ORIGINAL ARTICLE

Maternal age: a controversial factor in trisomy 21

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KEYWORDS
Trisomy 21; Aneoploidy; Nondisjunction; Maternal age; Down syndrome

Abstract
Background: Down’s syndrome (DS) is the most common autosomal aneuploidy in human beings and is characterized by a complex phenotype including characteristic facial features, skeletal appearance and it is most commonly diagnosed congenital malformation/mental retardation syndrome. Although advanced maternal age is a well established risk factor for the etiology of DS, controversy over it still continues.
Objective: The study was carried out to find the effect of maternal age in the etiology of trisomy 21.
Material and methods: Present study has been conducted on DS cases from various districts of Haryana State. DS cases were subjected to detailed morphological and cytogenetic analysis.
Results: In the present study more than eighty percent of DS children were born to young mother’s of <35 years and less than twenty percent to mother’s age >35 years. DS cases born to mother’s of age less than 30 years were 69.5%. Mean age of mother was 29.5 years. Partial correlation coefficient between mother’s age and number of DS cases (keeping father age constant) was calculated as r = 0.315.
Conclusion: Present study is not in favour of the effect of advanced maternal age on the occurrence of DS child. It can be concluded that risk of DS cases is not only due to the advanced maternal age and some others factors (genetic and environmental) may be involved in the formation of a trisomic zygote. Future studies are required to investigate the various factors that regulate the segregation & recombination in humans.
Introduction

Down’s syndrome is the most common autosomal aneuploidy in human beings, caused by a gene dosage-imbalance resulting from human chromosome-21 trisomy and it is characterized by a complex phenotype including characteristic facial features, skeletal appearance, low mental level, hearing loss and developmental delay. It is a cosmopolitan disease, having been reported in nearly all countries and ethnic groups. Although advanced maternal age is a well established risk factor for trisomy 21 Down’s syndrome, much remains to be learnt about the basis of the maternal age effect. For example, it is still uncertain whether the chronological age of mother or the physiological age of the ovary has any biological and clinical relevance. If oocyte reduction with advancing age is the basis of the maternal age effect, as suggested by Warburton, then women, who have a reduced number of oocytes for other reasons might have an increased risk for a conception with trisomy. Frequency of nondisjunction increases with the maternal age. This increased risk is due to factor that adversely affects meiotic chromosome behavior as a woman ages.

According to well documented studies it was found that excluding the eventual effects of viral disease, x-rays and others risk exposures, free trisomy 21 very often arises as second meiotic error and its frequency increases with ageing of mother i.e. 35 years and over. It has recently been shown that 95% of cases of trisomy 21 appear to result from nondisjunction occurring in the first meiotic division in the ovum. Several theories have been proposed to explain the increased incidences of Down’s syndrome with advanced maternal age. Another hypothesis proposes that structural, hormonal and immunologic changes that occur in the uterus with advanced age produce an environment which is less able to reject a developmentally abnormal embryo. Although the underlying cause of an extra copy of chromosome 21 has been known for a long time, the phenotype to genotype relationship is just beginning to be understood and many questions about the molecular pathophysiology of the condition have not yet been answered. These and other hypothesis are not mutually exclusive and it is possible that a combination of factors is responsible for the relation-ship between the incidence of trisomy 21 and advanced maternal age. Still majority of relations of maternal age to nondisjunction has been described as “one of the most important problem to be solved” in Down’s syndrome and in human cytogenetics.

Material and methods

Present study has been conducted on 200 cases of Down’s syndrome from 30 centers of 12 districts of Haryana. Detailed history with complete data on course of pregnancy, age of the parents at the birth of the child and neonatal period of Down’s syndrome patients were taken. Down’s syndrome cases were subjected to detailed morphological and cytogenetic analysis.
Results

Marked variation was noticed amongst the age of the mother of a Down’s syndrome child. It varied from 17 years to 46 years. Maximum (23.5%) Down’s syndrome children were born to the mother’s of age 26-28 year (fig. 1). To know the role of maternal age in Down’s syndrome six different age groups were made. Mean age of mother was 29.5 years in the Down’s syndrome cases. Down’s syndrome cases born to mother’s of age less than 30 years were 69.5% and to mother’s aged more than 30 years were 30.5% (table 1 and figure 2). Age and sexwise analysis of Down’s syndrome cases in different age group of parents showed that more number of male Down’s syndrome children were born to parents of 25 to 30 years of age. Partial Correlation coefficient between mother’s age and number of Down’s syndrome cases (keeping father age constant) was calculated as r = 0.315, which showed that increase risk of Down’s syndrome was not due to exclusively mother’s age factor.

In case of free trisomy, mother’s age at pregnancy was between 20-40 years. In the case of translocation and mosaicism the mother’s were of between 28-34 years (table 2). In free trisomy 21 cases maternal age at pregnancy was below 30 in 67.3% cases and above 30 in 27.2% cases (table 3). In maximum cases of free trisomy 21 (50.2%) mother’s age was between 26-30 years (table 4). Present study sup-
Maternal age: a controversial factor in trisomy 21

Table 4  Maternal age in free trisomy 21 cases

<table>
<thead>
<tr>
<th>Mother’s age (years)</th>
<th>Down’s syndrome cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>(4.9)</td>
</tr>
<tr>
<td>21-25</td>
<td>(12.2)</td>
</tr>
<tr>
<td>26-30</td>
<td>(50.2)</td>
</tr>
<tr>
<td>31-35</td>
<td>(20.1)</td>
</tr>
<tr>
<td>36-40</td>
<td>(7.1)</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>—</td>
</tr>
</tbody>
</table>

*Age below 30. **Age above 30.

