ORIGINAL RESEARCH PAPER

Volume-7 | Issue-3 | March-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

IMPACT OF AGE, CONSANGUINITY AND CHROMOSOMAL ABERRATIONS ON FERTILITY: REVIEW

Anatomy

Dr. Pankaj R. Wadekar*

Assistant Professor, Department of Anatomy, Government Medical College, Akola, Maharashtra, India *Corresponding Author

ABSTRACT

Infertility is a critical component of reproductive health [1]. The inability to have children affects men and women across the globe. Infertility can lead to distress and depression, as well as discrimination and ostracism [1, 2]. Parental consanguinity might have deleterious effects for the reproductive health of future generations. Similarly, the trend of older parenthood is true for both men and women. Infertility is multi-factorial but it is important to understand the effect of advanced age, consanguineous marriages & chromosomal aberration on fertility.

KEYWORDS

Infertility, advanced age, consanguineous marriages, chromosomal aberration

Introduction:

The definition of infertility as proposed by the American Fertility Society states that "a marriage is to be considered barren or infertile when pregnancy has not occurred after a year of coitus without contraception." Sterility is total inability to reproduce. Infertility may be further classified as Primary infertility, in which no previous pregnancies have occurred, and Secondary infertility, in which a prior pregnancy, although not necessarily a live birth, has occurred [3]. Infertility is seldom, if ever, a physically debilitating disease. It may however, severely affect the couple's psychological harmony, sexual life and social function. Even in those societies which made family planning and birth control their official policy and social vogue, the individual couple desiring a child but unable to conceive one feels demeaned, deprived and bitter. In some cultures childlessness may cast a heavy shadow on the psychological and social adequacy of the female and diminish the social standing of the male partner. The inability to procreate is thus always perceived as a denial of basic rights, an injustice and a disappointment. One in every four couples in developing countries had been found to be affected by infertility [4].

Infertility is multi-factorial but the advanced age, consanguineous marriages & chromosomal aberration play a key role in etiology of infertility. This review will focus on these three factors.

A. Effect of Age:

1. The effect of Advanced Paternal Age (APA) on fertility:

Much more is known about the female role in reproductive success than that of males. Unfortunately, the data on the effects of Advanced Paternal Age (APA) on reproductive success are less well described. It does appear, however, on the basis of available studies, that men of APA (>45 years) exhibit decreased levels of reproductive success. Some of the work indicates that semen parameters, including semen volume, sperm motility and sperm concentration decline as men age. The decline in these parameters, however, does not prove that men of APA have a lower chance of inducing pregnancy or fertilization. These questions were addressed in a prospective study by Dunson et al. in 2004 [5]. After controlling for female age, the authors found that the time to achieve pregnancy, as well as the rate of conception was adversely affected in the partners of men with APA. Further evidence of this negative impact was identified in an observational study of pregnant women, in which a fivefold increase in the time to achieve pregnancy was observed when the man's age was >45 years. Moreover, when compared with men, 25 years old, men of APA (>45 years) were 4.6 times more likely not to induce pregnancy until after 1 year of regular unprotected intercourse. When those men who took longer than 2 years to induce a pregnancy with their partners were examined, men of APA (>45 years) were 12.5 times more likely to be included [6]. Interestingly, the effects of APA were not dependent on female age, suggesting that males alone contributed to this effect [6, 7]. There is an increased age-associated risk of sperm germ line mutations and specific genetic disorders, specifically AD type [8].

Table 1 A summary of the various conditions that may be affected in the offspring of men with advanced age [9].

Condition	Age (years)	Population risk	Adjusted risk with APA
Achondroplasia	>50	1 : 15 000	1 : 1923
Apert	>50	1 : 50 000	1 : 5263
Crouzon	>50	1 : 50 000	1 : 6250
Neurofibromatosis 1	>50	1 : 3000 –1:4000	1 : 810–1 : 1080
Retinoblastoma	>45	1 : 15 000–1:20 000	1 : 5,000–1 : 6667
Down syndrome (must use maternal age as baseline)	40-44	1 : 1200	1 : 876
Klinefelter syndrome	>50	1 : 500 men	1 : 312 men
Epilepsy	40-45	1 : 100	1 : 770
Schizophrenia	>50	1 : 100	1 : 22
Autism	>40	1 : 1000	1 : 174
Breast cancer	>40	1 : 8.5	1 : 5.3
Spontaneous miscarriage	>35	1 : 7	1 : 5.3
Preeclampsia	>44	1 : 62	1 : 50
Total risk (Ref. 9)	>40	1 : 50	1 : 42

2. Effect of Advanced Maternal Age:

Advanced maternal age is traditionally defined as being greater than 35 years of age [10]. This definition for maternal age was established because it is the age at which women demonstrate a decreased ability to conceive, as well as a prolonged time to achieve pregnancy [11]. The concept of advanced maternal age is synonymous with 'ovarian aging' and is associated with lower oocyte numbers and quality; both of which lead to lower reproductive success.

