

## RISK OF DOWN SYNDROME IN ELDERLY MOTHERS: A RETROSPECTIVE STUDY IN TUMKUR

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### ABSTRACT

**Background:** Down syndrome being the most common chromosomal disorder is researched extensively. The only etiology that is well established is increased maternal age. In the developing countries, the incidence of Down syndrome is increasing in younger mother.

**Method:** 75 cases of Down syndrome children and age matched 75 children without known congenital abnormalities were taken for this study. The parental age was noted and statistical analysis was done to correlate the maternal age with DS.

**Result:** Only 26.4% of DS children were born in mothers aged above 35. There was a decrease in number of children born in aged mothers of both group, but there was no much difference in the groups.

**Conclusion:** Maternal age is not only the risk factor for occurrence of DS. There is generally a tendency of early pregnancy in India, which leads to increase in number of DS children being born to mothers below 35.

**KEY WORDS:** Down syndrome, Maternal age.

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### INTRODUCTION

Chromosomal abnormalities are the leading cause of human congenital abnormalities contributing to human morbidity and mortality [1]. Down syndrome is the most common, easily recognized and probably the most common researched chromosomal disorder. Down syndrome results from the presence of an extra chromosome 21 (trisomy 21), or the 21 chromosome or a part of it being translocated

to any other chromosome in D group or G group (Robertsonian or reciprocal translocation) or existence of 2 cell lines in individual, some with 46 chromosomes and others with 47. It has been estimated that trisomy 21 occurs on 0.45% of conception; but more than 75% of these do not survive to birth. There seems to be decline in the birth prevalence of DS, probably due to increase in prenatal screening [2]. In India, annual birth of Down syndrome babies is around

23,000 – 29,000 taking incidence of down syndrome as 1.4/1000 live birth [3].

The cardinal clinical features of Down syndrome include characteristic features like oblique palpebral fissure, flat nasal bridge, brachycephaly, and high arched palate, low set ears, protruding tongue, simian crease, Sandle gap, brachydactly, hypotonia, congenital heart disease, short stature and mental retardation. No single phenotype is pathognomonic but the combination of dysmorphism is usually recognizable [4]. The diagnosis of DS is made by chromosomal analysis which can be done either prenatally (1<sup>st</sup> or 2<sup>nd</sup> term of pregnancy) or posnatally [5].

In 95% of cases, DS results from non –disjunction, with the error being predominantly in meiosis 1. The exact cause of non – disjunction remains unknown, although attempts have been made on association of maternal age with birth of DS [6]. Women who become pregnant first time after the age of 35 years are known as elderly primigravida. The elderly primigravida is generally believed to have decreased fertility and increased risk for adverse pregnancy outcomes including DS. Elderly primi is associated with poor oocyte quality which is associated with an increased risk for aneuploidy, chromosomal abnormalities, and spontaneous abortions [7].

Some reports suggest advanced paternal age also contributes to DS. Some evidence suggests that thyroid disorders in the mothers may increase the risk of bearing a DS child [2].

Studies have been conducted to assess whether maternal or paternal grandparents’ age is associated with the risk of Down’s syndrome [8]. This retrospective study was undertaken to compare and contrast the maternal age group in DS children and children with no known congenital abnormalities.

**MATERIALS AND METHODS**

This study was conducted after obtaining permission from the institutional review board. The study was conducted in Sri Siddhartha Medical College from October 2011 to April 2018. 75 children with posnatally diagnosed Down syndrome (by Karyotyping) were selected in group A or the case group. In the control group

or group B, 75 children, without any known deformity, with age matched were selected randomly. Informed consent was taken from parents of both group children. Epidemiological information on parental age and consanguinity was collected. The relation of maternal age and DS was calculated using 2\*2 contingency table for chi square test. Karl Pearson Correlation test was used to find the correlation of maternal age in both groups.

**RESULTS**

In group A, 56 children were born to mothers aged less than 35 years, whereas in group B the number was 60.

**Table 1:** The 2\*2 contingency table for chi square test.

	DS children	Children with no abnormalities	Total
MA less than 35	56 (a)	60 (b)	116 (a+b)
MA more than or equal to 35	19 (c)	15 (d)	34 (c+d)
Total	75 (a+c)	75 (b+d)	150 (a+b+c+d)

Using the Chi Square test

$$\text{Chi square} = \frac{N(ad-bc)^2}{(a+b)(c+d)(a+c)(b+d)} = 0.6$$

The degree of freedom is 1 and level of significance <5%. The critical value is 3.86 using the table.

