

Advanced Maternal Grandmother Age is a Risk Factor in Causing Sex Chromosomal Aneuploidy

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ABSTRACT Majority of the chromosomal abnormalities are incompatible with embryonic or fetal survival but trisomy 21 and sex chromosomal trisomies have a much higher viability surviving to term. In India, increased numbers of children with sex chromosomal aneuploidy are born to young mothers. Therefore, detailed analysis of the families with sex chromosomal aneuploidy is needed to find out the possible causative factors for nondisjunction. Twenty five families of suspected sex chromosomal aneuploidy children were investigated for cytogenetic analysis and pedigrees were constructed for these families. As controls 100 randomly selected families belonging to different religions were used. Of the 25 sex chromosomal aneuploidy cases studied, 16 were Turners with 45, XO chromosomes and 9 were Klinefelters with 47, XXY chromosomes. The number of sex chromosomal aneuploidy births was greater for the young mothers than the advanced age mothers. The logistic regression of case-control study of sex chromosomal aneuploidy children revealed that the odds ratio for the age of maternal grandmother was significant when all the four variables were used once at a time. However, the effect of age of mother and father was smaller than the effect of age of maternal grandmother. For every year of advancement of age of the maternal grandmother, the risk (odds) of births of sex chromosomal aneuploidy children increases by 36%. Therefore, the age of the maternal grandmother at the time of birth of mother is a risk factor for the occurrence of sex chromosomal aneuploidy.

INTRODUCTION

Majority of the chromosomal abnormalities are incompatible with embryonic or fetal survival but trisomy 21 and sex chromosomal trisomies have a much higher viability surviving to term (Hassold and Hunt 2001). Turner syndrome is a sex chromosomal abnormality present one in 2500-5000 live births, typically involving the presence of only one X chromosome, 45, XO. This may additionally occur in structural abnormalities include isochromosome 46, X, i (Xq), deletion 46, X, del (X), ring chromosome 46, X, r (X) and mosaicism (45, X/46, XX) or abnormal karyotype (45, X/47, XXX) (Jacobs et al. 1974; Kajii et al. 1980; Nielsen and Wohler 1990; 1991; Gravholt et al. 1996). Klinefelter syndrome is another common sex chromosomal aneuploidy present in 4.3-15.0 per 10,000 births or 8.4-29.0 male per 10,000 births, involves the presence of two or more X chromosomes and one Y chromosome, 47, XXY;

48, XXYY or chromosomal mosaicism 46, XY/47, XXY (Yoshida et al. 1996; Foresta et al. 2002; Lanfranco et al. 2004). As the characteristics of this syndrome can be subtle, it is often not diagnosed until adulthood when the affected individual is examined for fertility problems (Lanfranco et al. 2004).

Both Turner and Klinefelter syndromes result from nondisjunction of chromosomes. The well established risk factor for nondisjunction is advanced maternal age. There are contradicting reports regarding the influence of maternal age resulting in sex chromosomal aneuploidy (Warburton et al. 1980; Ferguson-Smith and Yates 1984; Gravholt et al. 1996; Robinson and Jacobs 1999; Thomas et al. 2000; Lowe et al. 2001; Ranke and Saenger 2001; Lanfranco et al. 2004). Even the evidences for paternal age as a risk factor for autosomal and sex chromosomal aneuploidy births remain ambiguous (de Michelena et al. 1993; MacDonald et al. 1994; Wyrobek et al. 1996). Despite the clinical importance of age dependent nondisjunction in human, the underlying mechanisms remain largely unexplained. Efforts to recapitulate age dependent nondis-

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junction in a mammalian experimental system have so far been unsuccessful. Malini and Ramachandra (2006) have reported that in India the increased numbers of children with Down syndrome are born to young mothers and the age of maternal grandmother at the time of birth of the mother is a risk factor for the occurrence of Down syndrome. However, there are no reports cited in the literature about the influence of maternal grandparental age in causing sex chromosomal aneuploidy. In view of this, an attempt has been made to find out the influence of parental and grandparental age on sex chromosomal aneuploidy in Mysore population. Here we report maternal grandmother age may be one of the possible risk factors for causing sex chromosomal aneuploidy.