The age related decline in fertility is accompanied by significant increase in the rates of aneuploidy and spontaneous abortion [10]. Autosomal trisomy is the most frequent finding and is related, at list in part, to changes in the meiotic spindle [12] that predisposes to nondisjunction [13]. Even for morphologically normal embryos selected for transfer in IVF cycles, the prevalence of aneuploidy is high in women of advanced maternal age [14]. The fetal loss rate is also significantly increased, even after fetal heart rate motion is detected by transvaginal ultrasonography Although 9.9% of women younger than 33 years who conceive during IVF with a fresh embryo transfer have a pregnancy loss after 7 weeks of gestation with fetal heart activity observed, the rates of miscarriages progressively increase from 11.4% for women aged 33-34 years to 13.7% for women aged 35-37 years, 19.8% for women aged 38-40 years, 29.9% for women aged 41-42 years, and 36.6% for women older than 42 years [15]. These data are similar to the increased rates of miscarriage reported nationally with IVF, where the rate of miscarriage increased progressively with age, from 13% in women younger than 35 years to 54% in women aged 44 years or older [16].

B. Effect of Consanguinity:

Consanguinity is a deeply rooted social trend among one-fifth of the world population [17]. The term "consanguinity" is used to illustrate unions between individuals who are known to share genes inherited

from one or more frequent ancestors. Additionally the most common consanguineous marriage is first cousin marriages which have 12.5% common gene pool [18]. Consanguinity increases the prevalence of rare genetic congenital anomalies and nearly doubles the risk for neonatal and childhood death, intellectual disability and serious birth anomalies in first cousin unions [19]. The frequency of congenital anomalies is higher in consanguineous marriages compared to non-consanguineous marriages [20]

If parents are unrelated, their risk for having a child with a birth defect or disability is between 2% and 3%. If parents are first cousins, the risk is a little higher at 5% to 6%. This is due to the increased chance that they will both carry the same autosomal recessive mutation, passed down through the family.

In general, when parents are consanguineous, they do not have an increased risk of having a child with genetic conditions that are due to X-linked or autosomal dominant gene mutations. However, there will be some increased risk for a child inheriting conditions that are due to a number of different genes acting together (polygenic) or where there is an interaction between genes and the environment such as spina bifida and some forms of congenital heart disease [21]. Consanguineous marriages might increase the rate of homozygous genotype expression [22]. This increases the risk of recessively inherited disorders. In recent studies it has been suggested that consanguinity is highly correlated with rare genetic sperm defect syndromes [22,23]. These defects cannot be treated and may be translated to male offspring. In most studies the evaluated parameter was whether parental consanguinity decreased the conception ratio or number of live births. It is proposed that the incidence of infertility is generally not higher in consanguineous marriages than in non-consanguineous marriages [24]. Suggested reasons are earlier marriage and so longer duration of the reproductive period.

C. Effect of Chromosomal Aberration:

Over 4,000 genes are involved in the control of human spermatogenesis [25]. The chromosomal abnormalities found in infertile couples are described below:

1. Klinefelter syndrome (47,XXY karyotype):

Described in 1942 by Harry Klinefelter, the syndrome that bears his name is seen in approximately 1/500 to 1/1000 male births. Klinefelter syndrome is a common cause of primary hypogonadism in males. Clinical examination of post pubertal patients reveals small testes (less than 10 ml in volume), and most patients with Klinefelter syndrome are sterile as a result of atrophy of the seminiferous tubules. Testosterone levels in adolescents and adults are low. Because of the subtlety of this disorder, Klinefelter syndrome is often not diagnosed until after puberty, and the condition is sometimes first ascertained in fertility clinics. The extra X chromosome is derived maternally in about 50% of Klinefelter cases, and the syndrome increases in incidence with advanced maternal age. Mosaicism, which is seen in about 15% of patients, increases the likelihood of viable sperm production. Individuals with the 48,XXXY and 49, XXXXY karyotypes have also been reported. Because they have a Y chromosome, they have a male phenotype, but the degree of mental deficiency and physical abnormality increases with each additional X chromosome [26].

