Chromosomal

abnormalities were found in 10.78% of the azoospermia group (35/325 patients) compared to 7.5% of the oligozoospermia group (14/186 patients).

Table 1 depicts the frequencies of each chromosomal abnormality in each of the azoospermia and severe oligozoospermia groups, as well as amongst Qatari and non-Qatari patients. Across the whole sample, for azoospermia patients, KF was the most common chromosomal abnormality followed by YCMD. For the severe oligozoospermia group, YCMD was the most common chromosomal abnormality followed by Robertsonian translocations. By nationality, generally, Qatari nationals exhibited a higher prevalence of KF (amongst the azoospermia group) and YCMD (amongst the severe oligozoospermia group) than non-Qataris. Table 2 shows the detailed chromosomal abnormalities of the patients.

Table 3 shows the characteristics of patients with chromosomal abnormalities vs those with idiopathic infertility across the whole sample and amongst the oligozoospermia patients. For the total sample, there were no differences between patients with chromosomal abnormalities and those with idiopathic infertility for demographic and infertility features. However, when comparing the hormonal profiles, patients with idiopathic infertility had significantly higher oestradiol and significantly lower LH and FSH values.

Table 4 shows the ICSI outcomes amongst patients with chromosomal abnormalities and patients with idiopathic infertility. Only 38 of the 49 patients with chromosomal abnormalities underwent a trial of ICSI. Sperm were successfully retrieved in 18 patients [four cases from semen; 14 cases from testis (14/34 patients, surgical sperm retrieval (SSR) rate = 41.2%)]. Of the 462 patients with idiopathic infertility, 234 patients underwent ICSI trial. Sperm was successfully retrieved in 154 patients [43casesfromsemen;111casesfromtestis(111/191patients,SSRrate = 58.1%)]. The chromosomal abnormalities group had a significantly lower total sperm retrieval rate (47.4% vs 65.8%), SSR rate (41.2% vs 58.1%), and lower clinical pregnancy rate (16.7% vs 26.6%) when compared to the idiopathic infertility group. All three clinical pregnancies reported in the chromosomal abnormalities group were amongst

**Table 2** Chromosomal abnormalities detected across the whole sample.

| Genetic abnormality                | Description  | Patients, <i>n</i> |
|------------------------------------|--|--------------------|
| Chromosomal KS                     | 47 XXY (non-mosaic)  | 19                 |
| Robertsonian translocation         | 45XY, der(14;15)(q10;q10); 45XY, der(14;21)(q10;q10)<br>45XY, der(13;14)(q10;q10); 45XY, der(13;14)(q10;q10)<br>45XY, der(15;21)(q10;q10); 45XY, der(13;14)(q10;q10) | 6                  |
| Reciprocal translocation           | 46XY, t(11;19)(p10;p10); 46XY, t(5;6)(p10;q10); 46XY, t(2;9)(p21;p22)<br>46XY, t(2;4)(P11.2;q31.3); 46XY, t(Y;10)(q11.2; q24);<br>46XY, t(11;22)(p10;q10)            | 6                  |
| Other (sex chromosome aberrations) | 45XO/46XY; MOS 47XY (Marker 11)/ 46XY (Marker 10)<br>46XX (X-Y translocation); mos 45X[7]/ 46XY[43]<br>46XY, Inv(9)(p13;q21.1)                                       | 5                  |
| YCMD                               | AZFb and c microdeletion<br>AZFa microdeletion<br>AZFc microdeletion<br>Total YCMD   | 5<br>1<br>7<br>13  |

patients with KS. Table 5 shows the sperm retrieval rate for each genetic abnormality.

## Discussion

We assessed the types and incidence of chromosomal abnormalities amongst infertile men presenting to the largest tertiary medical centre in Qatar, and explored the outcomes of ICSI in these abnormalities. Overall, 9.59% of our present sample had a chromosomal abnormality. A significantly lower sperm retrieval rate and ICSI pregnancy outcomes were seen amongst our infertile patients with chromosomal abnormalities than amongst our patients with idiopathic infertility.

Numerous chromosomal abnormalities exist, where about one in 150 babies is born with a numerical or

**Table 1** Chromosomal abnormalities amongst patients with azoospermia and severe oligozoospermia.

| Abnormality                     | Azoospermia, <i>n</i>    |                              |                         | Severe oligozoospermia, <i>n</i> |                              |                         |
|---------------------------------|--------------------------|------------------------------|-------------------------|----------------------------------|------------------------------|-------------------------|
|                                 | Qatari<br><i>n</i> = 119 | Non-Qatari<br><i>n</i> = 206 | Total<br><i>n</i> = 325 | Qatari<br><i>n</i> = 60          | Non-Qatari<br><i>n</i> = 126 | Total<br><i>n</i> = 186 |
| KS                              | 12                       | 6                            | 18                      | 1                                | 0                            | 1                       |
| Robertsonian translocation      | 1                        | 2                            | 3                       | 0                                | 3                            | 3                       |
| Reciprocal translocation        | 1                        | 3                            | 4                       | 1                                | 1                            | 2                       |
| YCMD                            | 2                        | 5                            | 7                       | 0                                | 6                            | 6                       |
| Other chromosomal abnormalities | 0                        | 3                            | 3                       | 1                                | 1                            | 2                       |
| Total (%)                       | 16 (13.5)                | 19 (9.2)                     | 35(10.7)                | 3 (5)                            | 11 (8.7)                     | 14 (7.5)                |



