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Paternal Age: The Considerable Confounding Risk Factor in Chromosomal Aneuploidies

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ABSTRACT The association of advanced maternal age with chromosomal aneuploidies has been widely discussed and debated over decades. The effect of paternal age was underreported and left room for analysis and discussion. In a retrospective study, the researchers observed the paternal age of three chromosomal aneuploidies from the Indian population. Patient data with confirmed karyotype included the paternal age. The paternal age was dichotomized into two groups (<30 years) and (>30 years). Linear regression analysis was applied to observe the correlation of paternal age with children born with aneuploidies. Interestingly, the researchers could deduce the statistically significant paternal age as a confounding risk factor in chromosomal aneuploidy in both age groups for Down and Turner syndrome. These observations facilitated the need of a strategic approach in the management of couples at risk of cytogenetic abnormalities.

INTRODUCTION

Gametogenesis represents an integral phenomena in the reproductive cycles. Meiotic errors incline towards the genesis of abnormal germ cells either with missing or extra chromosomes, causing aneuploidy. A higher proportion of abnormal oocytes (21%) had been seen than spermatozoa (9%) (Martin 2008); the difference may be due to checkpoints during spermatogenesis. Advanced maternal age, the principal factor for oocyte aneuploidy (Griffin1996), was widely discussed for decades. The reports on paternal age effect on the aneuploidy conditions left a scope for wider investigations and discussions. Hassold et al. (2000), opines that the paternal age is the causative factor for causation of five to ten percent of trisomy foetus. There are different views reported in recent literature associating paternal age and chromosomal aneuploidy. De Souza et al. (2010) pointed out the weak association of paternal age, whereas an inverse relationship of (parental) paternal age associating with aneuploidy was proposed by Steiner et al. (2015). It was estimated that about five to ten percent of trisomies have a proportional effect of paternal age, but the age analysis was limited to around 40 years (Zaragoza et al. 1994; Hook and Regal 1984; Hook et al. 1990).

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Objectives

There was limited evidence from epidemiological genetics to correlate the confounding paternal age factor on chromosomal aneuploidies. This left room for analysis of paternal age as a confounding factor for chromosomal aneuploidies.

MATERIAL AND METHODS

This is a retrospective study. The data has one autosomal trisomy, Down syndrome (DS) and two sex chromosomal aneuploidies, Turner syndrome (TS) and Klinefelter syndrome (KFS) obtained during the extensive research degree programs during the years of 2000 to 2010 at St. John's Medical College, Bengaluru. Paternal age of all the cases at the time of conceptionwas quantified in Excel. The paternal age at the time of conception was the independent variable and they were dichotomized into two groups: group 1 is <30 years of age and group 2 as> 30 years age. The upper paternal age limit was 65 years. The children born to these groups of father's age were confirmed cytogenetically with DS, TS, and KFS.

The dichotomized paternal age was quantified in EXCEL and linear regression analysis for r^2 and p-value for the significance of r was applied and calculated.

RESULTS

In the present study, the paternal age of 394 [155 DS-male, 127-DS female, 40- KFS and 71-TS] casesof confirmed chromosomal aneuploidies at the time of conception were observed. Autosomal aneuploidy [DS] was more in number than the sex chromosomal aneuploidies [KFS and TS] taken together.

The number of children born with chromosomal aneuploidies was plotted against the Group 1 (>30 years) paternal age in Figure 1. There were 67 DS-male, 16 KFS, 60 DS-female and 35 TS children tallied in this paternal age group. Live births of autosomal trisomy (trisomy 21) and Monosomy X (TS) were notably higher in number than KFS. The interesting observation was there were notably higher numbers of aneuploidies between the paternal ages of 27-30 years.

In Figure 2, Group 2 (>30 years) shows the number of aneuploidies trended high between 31-40 years of paternal age, but deflected down as the age progressed. There were 88 DS-male, 24 KFS, 67 DS-female and 36 TS children tallied in this paternal age group. The occurrence of trisomy 21 (DS) and monosomy X was higher than KFS.