MATERIALS AND METHODS

Sex Chromosomal Aneuploidy Cases: A total of 25 cases with suspected sex chromosomal aneuploidy referred for cytogenetic investigations from major Hospitals were confirmed using standard methods and grouped as to the karyotype. The age of the patients ranged from newborn to 15 years. An informed consent was obtained from the parents, before their inclusion in the study.

Control Population: Randomly selected 100 healthy families belonging to different religions as well as different localities in and around Mysore city, South India were used as controls. To generate case-control dataset for the analysis of sex chromosomal aneuploidy, 25 patients (16 females and 9 males) of sex chromosomal aneuploidy and one randomly selected child from each of the 100 control families were used.

Establishment of Genetic Register and Pedigree: Genetic register was maintained to collect the complete clinical assessment of the proband information pertaining to age, sex, religion, caste, place of birth, birth order, any associated medical problems of the proband and also reproductive histories of parents and parental age at the time of conception. Age of mother and father at the birth of the child as well as age of the maternal grandmother and maternal grandfather at birth of the mother of affected child was also recorded for all the families under study. With these informations, the pedigree of the families under study was constructed.

Statistical Analysis: Student's t-test was

used to compare the mean age of parents and grandparents in control and sex chromosomal aneuploidy families to ascertain the differences. Logistic regression was performed using the software, SPSS version 10.0 to record the effect of the variables. Case-control status was used as dependent variable and age of mother, father, maternal grandmother and maternal grandfather as covariates. Results were reported as odds-ratios from models with one variable at a time as well as from a model with multivariable simultaneously.

RESULTS

Of the total of 25 cases of sex chromosomal aneuploidy, 16 of them were having 45, XO with Turner stigmata and the remaining 9 were Klinefelters with 47, XXY karyotype. Most of these sex chromosomal aneuploidy showed low IQ, speech and language delays, dyslexia, poor motor coordination, delayed emotional maturity, poor relations with peers, timidity, along with Turner and Klinefelter stigmata. But the expressivity of these characters varied between individuals.

Generally Indian women will conceive the baby as soon as she gets married which is around 18 years. The age of mother, father, maternal grandmother and maternal grandfather has been classified into four types taking into the consideration of the frequency of births, which are: 18-24 (1st phase of young age), 25-29 (2nd phase of young age), 30-35 (1st phase of advanced age), 36-40 (2nd phase of advanced age) and above 41 (last phase of advanced age) years. Table 1 provides the mean age of parents and maternal grandparents in control and sex chromosomal aneuploidy families. Student's t-test revealed that the mean age of mothers in the control and sex chromosomal aneuploidy families was significant in the age range of 18-24 years, whereas the mean age of fathers showed no significant differences in all the age ranges. The mean age of maternal grandmothers had shown the significant differences in the age range of 18-24, 25-29, and 36-40 years. Similarly, the mean age of maternal grandfathers had shown the significant difference in the age range of 30-35 and above 41 years.

Table 2 presents the age of parents and number of children born in 25 sex chromosomal aneuploidy and 100 control families. Figure 1 and

2 provide the number of parents and maternal grandparents in different age range in control and sex chromosomal aneuploidy families. The analysis revealed that both mothers of control and sex chromosomal aneuploidy families produced more number of children in their young age than advanced age, whereas the fathers produced large number of children in their advanced age. The maternal grandmother of sex chromosomal aneuploidy families produced more number of affected children in their advanced age compared to controls, whereas maternal grandfather produced more children in their advanced age in both the control and sex chromosomal aneuploidy groups.

Figure 3 illustrates the pedigrees of Turner syndrome families with (a) 24 years young age mother, (b) 26 years young age mother and (c) 32 years advanced age mother. Figure 4 represents the pedigrees of Klinefelter syndrome families with (a) 20 years young age mother, (b) 28 years young age mother and (c) 34 years advanced age mother. A perusal of these pedigrees indicates that there is inversely proportional relationship of age of mother and maternal grandmother in the family, wherein, as the maternal grandmother age increases the mother age decreases.

Table 2 also shows the result of the logistic regression analysis of case-control study of sex chromosomal aneuploidy children. The analysis

Table 1: Distribution of mean parental and maternal grandparental age of control and sex chromosomal aneuploidy (SA) families with Student's t-test.