**Table 3** Characteristics of infertile patients with chromosomal abnormalities and idiopathic infertility.

| Variable                            | Infertile patients        |                        | P     |
|-------------------------------------|---------------------------|------------------------|-------|
|                                     | Chromosomal abnormalities | Idiopathic infertility |       |
| Total sample, <i>n</i>              | 49                        | 462                    |       |
| Demography, mean (SD)               |                           |                        |       |
| Age, years                          | 34.5 (9.5)                | 35.5 (8.2)             | 0.24  |
| Wife's age, years                   | 28.3 (6.5)                | 28.6 (6.3)             | 0.43  |
| Infertility features                |                           |                        |       |
| Type, <i>n</i>                      |                           |                        |       |
| Primary                             | 47                        | 411                    |       |
| Secondary                           | 2                         | 51                     |       |
| Duration, years, mean (SD)          | 5.4 (4.8)                 | 5.6 (5.7)              | 0.56  |
| Baseline hormone profile, mean (SD) |                           |                        |       |
| Oestradiol, pmol/L                  | 96 (45.2)                 | 152.6 (740.1)          | 0.001 |
| LH, IU/L                            | 9.6 (7.3)                 | 5.7 (5.8)              | 0.001 |
| FSH, IU/L                           | 16.1 (12.8)               | 9.7 (9.5)              | 0.001 |
| Prolactin, mIU/L                    | 341.5 (195.3)             | 277.3 (170.5)          | 0.5   |
| Testosterone, nmol/L                | 11.02 (5.97)              | 15.55 (7.98)           | 0.11  |
| Oligozoospermia group, mean (SD)    |                           |                        |       |
| Sperm count, million/mL             | 0.38 (1.1)                | 0.88 (1.8)             | 0.12  |
| Total sperm motility, %             | 5.7 (3.8)                 | 3.8 (2.8)              | 0.1   |

structural chromosomal abnormality [20]. Whilst most abnormalities are detected early in life due to apparent phenotypic anomalies, a good percentage may not impact the patients' health, particularly when no genetic material is missing or duplicated. In such cases, the indolent effect of the genetic aberration may be detected later in life. Male infertility is one such example, where the effect of inherent chromosomal anomalies cannot be known prior to adulthood. Epidemiological studies have reported an inverse relationship between the incidence of chromosomal abnormalities and the severity of male infertility, with rates reaching up to 19% in infertile men with azoospermia [3]. In the present study, the percentage of chromosomal abnormalities amongst infertile men with severe oligozoospermia and azoospermia was 7.5% and 10.7%, respectively. The most frequent chromosomal anomalies we observed were sex chromosome abnormalities, where KS was most frequent (3.7%), followed by YCMD (2.5%), and then autosomal translocations (2.3%).

Our present observed incidence of chromosomal abnormalities falls within previously conveyed rates

from the region. A study in Morocco evaluated 444 azoospermic and 129 oligozoospermic men for the presence of chromosomal abnormalities to report an overall incidence of 10.5%, where 41 (7.1%) patients had KS, 16 (2.7%) had YCMD, and four (0.7%) had autosomal abnormalities [9]. Likewise, in Tunisia (401 infertile men with non-obstructive azoospermia), the overall incidence of chromosomal abnormalities was 12.22% [10]; and in Iran (222 men with infertility) the incidence of chromosomal abnormalities was 13.9% [21].

Chromosomal abnormalities contribute to infertility by influencing a variety of physiological processes including hormonal homeostasis, spermatogenesis, and sperm quality. Therefore, an understanding of the genetic basis of reproductive failure is essential to not only understand the possible cause of infertility, but to also appropriately manage an infertile couple.