The coefficient of determination for correlation was analysed through linear regression. There was a strong positive correlation between group 1 (<30 years) with autosomal aneuploidy (trisomy 21) for both male and female DS children and Monosomy X. Sex chromosomal trisomy (KFS) reflected a marginal correlation. The group 2 (>30 years) displayed the significant negative correlation with the incidence of chromosomal aneuploidies. The rationale of negative correlation can be due to limited aneuploidy children in group 2 principally after 45 years of age.

DISCUSSION

The present study was designed to explore the correlation between paternal age and the chromosomal aneuploidies, Down, Turner and Klinefelter syndromes (DS, TS, KFS). The unusual factor was noticed in the study – there is a

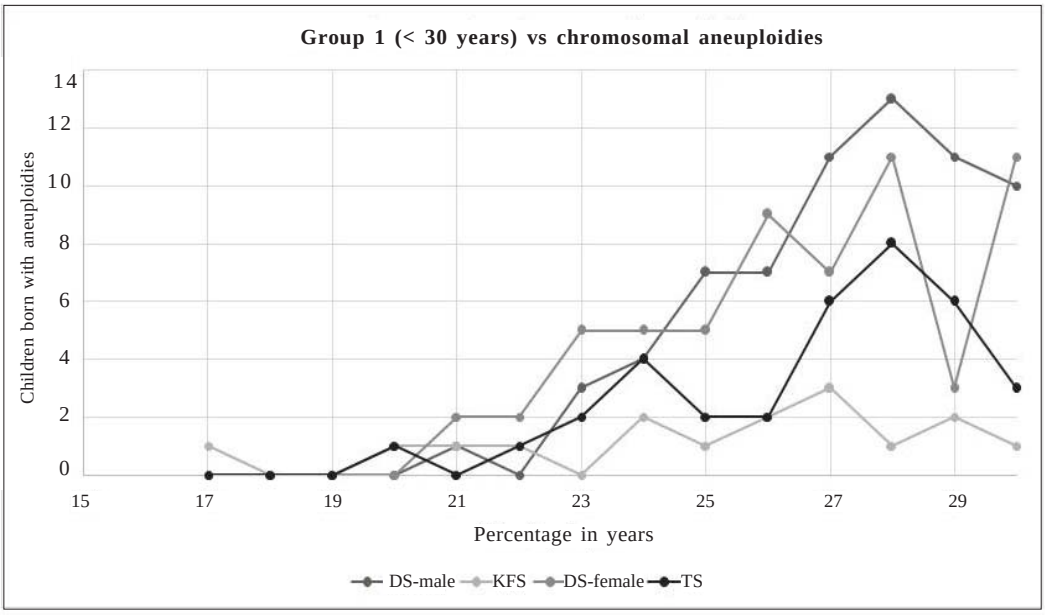

Fig. 1. Group 1 (< 30 years) versus chromosomal aneuploidies

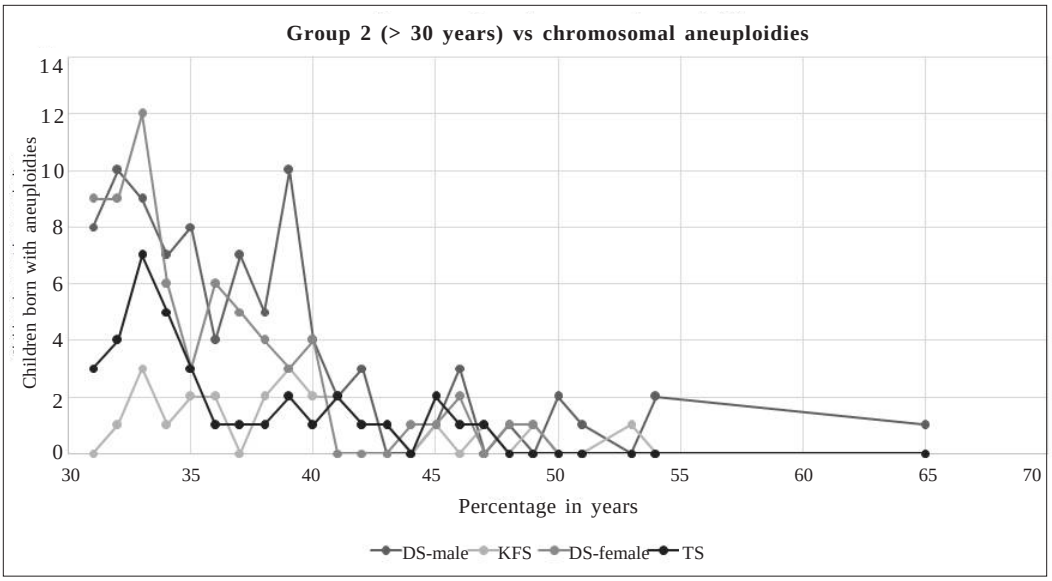

Fig. 2. Group 2 (> 30 years) versus chromosomal aneuploidies

potential age effect that existsfor young paternal age with the birth of DS and TS than KFS.

Down Syndrome (Trisomy 21)

Ninety percent of Meiotic I error during oogenesis in women of older age have a strong association with DS, whereas it accounts for only five percent for spermatogenesis. A strong association was noticed with Meiotic I and II error during spermatogenesis and paternal age (Peterson et al. 1993; Nicolaidis and Petersen 1998; Sherman et al. 1991). Most of the previous studies reflect that advanced paternal age even though minimal, can be considered as risk factor for causation of DS (McIntosh et al. 1995;Hook and Regal 1984). Very limited studies had an inverse proportional view that even younger paternal age (<20) may have a risk of fathering a DS child. The observations, in the present study, reflected the significantly higher risk of fathering a Down child at a younger paternal age.

Research studies on the parental age effect on sex chromosomal aneuploidies indicate that advanced paternal age may result in 0.2 percent of live births with sex chromosomal aberrations.

Klinefelter Syndrome (47, XXY)

