Effect of oral contraceptive use in medical history on the prevalence of common fetal trisomies in advanced maternal age

PhD thesis

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Budapest
2019

Introduction

Trisomy 21, the underlying cause of Down syndrome is the most common autosomal chromosome disorder associated with cognitive impairment and mental retardation. It occurs more frequently in advanced maternal age.

Several hypotheses were published concerning the relationship of the trisomies' classic model of origin with maternal age which is a widely known risk factor of these chromosome disorders.

According to a currently popular theory, they are caused by meiotic non-disjunction in a disomic oocyte. However, more recent research suggests another underlying mechanism. In an article published in 2008, a paradigm shift in the development of Down syndrome was envisioned: the authors suggested that this syndrome is caused by ovarian mosaicism.

The foundation of the model – and in the same time, its main difference compared to the classic interpretation – is that the error takes place in the pre-meiotic mitosis phase (when the primitive germ cells are formed) and therefore the "inevitable", so-called secondary non-disjunction of an oocyte with a pre-existing trisomy 21 takes place during the meiosis.

Therefore, based on the oocyte mosaicism model (OMM), trisomy 21 originates from a segregation error taking place during the premeiotic mitosis. It is an important observation that cells with trisomy 21 seem to lag behind in maturation as compared to their normal (disomic) peers. Disomic oocytes mature faster, therefore their number decreases more rapidly than that of the trisomic oocytes. As a result, the proportion of trisomic oocytes may be increased at advanced maternal age. This explains the increase in the risk of trisomic pregnancy with age and may suggest a method to help reduce the loss of oocytes. Oral hormonal contraception may be an appropriate method.

Environmental studies explaining the occurrence of trisomies also mention smoking and tobacco chewing as underlying causes of chromosome disorders.

Other studies suggest the role of ovarian surgeries: some say that the frequency of trisomies may be increased by reduced ovarian volume (partial or even total oophorectomy).

Objective

1 Based on the oocyte mosaicism model, there may be an increased chance that conception of an oocyte with trisomy 21 takes place in advanced maternal age. Due to a more rapid reduction in the number of disomic oocytes, there may be a relative accumulation of trisomic cells with advanced age. If ovulation is inhibited, a more favorable proportion of disomic and trisomic cells may be conserved as only a uniform reduction in the number of both trisomic and disomic oocytes caused by apoptosis is expected. The objective of my paper is to investigate which factors restricting ovulation may have substantial effect on the reduction of the risk of trisomic pregnancies. I paid special attention to the role of oral hormonal contraceptives.

2 When investigating the underlying cause of various trisomies, the suggested environmental factors included smoking. In addition to taking oral hormonal contraceptives, does smoking affect the occurrence of trisomies? Finding an answer to this question was one of the objectives in my thesis. Is there a relationship between smoking and the occurrence of trisomic pregnancies in case of advanced maternal age?

3 Nowadays, ovarian surgeries are seen increasingly often among patients with pregnancies in an advanced maternal age. With surgeries performed for various reasons and techniques, reduced ovarian reserve should by all means be taken into consideration. Earlier studies suggested a relationship between frequent fetal trisomies and ovarian surgeries, therefore I collected information in this regard too: can ovarian surgery in the patient's history be a relevant factor here? Among factors organically connected to and affecting ovarian function, mapping the impact of surgeries was added to my objectives.

Methods

I collected data regarding the two-year period from 1 September 2013 to 1 September 2015 at the 1st Department of Obstetrics and Gynecology, Semmelweis University. During this period, 12,776 patients attended genetic counseling and 2,332 of them were required to undergo amniocentesis. Structural or numeric disorders were found in 75 cases. I selected the cases where the test was taken in advanced maternal age and trisomy 21, 18 or 13 was detected. In our study, all relevant historic data to assess the number of ovulations were available in 35 cases: date of first period, date of last period, number and duration of previous pregnancies, number of previous miscarriages and the gestational age at miscarriage as well as the duration of oral hormonal contraceptive use. These data were collected from the patients' medical history data sheets and records. In order to follow-up the accuracy of data, I made telephone interviews. It was important to verify existing data and to add the missing information to the database. The number of ovulations was estimated based on the age at menarche, the length of the menstrual cycle, the date of the last period before pregnancy as well as data regarding previous pregnancies and miscarriages. Data collection also included the duration of hormonal contraceptive use as a factor affecting ovulation as well as smoking habits and ovarian surgeries in the patients' history.

In our study, it was important to include cases in the affected group where trisomic amniocentesis result was obtained in advanced maternal age, without taking into consideration what screening result/s led to the indication of the invasive genetic testing. The control group without significant age difference was recruited from cases showing no chromosome disorders. That is, the control group consisted of patients undergoing genetic amniocentesis because of an increased risk suggested during prenatal screening and advanced maternal age, where normal karyotype was verified.