A variable degree of hypothalamic–pituitary–gonadal axis disruption can be expected to occur with chromosomal abnormalities. KS represents a typical example of hypergonadotrophic hypogonadism that occurs secondary to testicular failure; Kallmann syndrome, on

**Table 4** ICSI outcomes amongst infertile patients with chromosomal abnormalities and those with idiopathic infertility.

| Parameter                  | Total, <i>n/N</i> (%)<br><i>N</i> = 272 | Infertile patients, <i>n/N</i> (%)         |  | P      |
|----------------------------|---|--|--|--------|
|                            |   | Chromosomal abnormalities<br><i>n</i> = 38 | Idiopathic infertility<br><i>n</i> = 234 |        |
| Sperm retrieved from semen | 47                                      | 4  | 43                                       |        |
| SSR                        | 125/225 (55.5)                          | 14/34 (41.2)                               | 111/191 (58.1)                           | 0.023* |
| Total sperm retrieval      | 172/272 (63.2)                          | 18/38 (47.4)                               | 154/234 (65.8)                           | 0.001* |
| Pregnancy outcome          | 44/171 (25.7)                           | 3/18 (16.7)                                | 41/154 (26.6)                            | 0.001* |

\**P* < 0.05.

**Table 5** Sperm retrieval rate in different chromosomal abnormalities.

| Genetic abnormality                   | Patients who underwent ICSI, <i>n</i> | Sperm retrieved      |                        |
|---------------------------------------|---------------------------------------|----------------------|------------------------|
|                                       |                                       | from semen, <i>n</i> | by SSR, <i>n/N</i> (%) |
| KS                                    | 19                                    | 0                    | 6/19 (31.6)            |
| Translocation                         |                                       |                      |                        |
| Robertsonian                          | 4                                     | 2                    | 1/2                    |
| Reciprocal                            | 5                                     | 0                    | 4/5                    |
| Others                                |                                       |                      |                        |
| Mos 45X [7]/46XY [43]                 | 1                                     | 0                    | 1/1                    |
| MOS 47XY (Marker 11)/46XY (Marker 10) | 1                                     | 0                    | 0                      |
| 46XY, Inv(9)(p13; q21.1)              | 1                                     | 0                    | 0                      |
| YCMD                                  |                                       |                      |                        |
| Absent B and C                        | 2                                     | 0                    | 0                      |
| Absent C                              | 5                                     | 2                    | 2/3                    |

the other hand, impairs gonadotrophin secretion resulting in a state of hypogonadotrophic hypogonadism [22]. Few studies have assessed the hormone status of infertile men with chromosomal abnormalities. Our present study found significantly higher FSH, LH, and oestradiol levels amongst infertile patients with chromosomal abnormalities in comparison to those with idiopathic infertility; and whilst the serum testosterone level was lower in men with chromosomal abnormalities, the difference did not reach statistical significance. In agreement with our present findings, a study of the influence of chromosomal abnormalities on reproductive hormone levels (691 infertile vs 78 fertile men) by Elfateh et al. [8] reported chromosomal abnormalities amongst 83 men (12.01%) in the infertile group. The authors also found significantly lower testosterone levels and testosterone/LH levels amongst infertile patients with chromosomal abnormalities compared with fertile men ( $P < 0.001$  for all) [8]. Moreover, significantly higher FSH and LH levels were detected in men with KS (both  $P = 0.001$ ), Robertsonian translocations ( $P = 0.08$  and  $P = 0.007$ ), chromosome polymorphisms ( $P = 0.001$  and  $P = 0.002$ ) and YCMD (both  $P < 0.001$ ); whilst patients with reciprocal translocations had only significantly higher LH levels ( $P = 0.03$ ) [8]. Others compared the hormone levels of 33 infertile men with chromosomal abnormalities and 139 infertile men with no known chromosomal abnormalities, and detected significantly higher FSH and LH levels (both  $P < 0.001$ ), and significantly lower testosterone levels ( $P = 0.004$ ) amongst the infertile men with chromosomal abnormalities [23].

The advent of ICSI emphasises the need to acknowledge the role of genetics in male factor infertility because it enables men with sub-optimal sperm quality to overcome natural selection mechanisms and produce a viable zygote [4]. Nonetheless, the frequencies of mutations that may be inherited through these procedures and their impact on future generations are not yet fully understood. Furthermore, chromosomal abnormalities may in fact offer prognostic information on the sperm

retrieval rates of men undergoing testicular sperm extraction (TESE) and their ICSI outcomes [24,25]. In agreement with such findings, our present study found significantly lower sperm retrieval rate amongst infertile patients with abnormal genetics compared to those with normal genetics.

The Y chromosome contains many genes that are critical for spermatogenesis and development of male gonads, and YCMD are major causes of severe male factor infertility [26]. A particular area of interest on the Y chromosome is the AZF region. Molecular mapping analyses of patients with YCMD revealed three non-overlapping regions of the Y chromosome (AZFa, AZFb, and AZFc), and their deletion significantly alters spermatogenesis causing primary testicular insufficiency [27]. About 60% of YCMD occur in AZFc, 15% occur in AZFb, and 5% in AZFa. The other 20% involve more than one AZF region [28]. AZFa, AZFb or AZFa/b microdeletions are associated with the worst prognosis for sperm retrieval. Although previously sperm retrieval in AZFa and b cases were thought to be deemed to failure [29], recent studies have reported sperm recovery from a few such cases [30]; whereas patients with AZFc and AZFb/c microdeletions have a SSR rate of 54.8% and 7.1%, respectively [29]. Moreover, AZFc patients are not necessarily azoospermic, and may be candidates for ICSI using sperm from their ejaculate. In the present study, no sperm could be retrieved from cases with combined AZFb and c deletions. Of our five AZFc deletion patients who underwent ICSI, two provided sperm from ejaculate and three underwent SSR, with a sperm retrieval rate of two out of three.

