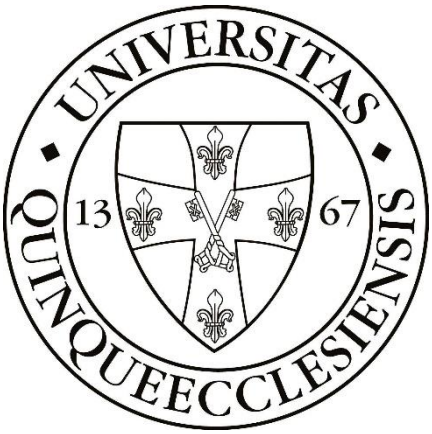

UNIVERSITY OF PÉCS

FACULTY OF HEALTH SERVICES

DOCTORAL SCHOOL OF HEALTH SCIENCES

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The effect of the mother's age and process of labor on the risk of development abnormalities occurring

Doctorate (Ph.D.) Assessor

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1. Introduction

As an obstetrician-gynecologist, I have developed a specialization for fetal ultrasound diagnosis in recent years. Advanced maternal age and certain medical conditions (epilepsy and diabetes) are associated with higher multiplex risk of chromosome and congenital abnormalities. It is necessary, however, to systematically assess the potential impact of maternal age and birth order on an increased the risk of isolated congenital abnormalities, which cause 90 of all congenital abnormalities. Is there a correlation between birth order and maternal age and the frequency of isolated congenital abnormalities? Identifying these associations would make it possible to diagnose these abnormalities more effectively with targeted ultrasound examinations.

The data required to support this study is contained in the Hungarian National Registry of Congenital Disorders (VRONY) and the Case-Control Study of Congenital Abnormalities (FREKF) database.

Age and birth order are recorded in proportion to fetal abnormalities/birth defects in the VRONY system. The FREKF database allows this data to be verified and – if necessary – corrected. For every case of abnormality in FREKF, two normal 'case-matched controls' are selected from the Hungarian Central Statistical Office (KSH) Central Population Record based on gender, year, month, week and place of birth. As far as I know, this is the first population-based epidemiological study to compare all congenital abnormalities against maternal age and birth order using case-matched control samples.

Professor Czeizel assisted me in choosing this topic. It was his recommendation to evaluate cases registered by FREKF and released into the public domain between 1980 and 1996, during which time he was director of FREKF. The data was repeatedly validated in the course of international research projects. As a colleague of Dr. Andrew E. Czeizel, Erika Varga made the necessary data available to me. My topic mentor was Dr Béla Veszprémi, adjunct professor at the University of Pécs.

2. Objectives

My Ph.D. research topic is the assessment of the impact of maternal age and birth order on isolated congenital abnormalities (CA) based on analysis of the frequency with which they are recognized at birth. Maternal age or, more precisely, the correlation (association) between advanced age and numerical chromosome aberrations are well known, primarily with regard to increased risk of Down syndrome. Studies of this nature into the CAs responsible for as much as 90% of congenital abnormalities are rare. As far as I know, systematic analysis of individual congenital abnormalities and their case-matched control has not taken place for a study sample based on the entire population. This research would have three theoretical and practical benefits:

1. To what extent should maternal age and birth order be taken into account as so-called 'confounding variables' in the course of research into the pathological causes of congenital abnormalities when calculating the standardized proportional probability of individual associations?

2. Woman are increasingly choosing to have children is later in life, so establishing any connection between age and isolated congenital abnormalities is an important issue. In addition, the number of children per family is 1.3, which indicates that the frequency of single children and therefore firstborns is high. For this reason, it would be valuable to know the effects of this and of birth order on the risk of isolated congenital abnormalities.

3. Analysis of gender split for isolated CAs.

4. In addition to the customary general assessment carried out during ultrasound examinations, it is important to be aware of risk factors (e.g. age group) that might make targeted examination necessary.

3. Materials and methods

For our research, we processed the VRONY and FREKF databases and performed a case-matched control study. We also used distribution of Down syndrome cases as a reference.

Statistical analysis of the data was primarily carried out with the SAS 9.1 (SAS Institute, Cary North Carolina, USA) software package. Results of $p<0.01$ were considered significant. The mathematical analysis was carried out by Éva Susánszky and Róbert Urbán.