The most accepted statement is that the risk of the disease increases exponentially with the increasing age, leading to the observed maternal age effect. One reason for urgency in gaining an understanding of the causes of nondisjunction and the maternal age effect is that many professional women are effectively delaying child bearing until their mid-thirties or later, when their risk of having a trisomic child increases significantly. In some populations there are already indications that this delay of pregnancy is beginning to produce detectable increase in the incidence of Down’s syndrome. Much more data are needed on trisomic incidence in offsprings of very young mothers. This would help to determine whether the maternal age effect is indeed restricted to women of older reproductive ages, as is now widely believed. Such data would also be helpful in better assessment of the hypothesis involving hormonal imbalance. A multidisciplinary approach to know the trisomy induction and influence of maternal age is required. Molecular approaches to the classical ones of biochemistry, cell biology, cytogenetics, epidemiology, genetics and physiology may be considered. We hope that eventually knowledge of what is responsible for natural aneuploidy may be identified and further damage to the oocyte could be prevented.

Discussion

Though maternal age was dismissed by the Penrose as insignificant in the etiology of Down’s syndrome, controversy over maternal age continues, mainly because an equivocal data could not be obtained either supporting or rejecting it. Important factors in the conception of trisomies are delayed fertilization, advanced maternal age and increased satellite association. Other factors such as physical, biological and chemical mutagens, have also been found to cause non disjunction. The most accepted statement is that the risk of the disease increases exponentially with the ageing of the mother, as first recognized by Shuttleworth (1909). The analysis of Down’s syndrome patients in the present study depicted that mean maternal age was 29.5 years for Down’s syndrome cases. In the western studies the mean maternal age at the conception of Down’s syndrome was found to be 34.4 years. There must be other factors playing role in birth of Down’s syndrome child. In another study, the percentage of trisomies among all clinically recognized pregnancies climbed from 2% for women <25 years of age to 35% for women >40 years of age. On contrary, reports from Sweden revealed that despite the rising maternal age, there was no increase in the number of births of children with Down’s syndrome. Present study reveals that more than 80% of Down’s syndrome children were born to young mother’s of <35 years and less than 20% born to mother’s age >35 years (table 5). The result of present study is not in favour of the effect of age of mother on the occurrence of Down’s syndrome child. Therefore, Shuttleworth explanation does not provide answer to the cases where Down’s syndrome child is born to a young mother. It has recently been shown that 95% of cases of trisomy 21 appear to result from nondisjunction occurring in the 1st meiotic division on the ovum. Along with the advanced maternal age, altered recombination pattern is the only other factor that is consistent with maternal meiotic nondisjunction.

The explanation for increased risk of nondisjunction to maternal age is suggested by hypothesis that the very long prophase of meiosis, in the state of suspended animation of the ovum before the 1st meiotic division at ovulation, alter the segregation of the chromosome resulting in nondisjunction. The compromised microcirculation hypothesis explains the occurrence of aneuploidy in primary and secondary oocytes, sperm precursor cells, tumor and embryonic cells. It also explains why women of all reproductive ages may have a Down’s syndrome child. It was also suggested that the greatest risk factor for nondisjunction among younger women is the presence of a susceptible exchange pattern. It was hypothesized that environmental and age related insults accumulate in the ovary as a woman ages, leading to malsegregation of oocytes with stable exchange patterns. It is the risk, due to recombination independent factors, that would be most influenced by increasing age, leading to the observed maternal age effect.

One reason for urgency in gaining an understanding of the causes of nondisjunction and the maternal age effect is that many professional women are effectively delaying child bearing until their mid-thirties or later, when their risk of having a trisomic child increases significantly. In some populations there are already indications that this delay of pregnancy is beginning to produce detectable increase in the incidence of Down’s syndrome. Much more data are needed on trisomic incidence in offsprings of very young mothers. This would help to determine whether the maternal age effect is indeed restricted to women of older reproductive ages, as is now widely believed. Such data would also be helpful in better assessment of the hypothesis involving hormonal imbalance. A multidisciplinary approach to know the trisomy induction and influence of maternal age is required. Molecular approaches to the classical ones of biochemistry, cell biology, cytogenetics, epidemiology, genetics and physiology may be considered. We hope that eventually knowledge of what is responsible for natural aneuploidy may be identified and further damage to the oocyte could be prevented.

Table 5  Maternal age and the percentage of Down’s syndrome (DS) cases in India

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>DS in other parts of India (%)</th>
<th>DS in present study (%)</th>
<th>Controls (normal) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>6-8</td>
<td>4.5</td>
<td>7.5</td>
</tr>
<tr>
<td>21-25</td>
<td>38-43</td>
<td>30.0</td>
<td>35.5</td>
</tr>
<tr>
<td>26-30</td>
<td>21-30</td>
<td>35.0</td>
<td>43.0</td>
</tr>
<tr>
<td>31-35</td>
<td>12-18</td>
<td>13.5</td>
<td>8.0</td>
</tr>
<tr>
<td>36-40</td>
<td>4-8</td>
<td>15.0</td>
<td>4.0</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>0-3</td>
<td>2.0</td>
<td>2.0</td>
</tr>
</tbody>
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Conflict of interests

Authors declare not to have any conflict of interests.

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