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# SHORT COMMUNICATION

## RIBEIRÃO PRETO, BRAZIL

## Down syndrome and precocious menopause

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***Purpose*:** To determine whether women who had children with Down syndrome (DS) had precocious menopause.
***Methods*:** We selected 104 mothers of children with DS and 121 normal women who had children with no genetic problems. We conducted an interview and compared their mean age at menopause.
***Results*:** We did not detect a statistically significant difference in mean age at menopause. When we stratified into women who had conceived when younger or older than 35 years of age, we found a statistically significant difference only for women who had conceived at the age of 35 years or older. We observed three cases of previous unilateral ovarian surgery in the study group and one case in the control group.
***Conclusions*:** We cannot conclude that mothers of children with DS will have precocious menopause. Nevertheless, our findings do not exclude the theory of reduced ovarian reserve as a primordial factor in the genesis of DS.

**KEY WORDS:** Down syndrome; menopause; oophorectomy; ovarian reserve.

## INTRODUCTION

Down syndrome (DS) corresponds to the phenotype produced by chromosome 21 trisomy and has been considered to be the most common aneuploidy observed in clinical practice (1,2). One in 800 newborns is affected and more than 50% of pregnancies with DS are aborted (2,3). The risk of having a baby with DS increases with maternal age (2,4–6). While a 20 year old woman has a risk of 1/1400, the risk increases to 1/100 when she reaches the age of 40 years (2,7,8). The free trisomy 21 is due to meiotic non-disjunction, but the exact mechanism underlying this event is still unclear. Oocytes do not complete meiosis until fecundation, and therefore the event may be due to a genetic error or deterioration of meiotic spindle components when old oocytes are recruited (3,9,10).

Kline *et al.* (11) found the age of menopause to be about 1 year earlier in women with a trisomic conception. Other authors observed that young women who gave birth to children with DS had an increased incidence of ovarian surgeries or unilateral ovarian agenesis (12). It had been suggested that the reduced number of ovarian follicles should be the primordial factor in meiotic non-disjunction and not the ovarian age per se (4,13,14). Normal oocytes would be preferentially recruited, while others with genetic errors would be left behind (15). An increased level of FSH was also observed in normal women (with the two ovaries) who had children with DS (16), and therefore it was proposed that these women would have precocious menopause as a result of the reduced number of ovarian follicles (oocyte pool) (14–17).

The objective of the present study was to determine whether women who had children with DS had precocious menopause compared to the normal population and whether these women were submitted to ovarian surgery prior to child birth more often than the control group.

## MATERIALS AND METHODS

### Participants

The study was first approved by the Research Ethics Committee of the University Hospital of the School of Medicine of Ribeirão Preto, University of São Paulo. Mothers of children with chromosome 21 trisomy were selected by a review of medical records. Only free trisomies detected by cytogenetic analysis were chosen. Of 635 women, 104 were in the climacteric period and satisfied the inclusion criteria established. The control group consisted of 121 healthy women with no children with genetic problems. We conducted an interview with questions about menarche, current age, menopause, previous surgeries, medication, and age at birth of the child with DS, or at last pregnancy for the control group. We included in all groups women with interruption of menses for at least 1 year and excluded the use of hormones, hysterectomy or bilateral oophorectomy. For control group were excluded nulligestas, mothers of children with any genetic disease and patients with any diagnosed disease.

**Table I.** Mean Age at Menarche, Age at Childbirth, and Menopause in the Two Groups

| | Down syndrome (mean) | | | Control (mean) | | |
|---|---|---|---|---|---|---|
| Type | <35 years ($n = 37$) | ≥35 years ($n = 67$) | Total ($n = 104$) | <35 years ($n = 93$) | ≥35 years ($n = 28$) | Total ($n = 121$) |
| Mc | 12.97 | 12.80 | 12.86 | 13.26 | 13.28 | 13.27 |
| C | 29.32 | 38.85 | 35.46 | 28.34 | 37.92 | 30.56 |
| Mp | 48.54 | 49.10 | 48.90 | 49.23 | 50.78 | 49.59 |

*Note*. Mc: Age at Menarche; C: Age at childbirth; Mp: Age at Menopause.

### Statistical Analysis

We compared the mean age at menopause between the two general groups. We stratified both groups to check if the age when women conceived was related to the beginning of the climacteric. Thus we divided both groups into two subgroups, one consisting of women who had conceived before 35 years of age and the other of women who had conceived at an age of 35 years or later. The data obtained were analyzed by the Student's *t*-test (one-tailed).

## RESULTS

The results are presented in Table I. There was no significant difference in mean ages at menopause between groups. A statistically significant difference in mean age at menopause was found only in women who had conceived at 35 years of age or later. With a significance of 0.05, it is possible to state that the women who had conceived children with DS after 35 years of age entered menopause before the control group. In addition, we observed three cases of previous ovarian surgery in the study group (3/104) and one case in the control group (1/121). Two cases in the study group and the only case in the control group were women who had conceived before 35 years of age.

## DISCUSSION

The age at menopause of the control group was similar to that of the study group, a fact that might represent a selection bias. We expected a mean age at menopause of 51 years in the control group, as per historical data (18,19). We excluded women with any diagnosed disease, but it may be possible that the selected group, apparently free from diseases, had a predominance of undiagnosed conditions. On the other hand, when we considered the historical mean age at menopause (51 years), there was no significant difference from the mean age at menopause observed in the study group.

A statistically significant difference in mean age at menopause between the two groups was found only in women who had conceived at an age of 35 years or later. However, we cannot say that this group had premature menopause (the cessation of menses before 40 years of age, with a precocious beginning of the climacteric) (20).

Considering the correlation between aneuploidy and reduced oocyte pool, young mothers of children with DS should present precocious menopause, a fact that was not observed in our sample. Women who conceive after 35 years of age are responsible for the majority of cases of aneuploid babies, and therefore this group has rare cases of paternal origin. Since we did not exclude paternal cases, it is possible that there are some cases of aneuploidy of paternal origin within the group of young mothers. The group of older mothers would be more "pure" in terms of maternal factor and more representative for the purpose of this study.

The reason for statistical significance in one age group and not the other may also be merely sample size. But the results of Kline *et al.* (11) are approximately what were found in the current study.

It is necessary to investigate if women who were submitted to unilateral oophorectomy have an increased incidence of aneuploid newborns. As done by us and by Freeman *et al.* (12), when analyzing mothers of children with DS and determining the incidence of ovarian surgeries, a reduced number of cases is obtained, which, in our opinion, is not representative. We suggest an inverse type of study, i.e., determining the incidence of DS babies among women with poor ovarian complement.

## CONCLUSIONS

We cannot conclude that mothers of children with DS will have precocious menopause. Nevertheless, our findings do not exclude the theory of reduced

ovarian reserve as a primordial factor in the genesis of DS. If this is true, pre-conceptional FSH measurement, although not considered useful for aneuploidy screening (15), will become an important tool in genetic counseling, mainly for infertile couples who seek in vitro fertilization due to maternal causes.

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**Ana Karina Bartmann,[1,3] Francielle M. Araújo,[1] Odilon Iannetta,[1] João C.C. Paneto,[2] Lúcia Martelli,[2] and Ester Silveira Ramos,[1,2,3]**

[1] Department of Obstetrics and Gynecology, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil.
[2] Department of Genetics, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil.
[3] To whom correspondence should be addressed at Departamento de Genética, Av. Bandeirantes, 3900, Ribeirão Preto, SP, CEP 14049-900, Brazil; e-mail: esramos@rge.fmrp.usp.br.