The paternal contribution to the causation of KFS is about fifty percent (Wyrobek et al. 2000). Klinefelter syndrome affects about 1 in 500 male births and is the most common cause of male infertility in humans. There were conflicting opinions about the effect of paternal age on KFS. Majority of the studies opine the insignificant contribution of paternal age on the occurrence of KFS (Jacobs et al. 1988; Thomas et al. 2000). There are studies that report an alternative view. An example to cite is from Lorda-Sanchez et al. (1992) observation, demonstrating a correlation with paternal age by paternally derived KFS. In the present study, the paternal age is observed to be of low significance in KFS compared to the other two aneuploidies irrespective of the age cohort.

Turner Syndrome (45, X)

Eighty percent of TS live births have an associated paternal contribution (Wyrobek et al. 2000). TS affects 1 in 5000 live births: however, there is a continuing debate on the presence of cryptic mosaicism in female TS live births (Turnpenny and Ellard 2012). Inverse paternal age is reported for TS cases by Carothers et al. (1980), however, lack of paternal age association was reported in studies by Mathur et al. (1991). The present study's observations closely relates with the Carothers observations, indicating a possible relationship between paternal age and concordance of TS.

CONCLUSION

Maternal age as a risk factor, is widely accepted consideration to account for non-disjunction during meiosis I and/or meiosis II, causing the chromosomal abnormalities. Genetic epidemiological studies reflect that there may be minimal or a lack of paternal age association with autosomal aneuploidies like trisomy 21. Contrary to this, paternal age factor laid a debate among the researchers to enroot its effect on sex chromosomal aneuploidies. In the present study of 394 cases [155 DS-male, 40 KFS, 127-DS female and 71 TS], significant correlation of paternal age was observed with DS and TS, but mild to insignificant association with KFS. This is an interesting factor raised and opened for further investigation and discussion about the effect of young paternal age and its correlation with chromosomal aneuploidies.

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