Ovulation is affected by several factors. The first oocytes become mature in adolescence and maturation continues until menopause. In my study, of the conditions associated with anovulation, I investigated the physiological conditions together with information on the duration of hormonal contraceptive use. [In addition, several pathologies may also result in anovulatory cycles (such as hyperandrogenic conditions, hypothalamic dysfunction, hyperprolactinemia, hypothyreosis, primary pituitary disorders, premature ovarian failure, due to radiation therapy or chemotherapy, premature menopause); however, no such substantial disorders were known in our

affected population or control group.]

I collected information on the factors affecting oocyte maturation (ovulation). By subtracting the date of birth and the date of menarche from the date of the last menstrual period, the result shows the fertile period when ovulations take place. The period of ovulations is further decreased by the duration of pregnancies and breast-feeding, as well as the duration of oral contraceptive use. Information collected regarding oral hormonal contraceptive use included the total duration of use in years, with year fractions, if necessary. Based on these factors, a formula was created to estimate the number of matured (ovulated) oocytes (estimated ovulation number, EON).

Results

Based on the data from the 2,332 amniotic fluid samplings: Structural or numeric disorders were verified in 75 cases. Of these, tests were performed in advanced maternal age and trisomy 21, 18 or 13 was detected in 45 cases. Of these, all necessary historical data was available in 35 cases and their accuracy was checked by telephone interviews. The number of ovulations was estimated based on the first menstrual period, the length of the menstrual cycle, the date of the last period before pregnancy, previous pregnancies, and miscarriages. No significant difference was found between the affected group and control group in terms of maternal age, average duration of the menstrual cycle, number of pregnancies, spontaneous miscarriages and abortions. However, oral contraceptive use showed significant differences: in advanced maternal age, the duration of oral contraceptive use in medical history was shorter in case of trisomic pregnancies than in normal pregnancies (3.2 vs. 6.0 years, $p<0.05$). In advanced age women pregnant with trisomic fetuses, the total duration of oral hormonal contraceptive use was shorter (3.2 vs. 6.0 years, $p<0.00037$) and the mean EON was higher (258.5 vs. 224.1, $p<0.012$). Similar results were obtained when looking at the cases of 21 trisomy only: shorter duration of oral contraceptive use was found (3.1 vs. 6.0 years, $p<0.00056$) and EON was higher too (258.4 vs. 224.1, $p<0.023$).

When comparing only trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome) cases with the control group, no statistically significant difference was found either in mean maternal age, duration of menstrual cycle, number of pregnancies and spontaneous and induced abortions, however, the duration of oral contraceptive use was also shorter before the pregnancy in question (3.4 vs. 6.0 years, p NS), and EON was also higher (258.8 vs. 224.1, p NS). However, these results did not show any statistically significant difference – probably due to the low number of cases. Data was also collected on the smoking habits of women taking oral contraceptives which is also a suspected risk factor of increased Down syndrome risk**.** Information on smoking habits was available in 14 cases of trisomic pregnancies and 54 cases in the control group. Based on data collected about smoking habits, periconceptional smoking did not show any significant difference between trisomic pregnancies and the control group (NS, $p=0.698$). Numerically, the total duration of smoking was longer in the affected group (7.8 vs. 6.2 years, p: NS), however, this did not constitute a statistically significant

difference. In addition, no association was found between the duration of oral contraceptive use and smoking either (p=0.835).

Of the 35 cases constituting the affected group, information on surgeries performed on appendages was available in 26 cases. In the control group of the study consisting of 100 subjects, we had information on whether there was any ovarian surgery in the medical history in 59 cases. According to our calculations, there was no statistically significant difference between the control group and affected group in terms of mean maternal age, age at menarche, cycle length, number of pregnancies or spontaneous or induced abortions. There were 2 cases (3.4%) of ovarian surgery in the control group and 1 case (3.8%) in the affected group, therefore relevant statistical significance could not be established.

Conclusions

1 In my study, I was able to confirm for the first time that oral hormonal contraceptives used for a longer period of time before pregnancy reduce the risk of Down syndrome in pregnancies in advanced maternal age. Based on our calculations, significant difference was found between the control group and pregnancies with trisomy 21 in the duration of contraceptive use. Similar results were found in pregnancies with trisomy 18 or trisomy 13, however, the difference was not significant. This may be explained by the lower number of cases, taking into consideration that the estimated number of ovulations (EON) resulted in similar data.

2 When projecting smoking habits on the study population, I came to the conclusion that there was no significant difference between the affected group and the control group in terms of the duration of smoking. Smoking did not have an effect on the results.

3 Ovarian surgeries lead to the reduction of the ovarian reserve. However, there is no chance to distinguish between disomic and trisomic cells, therefore their proportion can be considered as constant in a given volume. Taking our hypothesis into consideration, ovarian surgeries that are used nowadays are not likely to affect the risk of trisomies, however, due to the low number of cases in my study, no far-reaching conclusions can be made yet.

List of the author's publications

Primary papers published in the topic of the thesis

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Total impact factor - IF: 10.191