Age range (in years)	Mean age $\pm$ SE years of							
	Mother		Father		Maternal grandmother		Maternal grandfather	
	Controls	SA	Controls	SA	Control	SA	Control	SA
18-24	20.58 $\pm$ 0.21 ^a	21.6 $\pm$ 0.57 ^{a*}	23.3 $\pm$ 0.32	-	20.3 $\pm$ 0.22 ^s	23.0 $\pm$ 1.00 ^{s**}	22.85 $\pm$ 0.45	-
25-29	26.8 $\pm$ 0.36 ^b	26.5 $\pm$ 0.50 ^b	27.2 $\pm$ 0.21 ^d	27.0 $\pm$ 0.65 ^d	26.5 $\pm$ 0.42 ^h	28.00 $\pm$ 0.37 ^{h**}	27.28 $\pm$ 0.27	-
30-35	32.4 $\pm$ 0.33 ^c	33.5 $\pm$ 0.64 ^c	32.3 $\pm$ 0.36 ^e	33.0 $\pm$ 0.40 ^e	33.3 $\pm$ 0.57 ⁱ	32.84 $\pm$ 0.54 ⁱ	32.11 $\pm$ 0.27 ^k	33.62 $\pm$ 0.37 ^{k**}
36-40	38.0 $\pm$ 0.00	-	37.0 $\pm$ 0.63 ^f	38.4 $\pm$ 0.50 ^f	38.33 $\pm$ 0.66 ^j	36.5 $\pm$ 0.50 ^{j*}	37.5 $\pm$ 0.50 ^h	38.00 $\pm$ 0.40 ^l
>=41	-	-	41.6 $\pm$ 0.66	-	41.0 $\pm$ 0.00	-	44.62 $\pm$ 0.90 ^m	41.66 $\pm$ 0.33 ^{m**}

* = $P < 0.05$; ** = $P < 0.01$.

Table 2: Distribution of parental, maternal grandparental age and number of children born to 100 control and 25 sex chromosomal aneuploidy (SA) families and logistic regression analysis in Mysore population (c.i. = confidence intervals).

Age range (in years)	No. of children born to															
	Mother				Father				Maternal grandmother				Maternal grandfather			
	Controls		SA		Controls		SA		Control		SA		Control		SA	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
18-24	196	64.68	13	52	33	10.89	-	-	259	64.75	2	8	78	19.5	-	-
25-29	64	21.12	8	32	104	34.32	7	28	94	23.5	8	32	113	28.25	-	-
30-35	33	10.89	4	16	118	38.94	13	52	41	10.25	13	52	142	35.5	7	28
36-40	7	2.31	-	-	33	10.89	5	20	4	1	2	8	46	11.5	14	56
>= 41	3	0.99	-	-	15	4.95	-	-	2	0.5	-	-	21	5.25	4	16

Logistic Regression Analysis				
Variables	Univariate		Multiple	
	Odds ratio (95% c.i.)	p value	Odds ratio (95% c.i.)	p value
Mother (per year)	1.092 (0.998;1.196)	0.055*	0.985 (0.798;1.217)	0.892
Father (per year)	1.106 (1.01;1.211)	0.029*	1.172 (0.939;1.44)	0.16
Maternal grandmother (per year)	1.248 (1.141;1.365)	0.0001*	1.365 (1.116;1.670)	0.002*
Maternal grandfather (per year)	1.217 (1.108;1.336)	0.0001*	0.934 (0.769;1.133)	0.488