2. 47,XYY karyotype:

47,XYY karyotype is seen in about 1/1000 males. Each involves a slight degree of reduction in IQ but few physical problems [26]. 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 [27].

3. Trisomy X:

The 47,XXX karyotype occurs in approximately 1/1000 females and usually has benign consequences. Overt physical abnormalities are rarely seen, but these females sometimes suffer from sterility, menstrual irregularity, or mild mental retardation. As in Klinefelter syndrome, the 47,XXX karyotype is often first ascertained in fertility clinics. Approximately 90% of cases are the result of nondisjunction in the mother, and, as with other trisomies, the incidence increases among the offspring of older mothers. Females have also been seen with four, five, or even more X chromosomes. Each additional X chromosome is accompanied by increased mental retardation and physical abnormality [26].

4. Monosomy of the X chromosome (Turner Syndrome):

The phenotype associated with a single X chromosome (45, X) was described by Henry Turner in 1938. In most persons with Turner syndrome, streaks of connective tissue, rather than ovaries, are seen (gonadal dysgenesis). Lacking normal ovaries, they do not usually develop secondary sexual characteristics, and most women with this condition are infertile (about 5% to 10% have sufficient ovarian development to undergo menarche, and a small number have borne children).

The chromosome abnormalities in persons with Turner syndrome are quite variable. About 50% of these patients have a 45,X karyotype in their peripheral lymphocytes. At least 30% to 40% have mosaicism, most commonly 45,X/46,XX and less commonly 45,X/46,XY. Mosaics who have Y chromosomes in some cells are predisposed to neoplasms (gonadoblastomas) in the gonadal streak tissue. About 10% to 20% of patients with Turner syndrome have structural X chromosome abnormalities involving a deletion of some or all of Xp. This variation in chromosome abnormality helps to explain the considerable phenotypic variation seen in this syndrome.

Approximately 60% to 80% of monosomy X cases are caused by the absence of a paternally derived sex chromosome, occurring either during early mitosis in the embryo or during meiosis in the father (i.e., the offspring receives an X chromosome only from the mother). The 45,X karyotype is estimated to occur in 1% to 2% of conceptions, but Turner syndrome is seen in only about 1/2000 to 1/3000 live-born girls. Thus, the great majority (more than 99%) of 45,X conceptions are lost prenatally. Among those that do survive to term, many are chromosomal mosaics, and mosaicism of the placenta alone (*confined placental mosaicism*) is especially common. It is likely that the presence of some normal cells in mosaic fetuses enhances fetal survival [26].

5. Trisomy 21:

Trisomy 21 (karyotype 47,XY,+21 or 47,XX,+21) is seen in approximately 1 of every 800 to 1000 live births, making it the most common autosomal aneuploid condition compatible with survival to term. This trisomy produces Down syndrome, a phenotype originally described by John Langdon Down in 1866.

Males with Down syndrome are nearly always sterile, with only a few reported cases of reproduction. Many females with Down syndrome can reproduce, although approximately 40% fail to ovulate. A female with Down syndrome has a 50% risk of producing a gamete with two copies of chromosome 21 (which would then produce a trisomic zygote). However, because approximately 75% of trisomy 21 conceptions are spontaneously aborted, the risk of producing affected live-born offspring is considerably lower than 50% in women with Down syndrome. Because reproduction is uncommon, nearly all cases of trisomy 21 can be regarded as new mutations [26].

6. Translocation:

Robertsonian translocations are among the foremost common balanced structural rearrangements seen within the general population. Approximately seven fold excess of Robertsonian heterozygotes in infertile couples. 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 [28,29,30].

7. Inversion:

As with chromosomal translocations, inversions can cause infertility, spontaneous abortions and birth defects. During meiosis, chromosomes are forced to form specialized structures (inversion loops) to enable homologous chromosomes to pair. The formation of these loops can impact fertility due to the mechanics and time constraints associated with the formation of the inversion loop [31]. Single-sperm PCR has also demonstrated that recombination within these loops is reduced which can lead to a breakdown in meiosis [32] and hence, may lead to apoptosis of the cell leading to a reduced sperm count. In addition, should recombination take place within the inversion loop, this will produce a proportion of unbalanced gametes [33]. As with reciprocal chromosomal translocations, the relative frequency of normal or unbalanced gametes will depend on the chromosomes involved, the size of the region involved and likelihood of recombinational events to take place within the inverted segments.

Investigations into the production of unbalanced gametes in balanced inversion carriers have been made to a much lesser extent than translocations; nevertheless, a handful of studies have reported ranges of unbalanced sperm of 1%– 54% [34].

