Introduction: Infertility resulting in humans has evoked considerable legal, medical and social interests. Infertility remains a major public health problem. Epidemiological studies reveal that genetic and environmental factors are responsible for infertility. As an estimate nearly 15-20% of couples have difficulty or is unable to conceive. Infertility is multifactorial but primarily it is because of male factor, female factor or a combination of both. Infertility can be hormonal, related to age, obesity, and infectious diseases, psychological or genetic. The genetic causes of infertility can be Y chromosome deletion, single gene disorder, multifactorial causes and chromosomal abnormalities. The incidence of autosomal chromosome abnormalities is 1.1 to 7.2% in infertile men, about 3% in the azoospermia group and up to 10.2% in the oligozoospermia group. Genetic research on infertility aims to correlating clinical consequences and genotype.

Key words: azoospermia, chromosomal aberrations, cytogenetics, infertility, syndromes, Y chromosome microdeletion.

I.  Introduction:

Infertility is the most significant human health problem of the reproductive years. Infertility is described as failure to conceive after one year of unprotected intercourse. The World Health Organization has described “infertility” as a health problem of global concern, one in seven couples experience infertility. Shah et al. have also reported that one in every six couples wishing to start a family fall into this category. The prevalence of infertility is reported to be 10-15% worldwide. It is estimated that infertility affects nearly 50 to 80 million people around the world. Currently 8-10 million infertile couples are estimated to be in India. The recent National Family Health Survey estimated childlessness as 2.4% of currently married women over 40 years of age in India.

Primary and secondary infertility rates have been reported as 3% and 8%, respectively. A village level study conducted in the state of Maharashtra, India revealed infertility in the range between 6 to 7 per cent. In other states such of Haryana, Rajasthan, Madhya Pradesh, Punjab, Karnataka, Arunachal Pradesh and Tamilnadu have 2.25%, 3.57%, 4.23%, 4.93%, 6.73%, 8% and 10.2% childless couples respectively. In the same study, 6% of male infertility and 14% of ovarian failure have been reported due to chromosomal abnormalities.

Infertility is multifactorial, but mainly it is because of male or female factors or a combination of both. Infertility can be hormonal, related to age, exercise, obesity or infectious diseases. It can be immunological, psychological, result from surgery or blockage or may be associated with defined abnormalities in the gametes. The most common causes of infertility are simply “unexplained” and these account for about 20% of such couples.

II.  Chromosomal Abnormalities:

The chromosomal abnormalities found in infertile couples are numerical or structural. Gianotten et al., reported that over 4,000 genes are involved in the control of human spermatogenesis.

I. Numerical abnormalities

1) Klinefelter’s syndrome (47, XXY): Klinefelter’s syndrome is found in approximately 1 in 1,000 males and due to non-disjunction of the X chromosome during meiosis. This syndrome is generally associated with the karyotype 47, XXY, which can be in all cells or in mosaic form. There are various extents of spermatogenetic failure, but males are generally sterile.

The gonadal defect in XXY male seems to be related to germ cell survival and sex chromosome constitution. It is through that the testicular atrophy seen in patients with Klinefelter’s syndrome is due to failure of the germ cells, containing two X chromosomes (instead of one) to survive. Beside this, the spermatogonomic picture of XXY men shows a great diversity, ranging from severe impairment to apparent normalcy. Other sexual numerical changes mainly involved other types of Klinefelter mosaics (45 X/47, XXY; 46, XY/47, XXY/48, XXXY) and 47, XYY males. These changes were seen in azoospermic and oligozoospermic males.
2) 47, XYY males: 47, XYY syndrome is found in approximately one in 1,000 male births. This syndrome arises due to non disjunction of the Y chromosome in paternal meiotic II. In 47, XYY male causes an aberrant hormonal balance in the gonadal environment which affects the normal function of human chorionic gonadotrophin. Inclusion of extra sex chromosome (47, XYY) has been reported by May et al., Hassold et al. and Jacobs et al.17,18,19.

3) Turner syndrome: A loss of X chromosome (45, X) is the characteristic karyotype of Turner syndrome. Frequency of Turner syndrome is one in 5,000 to one in 10,00020. Loss of chromosomes (X) resulting in numerical changes may be due to non-disjunction of chromosomes during gametogenesis. Due to non disjunction there is a possibility that a particular pair of chromosomes is transmitted to a gamete or it may be lost. There can be error in the gametogenesis due to the accumulation of mutations which might have taken place during the life span of an individual. These mutations are likely to be more in persons with advanced age.