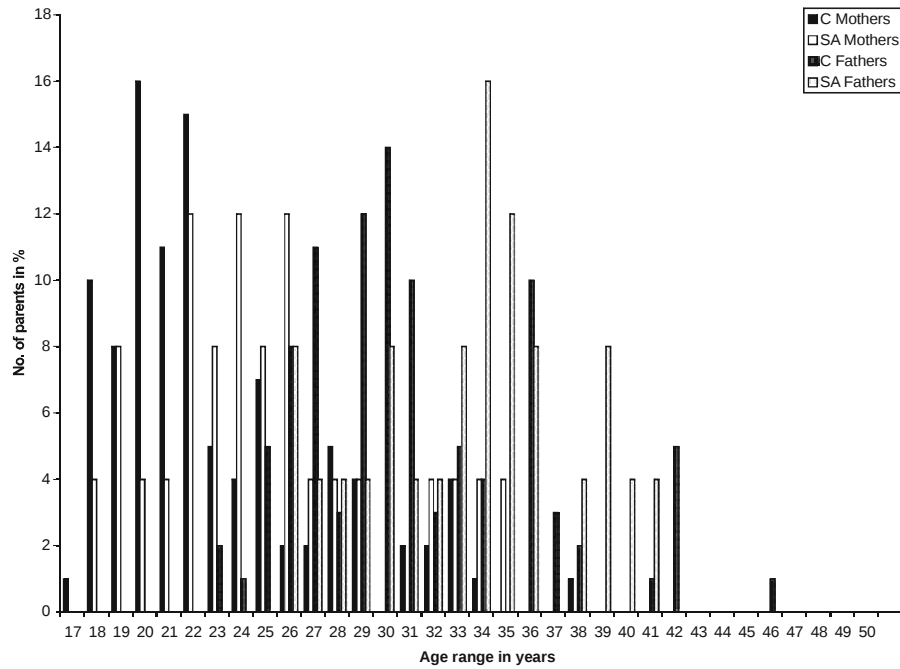


Fig. 1. Number of parents (in percent) in different age range of control and Sex chromosomal aneuploidy families (C=Control, SA=Sex chromosomal aneuploidy).

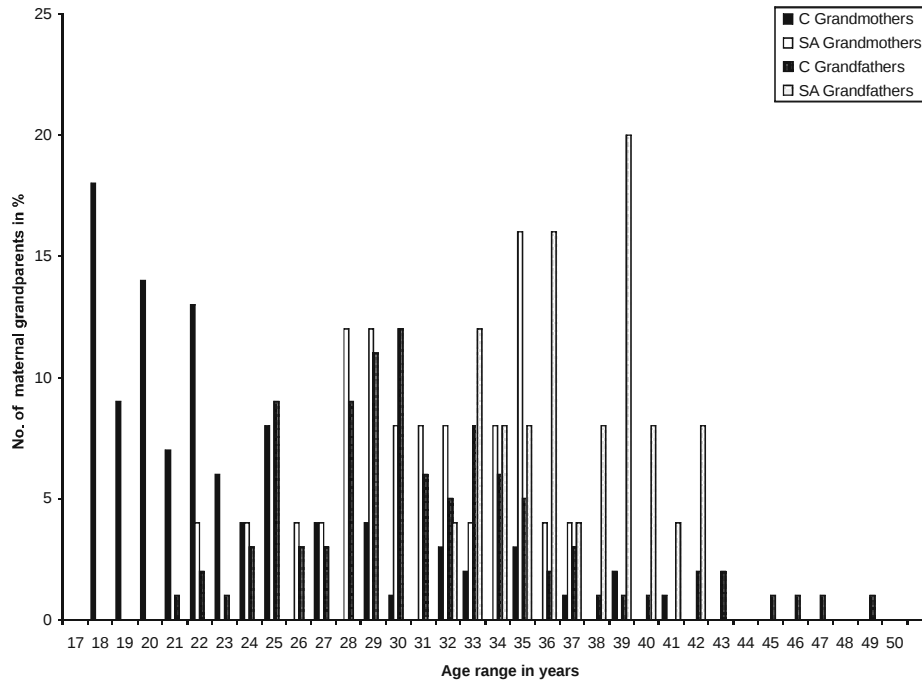


Fig. 2. Number of maternal grandparents (in percent) in different age range of control and sex chromosomal aneuploidy families (C=Control, SA=Sex chromosomal aneuploidy).

