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ADVANCED MATERNAL AGE AND PREVALENCE OF CHROMOSOMAL ABNORMALITIES IN CASES OF DISORDERS OF SEX DEVELOPMENT (DSD)

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Abstract
Disorders of Sex Development (DSD) encompass a diverse group of congenital conditions in which the development of chromosomal, gonadal, or anatomical sex is atypical. While DSDs are primarily genetic or sporadic in origin, emerging evidence suggests that advanced maternal age (AMA) may influence the prevalence and expression of chromosomal abnormalities in DSD cases. This review explores the association between AMA and chromosomal anomalies contributing to DSDs, with an emphasis on meiotic nondisjunction, sex chromosome aneuploidy, and diagnostic implications in the prenatal and neonatal period.

Introduction
Advanced maternal age (AMA) has long been associated with an increased risk of chromosomal abnormalities due to age-related meiotic errors in oocytes. While much of the literature has focused on autosomal aneuploidies such as Trisomy 21, there is growing interest in understanding the implications of AMA on Disorders of Sex Development (DSDs). DSDs, which include conditions such as Turner syndrome, Klinefelter syndrome, 46, XY DSD, and 46, XX testicular DSD, may arise from both structural and numerical chromosomal abnormalities, many of which can be traced back to nondisjunction events during gametogenesis.
According to the Chicago Consensus (2006) [1-3], DSDs are classified based on chromosomal

karyotype:

- **Sex chromosome DSD** (e.g., Turner syndrome [45, X], Klinefelter syndrome [47, XXY])

- **46,XY DSD** (e.g., androgen insensitivity syndrome, gonadal dysgenesis)
- **46,XX DSD** (e.g., congenital adrenal hyperplasia, ovotesticular DSD)

Chromosomal abnormalities, particularly involving sex chromosomes, play a significant etiologic role in many of these disorders. While some cases are inherited, most arise sporadically, often due to de novo chromosomal anomalies.

Maternal Age and Chromosomal Abnormalities in DSD

1. Sex Chromosome Aneuploidies and AMA

Sex chromosome aneuploidies, such as 45,X (Turner syndrome), 47,XXY (Klinefelter syndrome), and 47,XYY, are among the most common chromosomal abnormalities linked to DSD phenotypes. Several studies have suggested a modest but statistically significant association between AMA and the incidence of sex chromosome aneuploidies, though the correlation is less robust than with autosomal trisomies [4,5].

- **Turner syndrome (45,X):** Although monosomy X typically results from paternal meiotic errors, maternal age may still influence nondisjunction rates in a subset of cases involving mosaicism or structural abnormalities (e.g., isochromosomes).
- **Klinefelter syndrome (47,XXY):** Both maternal and paternal nondisjunction contribute, with advanced maternal age implicated in approximately 50% of cases [6].
- **47,XYY syndrome:** Arises exclusively from paternal nondisjunction; however, maternal age is not directly associated with this abnormality.

2. Structural Chromosomal Abnormalities and Advanced Age

Structural chromosomal rearrangements (e.g., translocations, deletions, duplications) involving sex-determining regions—such as SRY on Yp11.3—can lead to 46,XX testicular DSD or 46,XY gonadal dysgenesis. These de novo rearrangements may occur more frequently in offspring of older mothers due to increased genomic instability and impaired meiotic checkpoint fidelity [7].

3. Meiotic Nondisjunction and Oocyte Aging

As women age, oocytes are increasingly susceptible to nondisjunction due to weakened cohesin complexes, spindle dysfunction, and compromised chromosomal segregation. While the most studied outcome is autosomal trisomy, these same processes may also lead to sex chromosome missegregation, contributing to karyotypic anomalies associated with DSD [8].

Prenatal Diagnosis and Screening Implications

With the advent of non-invasive prenatal testing (NIPT), detection of sex chromosome aneuploidies has become feasible during the first trimester. However, the interpretation of these findings—particularly mosaicism and variants of uncertain significance—requires expert genetic counseling, especially in the context of advanced maternal age [9].

- **NIPT**: Detects common aneuploidies including 45,X, 47,XXY, and 47,XYY with high sensitivity.
- **Confirmatory Testing**: CVS or amniocentesis is necessary for definitive karyotyping and microarray analysis.
- **Counseling Considerations**: Families with AMA pregnancies should be counseled about the potential for sex chromosome abnormalities and DSDs, even in the absence of ultrasound markers.

Neonatal Evaluation and Genetic Workup

In neonates presenting with ambiguous genitalia or other DSD phenotypes, a high index of suspicion for chromosomal anomalies should be maintained, particularly if maternal age is advanced. Comprehensive evaluation includes:

- Karyotyping and chromosomal microarray
- SRY gene analysis

- Hormonal assays (e.g., AMH, testosterone, 17-OHP)
- Imaging of internal genitalia

So keeping in mind we took an opportunity to do a study on DSD cases with the help of one of the diagnostic technique the karyotyping.

Aim and objective

Aim of present study was to find out role of advanced maternal age in causation of chromosomal abnormalities in DSD cases.