4) 47, XXX: The frequency of 47, XXX is one in 1,000 females and 95% of cases the extra X chromosome is maternal origin. Most these females are normal height, weight and mental function and fertile but have an early onset of menopause at about age of 30 years compared with the average of about age of 50 years.17

5) Down syndrome (Trisomy 21): Trisomy 21 is the most common cause of mental retardation, sexual dysfunction in humans. Affected females in rare cases can reproduce, however, most if not all, affected males are sterile, and the phenotype included spermatogenic arrest, reduction in the number of germ cells and bronchial tubes.21

II) Structural abnormalities:
1) Translocation: Robertsonian translocations are among the foremost common balanced structural rearrangements seen within the general population with a frequency in newborn surveys of regarding one in 1,000.22 Tharapel et al. reported that an approximately seven fold excess of Robertsonian heterozygotes in infertile couples23. In autosome-autosome translocation, reduce fertility is mediated by the fact that the translocated chromosomes, in order to progress through meiosis, need to synapse through a pairing crossing.24,25

The most common Robertsonian translocation observed in infertile males is t(13q14q). Meiotic studies of infertile carriers of t (13q14q) and t (14;21) reveal abnormal behavior of the rearranged autosomes in meiosis during spermatogenesis causing infertility.3,26

2) Inversion: An inversion happens when a solitary chromosome experiences two breaks and is reconstituted with the fragment between the breaks inverted. The result of inversion is for the offspring, a carrier of either kind of inversion is at risk of producing abnormal gamete. The most widely recognized reversal is 46, XY, inv (9) (p11q13) in oligozoospermic infertile male. Nemeth et al. reported an infertile man with a Klinefelter like phenotype having an X inversion with 46,Y,inv(X) (q12q25).27

Dar et al. reported that a woman had dysgenesis with primary amenorrhea and she had a de novo inv (X) (q13 q24).28 Pericentric inversion of chromosome 1, 3, 5, 6 and 10 are related to abnormal sperm production in infertile men.

3. Marker chromosome: Marker chromosome is very small, unidentified chromosome. Marker chromosomes are additional chromosomes that are not effectively recognized by typical cytogenetic methods. Marker chromosome is occasionally seen in chromosome preparation, frequently in a mosaic state. Chromosome banding it is difficult to characterize marker chromosome. Carriers of marker chromosomes are at risk of infertility because of meiotic arrest and instability.29

Table 1: Cytogenetic studies in different infertile couples.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Author</th>
<th>Year</th>
<th>Male Karyotype</th>
<th>Female Karyotype</th>
<th>Abnormal karyotype in males (%)</th>
<th>Abnormal karyotype in females (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Hens et al.20</td>
<td>1988</td>
<td>500</td>
<td>500</td>
<td>0.8</td>
<td>1.8</td>
</tr>
<tr>
<td>2.</td>
<td>Lange et al.31</td>
<td>1990</td>
<td>72</td>
<td>72</td>
<td>2.8</td>
<td>15.3</td>
</tr>
<tr>
<td>3.</td>
<td>Baschatt et al.22</td>
<td>1996</td>
<td>32</td>
<td>--</td>
<td>6.2</td>
<td>--</td>
</tr>
<tr>
<td>4.</td>
<td>Peschka et al.24</td>
<td>1996</td>
<td>200</td>
<td>200</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>5.</td>
<td>Testart et al.32</td>
<td>1996</td>
<td>261</td>
<td>261</td>
<td>4.2</td>
<td>1.1</td>
</tr>
<tr>
<td>6.</td>
<td>Mau et al.25</td>
<td>1997</td>
<td>150</td>
<td>150</td>
<td>12.0</td>
<td>6.0</td>
</tr>
<tr>
<td>7.</td>
<td>Montag et al.33</td>
<td>1997</td>
<td>434</td>
<td>434</td>
<td>3.7</td>
<td>3.7</td>
</tr>
<tr>
<td>8.</td>
<td>Meschede et al.34</td>
<td>1998</td>
<td>432</td>
<td>436</td>
<td>2.1</td>
<td>5.5</td>
</tr>
<tr>
<td>9.</td>
<td>Scholtes et al.26</td>
<td>1998</td>
<td>1116</td>
<td>1164</td>
<td>4.5</td>
<td>9.8</td>
</tr>
<tr>
<td>10.</td>
<td>Van der Ven et al.35</td>
<td>1998</td>
<td>1792</td>
<td>--</td>
<td>4.0</td>
<td>--</td>
</tr>
<tr>
<td>11.</td>
<td>Peschka et al.24</td>
<td>1999</td>
<td>305</td>
<td>305</td>
<td>3.3</td>
<td>1.3</td>
</tr>
<tr>
<td>12.</td>
<td>Gekae et al.24</td>
<td>2001</td>
<td>781</td>
<td>781</td>
<td>2.6</td>
<td>5.8</td>
</tr>
</tbody>
</table>

www.iosrjournals.org
4. Microdeletion of Y chromosome:

The variation of Y chromosome size in human is well known and there have been studies on the correlation of Y chromosome size with mental state, behavioral disorders and miscarriage. Debraekeleer and Dao had reviewed several series reported on the type and the frequencies of chromosome abnormalities based on the type of male infertility problems. They also provided data on the relationship between meiotic abnormalities and male infertility. The underlying genetic basis of male infertility remains largely unknown. It has been reported that 13.7% of azoospermia males and 4.6% of severe oligozoospermic males have abnormal karyotype. Genes located on the long arm of Y chromosome of men are likely to be involved in the complex process of spermatogenesis.

Azoospermic factor (AZF) due to microdeletion of the long arm of the human Y chromosome involving three regions is associated with complete absence of spermatozoa or reduced sperm count.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Gene region</th>
<th>Candidate genes</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AZFa</td>
<td>USP9Y DBY</td>
<td>Absence of germ cells, aka sertoli cell only syndrome (SCOS)</td>
</tr>
<tr>
<td>2</td>
<td>AZFb</td>
<td>EIF1AY RBMY (RBMYA1)</td>
<td>Maturation arrest at spermatocyte stage</td>
</tr>
<tr>
<td>3</td>
<td>AZFc</td>
<td>DAZ CDY1 BPY2 PRY TTY2</td>
<td>Variable from SCOS to severe oligospermia</td>
</tr>
</tbody>
</table>

The frequency of Y chromosome structural rearrangements was found to be higher than the frequency observed in newborn series. Much has been said on the possible deleterious effects of short and long Y chromosome (Yq- and Yq+) but no definite conclusions were drawn. These rearrangements were preferentially seen in azoospermia and severe oligozoospermia (Sperm count <10x10^6/ml) exhibiting 1 and 0.6% respectively. A few cases of Y chromosome structural rearrangements involved failure of pairing between the X and Y chromosomes. These include a dicentric Y chromosome and a pericentric inversion of the Y chromosome. Several oligozoospermic males were found to have a deletion of the long arm of the Y chromosome.

The frequency of Y chromosome structural rearrangements was found to be higher than the frequency observed in newborn series. Much has been said on the possible deleterious effects of short and long Y chromosome (Yq- and Yq+) but no definite conclusions were drawn. These rearrangements were preferentially seen in azoospermia and severe oligozoospermia (Sperm count <10x10^6/ml) exhibiting 1 and 0.6% respectively. A few cases of Y chromosome structural rearrangements involved failure of pairing between the X and Y chromosomes. These include a dicentric Y chromosome and a pericentric inversion of the Y chromosome. Several oligozoospermic males were found to have a deletion of the long arm of the Y chromosome.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Author</th>
<th>Year</th>
<th>No. of patients</th>
<th>No. of deleted patients</th>
<th>Microdeletion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Tse et al.55</td>
<td>2000</td>
<td>58</td>
<td>4</td>
<td>6.90</td>
</tr>
<tr>
<td>2.</td>
<td>Tzschach et al.56</td>
<td>2001</td>
<td>97</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>3.</td>
<td>Peterlin et al.57</td>
<td>2002</td>
<td>226</td>
<td>10</td>
<td>4.42</td>
</tr>
<tr>
<td>4.</td>
<td>Deda et al.58</td>
<td>2003</td>
<td>83</td>
<td>8</td>
<td>9.64</td>
</tr>
<tr>
<td>5.</td>
<td>Athalye et al.59</td>
<td>2004</td>
<td>100</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>6.</td>
<td>Medica et al.60</td>
<td>2005</td>
<td>105</td>
<td>1</td>
<td>0.95</td>
</tr>
<tr>
<td>7.</td>
<td>Hsu et al.61</td>
<td>2006</td>
<td>460</td>
<td>24</td>
<td>5.22</td>
</tr>
<tr>
<td>8.</td>
<td>Mohammed et al.62</td>
<td>2007</td>
<td>266</td>
<td>7</td>
<td>2.63</td>
</tr>
<tr>
<td>9.</td>
<td>Balkan et al.63</td>
<td>2008</td>
<td>80</td>
<td>1</td>
<td>1.25</td>
</tr>
<tr>
<td>10.</td>
<td>Ceylan et al.64</td>
<td>2009</td>
<td>90</td>
<td>11</td>
<td>12.22</td>
</tr>
<tr>
<td>11.</td>
<td>Stahl et al.65</td>
<td>2010</td>
<td>1591</td>
<td>149</td>
<td>9.37</td>
</tr>
<tr>
<td>12.</td>
<td>Behulova et al.66</td>
<td>2011</td>
<td>226</td>
<td>8</td>
<td>3.54</td>
</tr>
<tr>
<td>13.</td>
<td>Kim et al.67</td>
<td>2012</td>
<td>1306</td>
<td>101</td>
<td>7.73</td>
</tr>
<tr>
<td>14.</td>
<td>Chellat et al.68</td>
<td>2013</td>
<td>80</td>
<td>1</td>
<td>1.25</td>
</tr>
<tr>
<td>15.</td>
<td>Omar et al.69</td>
<td>2014</td>
<td>36</td>
<td>3</td>
<td>8.33</td>
</tr>
<tr>
<td>16.</td>
<td>Yuanjuan et al.61</td>
<td>2014</td>
<td>1218</td>
<td>105</td>
<td>8.62</td>
</tr>
</tbody>
</table>