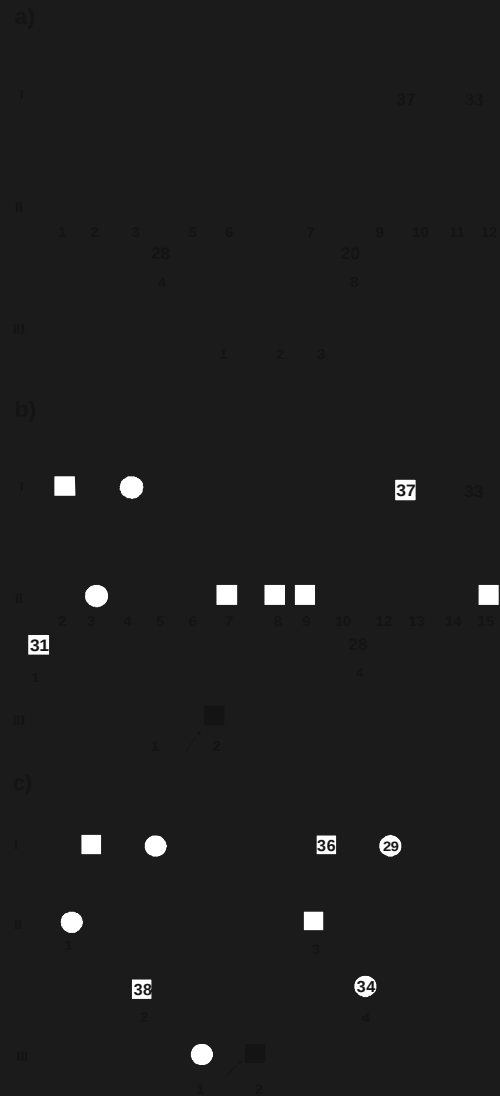


Fig. 4. Pedigrees of Klinefelter syndrome children at different age range of mothers (a) 20 years age mother, (b) 28 years age mother and (c) 34 years age mother. The Roman number in the left side of the figure indicates the number of generation. The Arabic number below the symbol denotes the number of individual in the generation. The number inside the symbol of grandmother represents the age when she gave birth to the mother of Klinefelter syndrome. The number inside the symbol of father and mother in the 2nd generation indicates their age when they gave birth to Klinefelter syndrome child. These are the representative pedigrees out of 9 Klinefelter syndrome families.

was done at all combinations to establish specific relationship of maternal grandmother's age with other variables. The 95% confidence intervals for the effect of age of mother, age of father, and age of maternal grandfather were lower than the age of maternal grandmother. The odds ratios were significant when all the four variables were used one at a time. When the age of father, and mother were considered as covariates there was no significant difference in the odds ratios. At the four variables level, only maternal grandmother's age showed significant difference in the odds ratios. These analyses also support that the advanced age of the maternal grandmother may be a risk factor for causing nondisjunction in sex chromosomal aneuploidy.

DISCUSSION

In the present study, both in control and sex chromosomal aneuploidy families, more children were born to young mothers (18-24 years), which indicate that in Indian families women get married and produces more children in their young age. Another possibility is that in India, younger women giving birth to sex chromosomal aneuploidy children are completely neglected for prenatal diagnosis, as most of the physicians may have the established concept "The advanced maternal age is the risk factor for nondisjunction of chromosome". Thus, the age distribution between the mother of sex chromosomal aneuploids and controls indicate that advanced maternal age has no decisive influence for the manifestation of sex chromosomal aneuploidy. The father belonging to the age group 30-35 years gave birth to maximum number of children both in control and sex chromosomal aneuploidy families. In Indian families, the age difference between husband and wife are in the range of 1-12 years. The social, cultural, and economical strategy made the male parental age higher than female parent. Therefore, fathers gave birth to more number of children in their advanced age in both the control and sex chromosomal aneuploidy families.

There are few earlier reports indicating the influence of grandmaternal age, on the risk of their grandchild being born with Down syndrome (Aagesen et al. 1984; Mikkelsen 1985). Recently, Malini and Ramachandra (2006) have reported the age of maternal grandmother at the time of birth of mother is the risk factor for the occurrence

of Down syndrome in Indian families. Similarly, in the present study, the maternal grandmother of control families produced maximum number of normal children in their young age. While the increased number of sex chromosomal aneuploidy children were born to the advanced age maternal grandmother of sex chromosomal aneuploidy families. Logistic regression analysis was done for all the four covariates considered together, the effects of mother's age, father's age and maternal grandfather's age were not statistically significant. However, the effect of the maternal grandmother's age was not diluted, showing an increase in odds by 36% per extra year. This supports the birth of young mothers of sex chromosomal aneuploidy children to advanced aged mothers. Further it clearly indicates the age of the maternal grandmother is a risk factor to cause sex chromosomal aneuploidy. This kind of situation is not found in majority of western population studied so far. In addition to this, the advanced age mother influencing the nondisjunction is not found in the sex chromosomal aneuploidy families under study.