4. Study results and discussion

4.1 Down syndrome, as reference CA

The FREKF records contain 834 Down syndrome cases and a case-matched control sample of 1,432 mothers distributed by age group. There was a significant deviation in their mean age (29.1 vs. 25.7 years) and birth order (2.3 vs. 1.8). When comparing age groups, we considered the 25-29 group to be the reference.

In 30-34 year-olds, risk was increased by a factor of 1.5, rising to 3.1 and 11.6 among the 35-39 and the over 40 age groups respectively. All these values correspond to those in the scientific literature, verifying that the FREKF material is also suitable for analyzing maternal age with regards to congenital abnormalities.

4.2 Maternal age and association with isolated congenital abnormalities

Of 22,843 CA cases recorded in the FREKF database from between 1980 and 1996, 21,494 (94.1%) were isolated CAs. Of these, 21,056 (98.0%) were live births, while 335 (1.5%) and 103 (0.5%) were stillbirths, or abnormal fetuses identified in the uturus. In these cases, the pregnancies were terminated.

During the period observed, 2,146,574 births were registered in Hungary, so the 38,151 newborns in the FREKF case-matched group represent 1.8% of the total population. For my study, I only evaluated the case-matched control samples of 34,311 isolated CA cases.

Maternal age for the cases of isolated congenital abnormalities and their case-matched control samples only deviated significantly in four congenital abnormality groups. For the cardiovascular (25.7 vs. 25.4 years) and cleft palate (26.2 vs. 25.4 years) cases, the mother was older, while for cases of polysyndactyly (24.8 vs. 25.5 years) and abdominal wall abnormalities (24.1 vs. 25.7 year), the mother was younger.

The ratio of women aged 35 and above only showed a deviation for club foot in the comparison of the 24 isolated congenital abnormality groups and their case-matched controls. The proportion of cases where the mothers were older was somewhat higher for these abnormalities (6.4% vs. 4.4%), but the upper odds ratio value was only 1.00, i. e. the deviation is close to significant.

The youngest age group was 19 and under, which is relatively rare with 10.9% of all cases and 8.6% of the all case-matched control cases. Three congenital abnormality groups showed significantly higher ratios in the younger age group: cardiovascular CAs (9.6% vs. 8.7%), undescended testes (10.7% vs. 8.2%) and club foot (12.7% vs. 9.1%). Translated into the language of medical practice, the risk of cardiovascular congenital abnormalities among this younger age group can be expected to increase by 30%, undescended tested by 17% and club foot by 16%.

Finally, I also separately evaluated sub-groups of three congenital abnormalities. Within the category of neural tube defects, I separated anencephaly and spina bifida aperta/cystica, of the cardiovascular CAs, ventricular septum defects, the ostium secundum atrial septum defect, the open ductus arteriosus, as well as combining conotruncal, left- and right-sided obstructive defects, and finally two sub-categories of abdominal wall congenital abnormality: exomphalos and gastroschisis.

The mean maternal age only showed a deviation in the atrial ostium septum defect (26.1 vs. 25.4 years). When analyzing all maternal age groups, anencephaly showed deviations between the cases and their case-matched controls due to the higher proportion among the 19 and under and 20-24 age groups. None of the CA categories/groups showed greater risk for the 35 and over category. By contrast, risks of left-sided obstructive heart defects, and particularly of gastroschisis, were significantly higher in the younger age group.

Analysis of the cases and their case-matched controls for the 24 isolated congenital abnormality groups based on the Hungarian population therefore produced two important results: For isolated CAs, advanced maternal age does not represent greater risk, while some isolated congenital abnormalities show significantly higher risk among the younger (19 and under) age group and should be taken account of in clinical practice, primarily in the course of ultrasound examinations.

4.3 The impact of birth order on the risk of isolated congenital abnormalities

Birth order may not only be significant as a misleading demographic factor, it may also play a role in the origin of certain congenital abnormalities. When evaluating birth order – as opposed to the order of delivery – multiple births do not present a technical problem as we randomly only considered one child in the case of twins. As a result, the number recorded for birth order and order of delivery is the same.

The number of firstborn among the case-matched control group was 16,409, or 47.8% of the study. The percentage of those born second (37.5%) or third (10.7%) was found to be considerably lower. The total number of those who were first, second or third born was 32,948, or 96.0% of the toral. For this reason, I will present rarer later birth orders (fourth, fifth and sixth or later) as a combined figure.