KS is the most common chromosomal abnormality occurring in about one in 580 newborn males, and has non-mosaic (47, XXY) and mosaic (47, XXY/ 46, XY) forms. Although previously believed to be sterile, 8.3% of patients with KS have sperm in their ejaculate [31]. Whilst spontaneous pregnancy has been reported in extremely rare occasions of KS, ICSI is perhaps the more realistic approach through which pregnancy might

be achieved. Few cases of successful pregnancies have been reported after ICSI with ejaculated sperm from patients with KS [24]. Despite this, most patients present with azoospermia and would require a sperm retrieval procedure before ICSI. TESE use in patients with KS yielded encouraging results with a sperm retrieval rate ranging from 30% to 70% [19]. Almost half of all published cases of patients with KS in whom TESE and ICSI were performed achieved pregnancy and live births [32]. Most of our present patients with KS (94.7%) presented with azoospermia and all of them required TESE, where sperm were retrieved from 31.6% of patients undergoing microsurgical TESE. Pregnancy was achieved in half of the TESE-positive cases (three of six).

Chromosomal translocations occur in 0.08–0.3% of the general population [33], and involve the transfer of genetic material from one chromosome to another. This can happen due to breakage of two non-homologous chromosomes with exchange of segments (reciprocal), or due to breakpoints occurring close to the centromere of two acrocentric chromosomes (Robertsonian). The translocations can result in a variety of sperm production phenotypes from normal spermatogenesis to an inability to produce spermatogonia [4]. Many of these translocations are identified after recurrent spontaneous abortions following ICSI [25]. In all, 12 of our present infertile patients had chromosomal translocation, and sperm was found in the ejaculate of two patients, whilst we performed SSR for seven patients. The sperm were retrieved in one of two patients with Robertsonian translocations and four of five with reciprocal translocations.

In the present study, of our 47 patients who had ICSI, pregnancy was achieved in 25.7%. Both total sperm retrieval rate and pregnancy outcome were significantly lower amongst our infertile patients with chromosomal abnormalities in comparison to those with idiopathic infertility. This observation, which is in agreement with a number of studies [34], can be explained by the higher rate of sperm aneuploidy often found with such chromosomal abnormalities resulting in worse embryo quality, implantation failure, and recurrent pregnancy loss [34]. Furthermore, the higher risk of transmission of reduced fertility due to chromosomal abnormalities to the offspring necessitates thorough patient counselling and use of pre-implantation genetic diagnosis prior to ICSI.

A limitation of the present research is that it is a single fertility centre study, although single centre studies are not uncommon in the literature [10,19–21]. However, our institution is the main male fertility unit in Qatar (a country with small population) and covers >80% of all infertility cases across the country. The present study's retrospective nature has the attending limitation of incomplete data; however, retrospective studies are also not uncommon in this type of research [8,9]. Nevertheless, our hospital has a well updated

patient database that restricts and minimises the possibility of incomplete data. Another limitation of the present study is that next generation DNA sequencing was not used to detect other genetic mutations that could not be detected by karyotyping or PCR; however, this technology is still new and is basically used for research and its incorporation in the clinical practice has not yet been globalised.

## Conclusion

The incidence of chromosomal abnormalities as a cause of severe male infertility in the State of Qatar, as an example of Eastern Mediterranean countries, is within a similar range as their incidence internationally. Chromosomal abnormalities affect the hormonal status of the patients, with significant increases in the FSH and LH levels, endowing more deleterious effects on spermatogenesis, which was reflected by the lower sperm retrieval rate and clinical pregnancy rates reported in patients with chromosomal abnormalities compared to patients with idiopathic infertility. Therefore, the negative prognostic effects of chromosomal abnormalities on sperm retrieval rate and ICSI outcomes should be clearly explained to these patients during counselling for *in vitro* fertilisation treatment. Future studies are definitely required to identify any new genetic abnormalities and assist in deeper understandings of the causes of male infertility. Higher rates of genetic abnormalities may be found by searching for different genetic causes, e.g. point mutations (single nucleotide substitutions), and smaller deletions and duplications, which currently fall below the threshold of detection of karyotyping.

## Conflict of interest

None of the authors have any conflict of interest to declare.

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