The timeline for oogenesis compared with spermatogenesis points to possible error-prone stages of meiosis. Meiosis is initiated in oocytes during fetal life. After homologous chromosomes synapse and initiate recombination, meiosis is arrested. Meiosis I resumes in the woman's adult life just before the ovulation. At this point, Meiosis I is completed and the first polar body is extruded. Meiosis II is initiated but goes through a short arrest as it travels down the fallopian tubes. Meiosis II is completed after fertilization and the second polar body is extruded. Thus, meiosis in a woman extends over a 10-50 years period with the oocytes being arrested in Meiosis I during most of its lifetime. This contrasts with spermatogenesis, which begins at puberty when cells entering meiosis move from one stage to the other without delay (Lamb et al. 2005).

In young woman, meiotic machinery like spindles, sister-chromatid adhesive proteins, microtubule motor proteins, function optimally and correctly segregates all but the most susceptible exchange close to either the centromere or the telomere. For young women, then, the greatest risk factor for nondisjunction is the presence of a susceptible exchange pattern in the oocytes. The ovarian environment becomes compromised as the woman ages and oocytes within it become

progressively less able to disjoin chromosomes normally. Changes in oxygen concentration, pH or hormone concentrations have been implicated as subsequently affecting chromosome segregation in later meiosis (Gaulden 1992). There are reports that the spindle apparatus is less well formed in eggs from older women which have a lower intracellular pH and are present in a more hypoxic environment (Van Blerkom et al. 1997; Van Blerkom 2000; Van Blerkom and Devis 2001). As a woman ages her meiotic machinery accumulates the effects of years of environmental and age related insults, becoming less efficient and more error prone. Suboptimal exchange bivalents are still susceptible to nondisjunction, but even correctly placed bivalents are now at risk. The proportion of nondisjunction occurring among oocytes with normal exchange configuration increases over a time as age dependent risk factors exert their influence. As a result, the most prevalent exchange profile of nondisjoined oocytes shifts from susceptible to nonsusceptible patterns (Lamb et al. 2005).

To explain the effect of maternal age on autosomal aneuploidy, nondisjunction of chromosome 21, Lamb et al. (1997) hypothesized a two hit model. The first hit is unrelated to maternal age and involves the formation of a susceptible tetrad resulting from a specific exchange pattern established prenatally during meiosis I. The second hit involves some age related disturbance of the meiotic process. Such a disturbance might involve any part of the meiotic apparatus. In addition to this, an altered recombination pattern along with nondisjoined chromosome is the first molecular correlate identified for nondisjunction in humans (Brown et al. 2000). Jeffery et al. (2003) have demonstrated that as the oocytes exhibit significant age-dependent meiotic nondisjunction, wherein achiasmate chromosomes become vulnerable to nondisjunction as *Drosophila* oocytes age. If all these data are put together, it can be proposed that advanced maternal grandmother age is responsible to bring meiotic disturbance in the germ cells of her daughter when the maternal grandmother had conceived.

As the woman age advances, the reproductive system exhibit changes like: accumulation of environmental damage, reduced efficiency of DNA repair, increased genomic instability, genetic factors, hormonal influences, suppressed apoptosis, or decreased effectiveness of antioxidants and micronutrients (Sloter et al. 2004). This

leads to a suboptimal resumption of first and second meiotic divisions a change in ovarian functioning due to suboptimal degradation of uterine environment, which are needed for proper meiotic segregation in the germ cells of her daughter. The nonavailability or nonfunctioning of proteins leads to impairment in the meiotic process, which in turn results in nondisjunction of chromosome in the oocytes of the daughter (Malini and Ramachandra 2006). This event takes place during the embryogenesis of the mothers of the sex chromosomal aneuploidy children when she was in grandmother's womb. Therefore, the advanced age of maternal grandmother at the time of birth of the mother is a possible risk factor for the occurrence of sex chromosomal aneuploidy.

The best way to reduce the frequencies of any particular genetic abnormality in the population is to reduce the rate of reproduction by those individuals capable of having affected offspring. At the moment there are attempts to cure genetic disorders, although treatment is often not possible. Access to prenatal testing of chromosomal disorder to all pregnant women may reduce social inequalities in health. To prevent births of unwanted children with anomalies, comprehensive maternity care services must be available to all pregnant women regardless of socio-economic status. It is therefore necessary that the prenatal diagnosis programme for pregnant women irrespective of their age should be established as a preventive public health programme on a priority basis as immunization program in India.

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