In 13 of the isolated congenital abnormality groups, the average birth order for the mothers of the cases and case-matched controls showed significantly deviation. In every case, the values for the mothers of the children born with congenital abnormalities were higher.

The percentages of first- and second born CA cases were 1.0% and 3.6% lower than for the case-matched controls. Conversely, for the third born (1.5%) and later born (fourth or later: 3.1%) the CA cases were in the majority.

Among the 24 isolated CA groups, 15 (62.5%) showed significant deviation in the distribution of birth order as against the case-matched controls. In the following two steps, I sought reasons for this.

The percentage of firstborns was significantly higher in the following three congenital abnormality groups: neural tube defects, esophageal atresia/stenosis and clubfoot. Conversely, the percentage of firstborns was significantly lower in four congenital abnormality groups: aural congenital abnormalities, cardiovascular congenital abnormalities, lip ± palate cleft and urethra-obstructing congenital abnormalities. For these reasons, the percentage of firstborns was lower in the isolated CA group than in the case-matched control group for all these isolated congenital abnormality groups.

Analysis of those born with more siblings (fourth or later) revealed that 14 of the 24 examined congenital irregularity groups showed a greater percentage of cases than in the case-matched control samples. Therefore, it is obvious that the percentage of those born later in succession

was higher among the cases than in the matched controls for all of the congenital abnormality groups.

In four congenital abnormality groups, there was a significant increase in risk in relation to birth order. In the aural congenital abnormality, cardiovascular congenital abnormality, lip ± palate cleft and urethra-obstructing congenital abnormality groups, the percentage of firstborns was lower and the percentage of children born fourth or later was higher. A not significant but similar trend was observable in primary microcephaly, aural CAs and intestinal atresia/stenosis.

Two congenital abnormality groups, neural tube defects and clubfoot, showed a so-called U-shaped distribution among cases for both firstborn and later born children, as opposed to their case-matched controls.

Finally, it appeared to be worthwhile to examine birth order in the key congenital abnormality subgroups. The two main groups for neural tube defects were anencephaly and spina bifida aperta/cystica, with the latter more common among firstborn and later born children. Examining the six most important individual and groups of cardiovascular congenital abnormalities, we found that later pregnancies meant greater risk in four cases. This also corresponded to the average higher birth order number. Of the two abdominal CA cases, exomphalos occurred in significantly greater numbers in both firstborn and later born children, while gastroschisis occurred in greater numbers only in children with multiple siblings.

The indicator showing a close relationship between the mother's age and order of birth clearly varies, but the independent impact of birth order on the incidence of CA has been previously verified. Our examination reinforced the considerably higher risk of esophageal atresia/stenosis in the firstborn. Previously, contradictory studies were published with regards to the relationship between birth order and neural tube defects. The likely explanation for this is that for anencephaly, but especially for incidents of spina bifida aperta/cystica, the order of birth shows a U-shaped association, which was particularly pronounced for incidents of spina bifida aperta/cystica. A similar tendency was observed in the occurrence of the two abdominal CAs, although it only reached a significant level in the case of exomphalos. According to our study, clubfoot is also more common in the firstborn. In addition to this, numerous CAs revealed associations with later birth order, the explanation for which may be that in Hungary it is primarily socially disadvantaged families who have more than the average number of children.

In summary, we can state that birth order is important not only because of the usual "distorting" factors in epidemiological studies, but because it is also of clinical importance. For example, in the firstborn it is worth paying attention to the significant risk of esophageal atresia/stenosis and exomphalos during ultrasound examinations. Additionally, it may be worth conducting echocardiograms on pregnant women carrying later children in view of the increased occurrence of cardiovascular congenital abnormalities.

4.4 The impact of maternal age on the gender ratio of isolated congenital abnormalities

Two facts motivated this study. On one hand, the gender split for seemingly all congenital abnormalities is different from the gender split for newborns. On the other, the mother's age also has an impact on the occurrence of various CAs, so the question of whether gender plays a role in this arises.

Of the total of 21,494 isolated CA cases recorded in the FREKF database from 1980 to 1996, 14,167 were male and 7,327 were female, so the gender split was 0.66 in favor of males.