Therefore the test concludes the incidence of DS is independent of maternal age.

**Table 2:** The distribution of children according to their maternal age group.

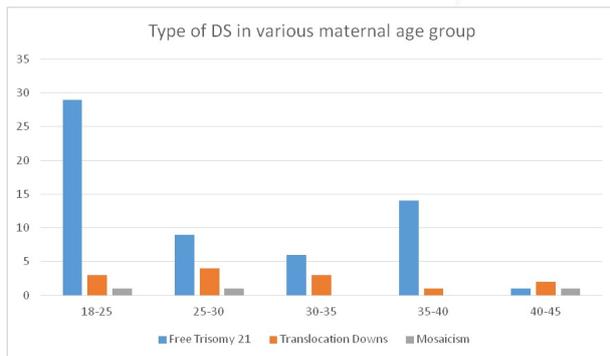
Age of Mother	No of children (Group A)	No Of children (Group B)
18 – 25	33	36
25 – 30	14	13
30 – 35	9	11
35 – 40	15	12
40 - 45	4	3

Using the Karl Pearson formula for calculating the correlation coefficient, the correlation factor for group A is -0.76, whereas for group B is -0.56. It can be seen that, while both are negatively correlated, there is no much difference of correlation coefficient in the case and control group. Therefore we can conclude that there is a negative relation between maternal age & birth of a child, i.e., the no of children born is reduced as the maternal age advances.

As there is no much difference of correlation coefficient between the case group and control group it can be concluded that maternal age has no effect on birth of DS children.

Out of the 75 children of group A, 59 had trisomy 21, 13 had translocation and 3 had mosaicism. One child showed trisomy 21 with chromosome 13 - 14 translocation.

**Graph 1:** The age wise distribution and the type of DS.



## DISCUSSION

All cases were diagnosed postnatal in the present study. An observation of 59 cases of free trisomy, 13 cases of translocation Down's and 3 cases of Mosaic Down's was made. The mean maternal age at conception was 28.5, ranging from 18 years to 42 years in the study.

In India early marriage and early reproductive life is customary, but in recent times women have changed their life style such as in the pursuit of higher education and entry into work forces and career advancement outside the home. Consequently, this has led to postponement of child bearing, resulting in an increasing maternal age. The increase in the rate of divorce followed by remarriage etc. contributes to this upward trend [6]. The mean age of marriage for females is 23.5 years in India according to the report of 2011 census. According to the same report the proportion of giving birth before age 18 declined by six percentage points (from 28% to 22%), and the proportion giving birth before age 20 fell by seven points (from 49% to 42%).<sup>(9)</sup> In our study it was observed that out of 150 children (both DS & normal), 34 (22.7%) were born to mothers aged above 35.

Increased maternal age has generally been associated with non disjunction of chromosomes. Trisomy 21 could be the consequence of non disjunction that might occur during meiosis

or in the 1<sup>st</sup> or 2<sup>nd</sup> cleavage division. Various hypotheses put forward to explain the non-disjunction in older women are

- Intrinsic ovarian aging in advanced maternal age predisposing to non-disjunction
- Fertilization involving an aging oocyte
- Ova initially selected for ovulation are more likely to be normal than those remaining in older women i.e., production line hypothesis

· Certain parental metabolic derangements common in older women like thyroid disorders also increase the incidence of aneuploidy [10].

It is estimated that 80% of DS children are born to women >35 years. However in the present study only 19 (25.3%) of DS children were born to mothers <35 years, which implies majority of mothers of DS children were >35 years [1].

**Table 3:** Percentage of DS children born to elderly mothers in various studies.

Study	Maternal age above (35%)
Azman et al [11]	41.4
Bertelli et al [12]	41.9
Sheth et al [13]	8.4
Present study	25.3

Non disjunction can occur at any time; therefore children with DS can be born to mothers of all ages. Since generally there is a negative correlation between maternal age and pregnancy, i.e., number of pregnancy generally itself reduces as age advances [1]. In our study also a similar negative correlation between maternal age and no of children born is seen.

According to Azman et al germinal aneuploidies could occur due to age –dependent or age independent phenomenon. Age – independent aneuploidy could occur due to accumulation of effects of radiation, hormonal imbalance and infection [11].