III. Syndromes

Many genetic syndromes associated with infertility in humans, such as Noonan syndrome, immotile cilia syndrome, Kallmann syndrome, Androgen insensitivity syndrome, polycystic kidney diseases, ushers syndrome etc.
Table IV: Some genetic syndromes associated with infertility.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Genetic syndrome</th>
<th>Incidence</th>
<th>Inheritance</th>
<th>Features</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Androgen insensitivity syndrome</td>
<td>1:60,000</td>
<td>X linked recessive syndrome</td>
<td>Mild spermatogenic defect, present at birth with ambiguous genitalia and signs of both male and female sexual development. Caused by mutations in AR gene</td>
<td>Patrizio and Broomfield</td>
</tr>
<tr>
<td>2.</td>
<td>Frasier syndrome and Denys-Drash syndrome</td>
<td>1:10,000</td>
<td>Autosomal dominant</td>
<td>Renal failure, Wilms’ tumor, hypertension, gonadal dysgenesis. Caused by mutation in the WT1 gene.</td>
<td>Swain and Lovell-Badge</td>
</tr>
<tr>
<td>3.</td>
<td>Kallmann syndrome</td>
<td>1:10,000 - 60,000</td>
<td>X linked, Autosomal dominant</td>
<td>Delayed or absent puberty and an impaired sense of smell. Caused by mutation in the KAL1G-1 gene.</td>
<td>Nudell and Turek</td>
</tr>
<tr>
<td>5.</td>
<td>Polycystic kidney disease</td>
<td>1:800</td>
<td>Autosomal dominant</td>
<td>Progressive cyst development and bilaterally enlarged kidneys with multiple cysts. Caused by mutations in the PKD1, PKD2 and PKHD1 genes.</td>
<td>Patrizio and Broomfield</td>
</tr>
<tr>
<td>6.</td>
<td>Ushers syndrome</td>
<td>1:30,000</td>
<td>Autosomal recessive</td>
<td>Combination of hearing loss and visual impairment, leading cause of deaf-blindness and degeneration of the sperm axoneme. Caused by mutations in the CDH23, MYO7A, PCDH15, USH1C, USH2A, GPR98 genes.</td>
<td>Patrizio and Broomfield</td>
</tr>
</tbody>
</table>

IV. Conclusions

Infertility is multi-factorial, but primarily it is because of male factors, female factors or a combination of both. Chromosomal anomalies in infertile subjects may be numerical and structural aberrations. Infertility resulting in men has evoked considerable legal, medical and social interests. Currently, the strongest known genetic marker for infertility leading to violent attitude in some men is the Y chromosome. Genetic research on this disorder aims at correlating phenotype and genotype. The elucidation of such correlations helps us to achieve a more thorough understanding of infertility in couples. The meaningful genotype-phenotype correlation can only image if sufficient attention is paid to sound documentation of the genotype and consequent clinical phenotype.

The underlying genetic basis of infertility remains largely unknown. Cytogenetic studies particularly on sex chromosome with special reference to Y chromosome in men are required to be explored.

References

The Cytogenetic Basis of Human Infertility: A Review


The Cytogenetic Basis of Human Infertility: A Review