8. CFTR gene mutation in male infertility:

Congenital bilateral absence of the vas deferens (CBAVD) is a genital form of cystic fibrosis (CF) that is responsible for 2-6% of male infertility. The incidence of CF varies in different populations; therefore, the incidence of CBAVD will also vary in different populations. The spectrum and distribution conductance regulator (CFTR) gene mutations differ between CBAVD and CF patients and are comparable to control individuals. Combinations of particular alleles at several polymorphic loci yield insufficient functional CFTR protein. About ninety seven of CF men are congenital bilateral absence of vas deferens that blocks transfer of spermatozoa from testis or epididymal structure to external genital tract. The CFTR gene contains 27 exons encompassing 180 kb of DNA on chromosome band 7q31.2. The CFTR protein is a glycosylated transmembrane protein, which functions as a chloride channel. Mammalian sperm for fertilizing need one process called capacitation that is related with increasing in intracellular pH and hyperpolarization of sperm's membrane. These changes are depended on extracellular HCO3-. CFTR is channels that conduct Cl- and HCO3- transportation and mutation in this gene cause non-capacitation of sperm. These situations ultimately cause male infertility [35].

9. Y chromosomal microdeletions and infertility:

One of the most commonly identified molecular genetics causes of male infertility has been sub-microscopic deletions (not visible by conventional cytogenetic analysis) on the Y chromosome. At present, three different spermatogenetic loci azoospermia factors (AZFa, AZFb and AZFc) have been mapped to the long arm of the Y chromosome. Deletions within the AZF region can result in varying degrees of spermatogenic failure and hence, infertility, the prevalence of which increases with the severity of infertility. Microdeletions within the AZF region occur in approximately 4% of males with oligozoospermia; 14% of males with severe oligozoospermia; and 18% in non-obstructive azoospermia males. The vast majority of microdeletions arise de novo and have been attributed to intra-chromosomal homologous recombination within unstable clustered within this region. Microdeletions remove one or more of these genes, and as a result cause varying defects in spermatogenesis. Candidate genes within the AZF regions have been studied extensively and are believed to play critical roles in germ cell cycle regulation and meiosis. Nevertheless, this has not yet led to the identification of the molecular basis for defective spermatogenesis. Despite this, clear genotype–phenotype correlations are emerging. The most common Yq microdeletions occur in the AZFc region, in part due to its relatively large size compared to the AZFa and b, and account for approximately 60% of reported microdeletions [36].

Conclusion:

Women have been increasingly delaying the start of motherhood in recent decades. The same trend is seen also for men. Advanced paternal age and advanced maternal age is associated with various reproductive hazards. Parental consanguinity has deleterious effects for the reproductive health of future generations. Similarly, chromosomal aberrations play a crucial role in the etiology of infertility. So it is very important to understand the impact of advanced age, consanguineous marriages and chromosomal aberrations on fertility. We should counsel and make people aware of deleterious effect of these three factors on fertility.

References:

1. Cui W, Mother or nothing: the agony of infertility. Bull World Health Organ, 2010, 88: 881–882. doi:10.2471/BLT.10.011210.
2. Chachamovich JR et al. Investigating quality of life and health-related quality of life in infertility: a systematic review. J Psychosom Obstet Gynaecol, 2010, 31: 101–110. doi:10.3109/ 0167482X.2010.481337.
3. Novak's Gynecology, Edited by Jonathan S. Berek, Lippincott Williams & Wilkins, 13th edition page: 973-1107.
4. http://www.who.int/reproductivehealth/topics/infertility/burden/en/
5. Dunson DB, Baird DD, Colombo B. Increased infertility with age in men and women. Obstet Gynecol 2004; 103: 51–6.
6. Hassan MA, Killick SR. Effect of male age on fertility: evidence for the decline in male fertility with increasing age. Fertil Steril 2003; 79(Suppl 3): 1520–7.
7. Stewart AF, Kim ED. Fertility concerns for the aging male. Urology 2011; 78: 496–9.
8. Zofnat Wiener-Megnazi et al, Advanced paternal age and reproductive outcome, Asian Journal of Andrology (2012) 14, 69–76.
9. Toriello HV et al, Statement on guidance for genetic counseling in advanced paternal age. Genet Med 2008; 10: 457–60.
10. Balasch J, Grataco´s E. Delayed childbearing: effects on fertility and the outcome of pregnancy. Curr Opin Obstet Gynecol 2012; 24: 187–93.
11. Sartorius GA, Nieschlag E. Paternal age and reproduction. Human Reprod Update 2010; 16: 65–79.
12. Battaglia DE, Influence of maternal age on meiotic spindle assembly in oocytes from naturally cycling women. Hum Reprod. 1996 Oct;11(10):2217-22.
13. Pellestor F, et al Maternal aging and chromosomal abnormalities: new data drawn from in vitro unfertilized human oocytes. Hum Genet. 2003 Feb; 112(2):195-203.
14. Munné S et al, Embryo morphology, developmental rates, and maternal age are correlated with chromosome abnormalities. Fertil Steril. 1995 Aug; 64(2):382-91
15. Farr SL et al, Pregnancy loss among pregnancies conceived through assisted reproductive technology, United States, 1999-2002, Am J Epidemiol. 2007 Jun 15; 165(12):1380-8.
16. Committee opinion, The American College of Obstetrician and Gynecologist Committee on Gynecologist Practice, Number 589, March 2014.
17. Hanan Hamamy, Consanguineous marriages, J Community Genet (2012) 3:185–192.
18. Bittles AH. Consanguinity and its relevance to clinical genetics. Clin Genet, 2001, 60,89-98.
19. WHO2013 http://www.who.int/genomics/public/geneticdiseases/en/index.html.
20. Tayebi N et al, The prevalence of congenital malformations and its correlation with consanguineous marriages. Oman Medical Journal, 2010, 25(1), 37-40.
21. www.genetics.edu.au / Publications...Fact-Sheets/Fact Sheet Consanguinity
22. B. Baccetti, S. Capitani, et al "Genetic Sperm Defects and Consanguinity," Human Reproduction, Vol. 16, No, 7, 2001, pp. 1365-1371.
23. D. Escalier and M. Albert, "New Fibrous Sheath Anomaly in Spermatozoa of Men with Consanguinity," Fertility and Sterility, Vol. 86, No. 1, 2006, pp. e211-e219.
24. A. H. Bittles, J. C. Grant, S. G. Sullivan and R. Hussain, "Does Inbreeding Lead to Decreased Human Fertility?" Annals of Human Biology, Vol. 29, No. 2, 2002, pp. 111-130.
25. Gianotten J et al, Idiopathic impaired spermatogenesis: genetic epidemiology is unlikely to provide a short-cut to better understanding. Hum Reprod Update 2004; 10: 533-539.
26. Lynn B. Jorde, John C Carey, Michael J. Bamshad. Medical Genetics, Fourth edition, MOSBY Elsevier publication, Pages: 106-113.
27. Attanasio A et al, Effect of human chorionic gonadotropin on the plasma levels of testosterone, estradiol, sex hormone binding globuline and free testosterone in Klinefelter syndrome. Endokrinologie 1982; 80: 129–134.
28. Bheem Prasad, Richa Jain, The Cytogenetic Basis of Human Infertility: A Review, IOSR Journal of Dental and Medical Sciences, Vol. 13, Issue 8 Ver. II (Aug. 2014), PP 83-88.
29. Luciani JM et al, Pachytene analysis of a man with a 13q;14q translocation and infertility. Cytogenet Cell Genet 1984; 38: 14–22.
30. Rosenmann A. et al, Meiotic association between the XY chromosomes and unpaired autosomal elements as a cause of human male sterility. Cytogene Cell Genet 1985; 39: 19–29.
31. Shah K, Sivapalan G, Gibbons N, Tempest H, Griffin DK. The genetic basis of infertility. Reproduction 2003; 126: 13–25.
32. Brown GM, Leversha M, Hulten M, Ferguson-Smith MA, Affara NA et al, Genetic analysis of meiotic recombination in humans by use of sperm typing: reduced recombination within a heterozygous paracentric inversion of chromosome 9q32–q34.3. Am J Hum Genet 1998; 62: 1484–92.
33. Chandley AC, McBeath S, Speed RM, Yorston L, Hargreave TB. Pericentric inversion in human chromosome 1 and the risk for male sterility. J Med Genet 1987; 24: 325–34.
34. Gary L Harton and Helen G Tempest, Chromosomal disorders and male infertility, Asian Journal of Andrology (2012) 14, 32–39.
35. Zohreh Hojat., Somaye Heidari, Majid Motovali Bashi, Exon 10 CFTR gene mutation in male infertility, Iran J Reprod Med Vol. 10. No. 4. pp: 315-320, July 2012.
36. Suganthi R et al, Y choromosomal microdeletion screening in the workup of male infertility and its current status in India. Int J Fertil Steril. 2014; 7(4): 253-266.