Non disjunction in chromosomes has been produced by some environmental factors like ionizing radiation, CO<sub>2</sub> and ammonia vapor. Also an interaction between them compounding the frequency is seen. Studies suggest if there are any environmental factors leading to chromosomal defects, they must be acting on parental gametes or on the fertilized ovum in the initial days of cleavage. Therefore an increase in the incidence of DS is expected since radiation

exposure, including exposure to medical radiation is increasing [14]. Koochupillai et al conducted a study in a coastal area of Kerala, South India where the background radiation is 1,500–3,000  $\text{mR}\cdot\text{Yr}^{-1}$  due to the presence of thorium-containing monazite mineral in the soil, noticed an apparently high prevalence of Down syndrome [15].

According to a study by James et al folate mechanism is abnormal in mothers with DS which may be explained partly by the mutation in methylene tetrahydrofolate (MTHF) gene. Genes involved in homocysteine metabolism and polymorphism have been implicated in the occurrence of DS [16]. Further research on the role of folate mechanism on chromosomal non disjunction is necessary, considering the increased frequency of DS children born to young mothers. Studies have been conducted to see effect of the application of folic acid supplementation to monitor pregnancies which are at risk of Down syndrome [17].

Some studies reported a high incidence of DS in mothers with thyroid abnormalities especially hypothyroidism. This may be explained by the cytogenetic studies which demonstrated “stickiness” of chromosomes increased by thyroxin hormone. This “stickiness” of the hormone can cause non disjunction [18,19].

The improvements in screening method and uptake mean that the proportion of pregnancies with DS being diagnosed increased from 1989 to 2003 according to a study conducted by Crane E & Morris J in England and Wales. It was also observed the percentage was consistently higher amongst women aged 35 and above (75% in year 2003) due to increasing awareness of DS. About 6% of DS pregnancies diagnosed prenatally result in a live birth, the majority (92%) being terminated and a small proportion (2%) resulting in a miscarriage or stillbirth according to the same study. The study concluded that the decrease in all pregnancies in women aged above 35, the corresponding decrease in DS pregnancies and an increase in proportion of prenatal diagnosis of DS led to decrease of incidence of DS in women above 35 years [20]. According to a study by Malini & Ramachandra advanced age of grandmother is responsible to bring disturbance in the meiosis

of her daughter. The study proposes at the advanced age the grandmother’s reproductive system may fails to make the essential proteins like spindle associated proteins, factors responsible for resting of oocyte, chiasm-binding proteins, DNA repair enzymes, etc. which are needed for proper meiotic segregation in the germ cells of her daughter. The non-availability or non-functioning of proteins leads to impairment in the meiotic process, which in turn results in nondisjunction of chromosome 21 in the oocyte of the daughter. This event takes place during the embryogenesis of the mothers of the DS children when she was in grandmother’s womb. It is also possible that recombination is reduced in the oocytes, which brings about the nondisjunction of chromosome 21. Therefore, DS not only depends on the age of the mother but also on the age of the maternal grandmother which results in nondisjunction of chromosome 21 [21].

Though this is a possible explanation for increase in birth of DS children, especially free trisomy type, like our study, more clinical evidence is required to accept the hypothesis. So it is recommended to conduct studies on DS considering the age of grandmother (maternal & paternal) in other geographical conditions.

Most of the studies with younger maternal age giving birth to DS children show that the translocation type or the mosaic type of DS is increased [22]. In our study 79.4% of DS children born to mothers younger than 30 were free trisomy type. 7 out of 16 (43.8) translocation DS and 2 out of 3 (66.7%) were seen in mothers below 30. The sample size of translocation and mosaic DS is too small to arrive at a conclusion. Further studies only including only translocation or mosaic DS in case group are necessary to evaluate the relation of maternal age to translocation or mosaic DS.

Genetic counseling: the parents have to go for genetic counseling, especially for the risk of recurrence. The risk is mainly based on the type of DS, and slightly on age. If the DS is free trisomy type the risk of recurrence is same as that for any other mother of same age. For translocation type, both parents have to undergo karyotyping to look for any balanced translocations. In case of male carrier it is about 1 – 3%

and 10 – 15% in female carrier.

## CONCLUSION

Though increased maternal age has been traditionally a risk factor for Down syndrome, it is common in mothers with younger age group also. Studies have to be conducted about other risk factors like radiation exposure, thyroid levels of mother, increased age of grandmother or other factors. The parents have to be genetically counseled based on the type of Down syndrome.

## ABBREVIATIONS

DS - Down syndrome

MA - Maternal Age

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**Conflicts of Interests: None**

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