MATERIAL AND METHODS

- This descriptive study was conducted at King George's Medical University (KGMU), UP, Lucknow, with ethical approval from the institution's review board (letter number 2083/Ethics/R.Cell-17). The research was a collaborative effort between the Anatomy Department's cytogenetic laboratory and the Paediatric Surgery Department.
- A total of 24 children with ambiguous genitalia were included in the study .Patient screening occurred in the Paediatric Surgery outpatient department (OPD). Participants included individuals with a clinical diagnosis of ambiguous genitalia, as determined by paediatricians and paediatric surgeons, who provided informed consent. Patients who declined consent were excluded. A thorough medical history, focusing on factors influencing disorders of sex development (DSD), was collected. Peripheral blood samples were obtained and analyzed in the cytogenetic laboratory. Karyograms were generated and evaluated to determine chromosomal abnormalities.
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Results

A total of 24 diagnosed cases of DSDs were taken detailed history was taken and examination was done. Later blood sampling was done then karyotyping was done.

Exactly half the cases were born at maternal age <25 years while remaining half were born at maternal age >25 years. Proportion of those with chromosomal anomalies was higher in maternal age >25 years (36.4%) as compared to that in maternal age <25 years (27.3%), however, this difference was not significant statistically (p=1.000) (Table 1 Figure 1).

Table 1: Correlation of maternal Age with prevalence of Chromosomal anomalies (n=22)

Age of mother (years)	Total	With anomalies (n=7)		Without anomalies (n=15)	
		No.	%	No.	%
≤ 25	11	3	27.3	8	72.7
>25	11	4	36.4	7	63.6
		p=1.000 (Fisher exact test)			

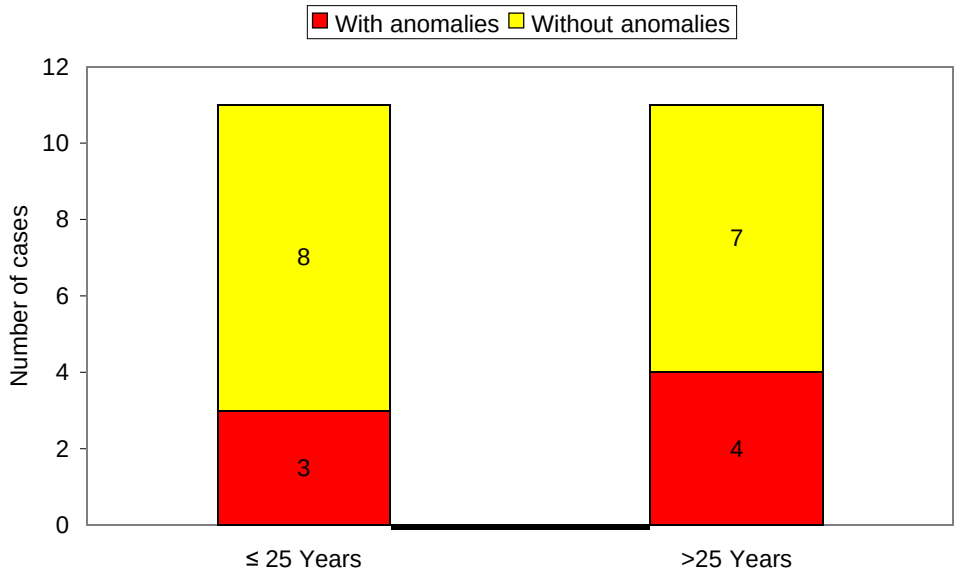

Fig. 1: Bar diagram representing Correlation of maternal Age with prevalence of Chromosomal anomalies

Discussion

While DSDs remain relatively rare (estimated incidence: 1 in 4,500–5,000 live births) [10, 11], the role of advanced maternal age in contributing to chromosomal variants within this group is non-negligible. The biological mechanisms underpinning age-related chromosomal abnormalities likely influence a subset of DSDs, particularly those associated with sex chromosome aneuploidy. The rise in maternal age at first birth worldwide necessitates increased vigilance, targeted screening, and patient education regarding DSDs and related chromosomal risks.

In our study, we observed that there was no specific correlation with maternal age half of the mothers of our cases were below and half above 25 years (Table 1, Figure 1). Although there are many chromosomal abnormality associated with increased maternal age mentioned by many authors **Sipila et al.(1990)** found that congenital anomalies were higher in grand multipara than women with low parity because essential hypertension was more common among grand multipara than among women of lower parity and this is probably a consequence of higher maternal age[12]. **Suguna Bai et al. (1982)** reported a higher incidence of malformation in the babies born to mothers aged over 35 years [13], whereas **Dutta et al. (2000)** documented statistically insignificant association of increased maternal age and congenital anomalies [14].

Hussain N et al.(2002) retrospectively reviewed 112 patients for hypospadias in Connecticut and found no significance of maternal age[15].

In the present study age of mothers were categorized as < or =25 and >25. Maternal age at the time of birth of the child was <or=25 years in half (n=11; 50%) cases and half (n=11; 50%) had age >25. However, proportion of those with anomalies was significantly higher in >25 years age group (36.4%) as compared to that in <25 years age group (27.3%) (p=1.000) (Table 1, Figure 1). As observed, in our study cases with anomalies were reported more in maternal age >25 years. This could be due to increased risk of congenital anomalies and malformations with advanced age.

Conclusion

Advanced maternal age is a recognized risk factor for chromosomal abnormalities, including those implicated in Disorders of Sex Development. Although the association is more modest compared to autosomal aneuploidies, it remains clinically significant. Prenatal screening strategies, timely genetic counseling, and thorough neonatal evaluation are essential in identifying and managing DSDs in pregnancies complicated by AMA.

DECLARATIONS:

Conflicts of interest: There is no any conflict of interest associated with this study

Consent to participate: There is consent to participate.

Consent for publication: There is consent for the publication of this paper.

Authors' contributions: Author equally contributed the work.

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