The gender split for seemingly all isolated congenital abnormalities deviates from the expected value of 0.51. The two exceptions were cardiovascular CAs and the heterogeneous groups of musculoskeletal CAs. The most obvious imbalance towards boys (aside from the two CAs that only occur in males) were occurrences of congenital hypertrophic pyloric stenosis (0.85), renal a/dysgenesis (0.69), anal/rectal atresia/stenosis (0.65), cleft lip ± palate (0.64), urethra-obstructing CA (0.63) and poly/syndactylia (0.62). The greatest imbalances towards girls were found for neural tube defect CAs (0.41) and rear cleft palate (0.41), other CAs of the genital organs (0.42) and primary microcephaly (0.43).

The mean maternal age for total isolated congenital abnormalities for boys and girls was 25.5 and 25.4, which does not represent a significant deviation. The situation was similar in the individual isolated CA units/groups, with one exception. For urethra-obstructing CAs, the mean maternal age for boys was 26.0, while for girls it was 24.1.

The essence of the study was to compare the ratio of boys and girls according to maternal age groups for the various isolated CAs. Only two CA categories/groups showed notable deviations for maternal age groups.

One was cleft lip ± palate. The commonly acknowledged surplus of boys was confirmed. The mean maternal age of boys was 25.5, while it was 26.1 in the girls group. This difference was not far from the significance level. This can be explained with the younger age for the mothers of this male-dominant CA as it is near significant for mothers under 19 (p=0.057), while the deviation is significant in favor of boys (0.69; p=0.28) for the 20-24 age group. For those pregnant above the age of 35, the gender ratios (0.59) are reduced, and for those above 40 there is an imbalance in favor of girls (0.44).

The other significant difference was shown in musculoskeletal system congenital abnormalities, although the entire group's gender ratio (0.51) was in line with the gender ratio of newborns. The mean age for mothers of boys was 25.3, which was almost significantly higher than the mean age of mothers of girls (24.5) (p=0.51). This can be attributed to a significant surplus of mothers of boys aged 25-29 (108 vs. 85; gender ratio: 0.56; p=0.194) and primarily mothers aged of 35-39. On one hand, the latter had a sample size of only 15 boys and 5 girls, on the other, this surplus of boys could not be observed for those pregnant above the age of 40. Additionally, this CA group contains very heterogeneous CAs (315 torticollis, 153 pectus excavatum, 74 vertebrae and rib CAs, 37 skull CA, 6 pectus carinatum). The surplus of boys observed in the two aforementioned maternal age groups cannot be attributed to any one of the mentioned CA subgroups.

Finally, we studied the gender split in congenital abnormalities in the youngest and 35 or older age groups. For mothers aged 19 and younger, the gender split did not show deviations in any of the CA categories/groups. Of the pregnant women of more advanced ages, there was only a significant surplus of boys in one isolated CA group. In response, we conducted a detailed study of the CAs in this group, but did not find an explanation for this surplus of boys.

In conclusion, this study revealed a significant increase only in the cases of cleft lip ± palate for pregnant women between the ages of 25-29 (0.69), a CA that is known to have an imbalance in favor of boys (0.64), while the ratio of boys for pregnant women of age 35 or older fell significantly (0.56).

5. Summary – key findings

This study of the 24 isolated congenital abnormality cases and case-matched controls based on the Hungarian population had two important results: the advanced age of the mother was not found to pose a significant risk for cases of isolated congenital abnormalities. A few congenital abnormalities in the youngest age group (19 and younger) carried significantly higher risk and this must be taken into consideration in clinical practice, primarily during ultrasound examinations.

This study reinforced the significantly higher risk of esophageal atresia/stenosis in the firstborn. In four congenital abnormality groups, risk significantly grew in relation to the order of birth. For aural congenital abnormalities, cardiovascular congenital abnormalities, lip ± palate cleft and urethra-obstructing congenital abnormalities, the risk was lower for the firstborn and higher for the fourth or later born. In the past, contradictory studies have been published on neural tube defects and their relation to birth order. The explanation for this is that for anencephaly, but especially for incidents of spina bifida aperta/cystica, the order of birth shows a U-shaped association, which was particularly pronounced for incidents of spina bifida aperta/cystica. A similar tendency was observed in the occurrence of the two abdominal abnormalities as well, but this only reached a significant level in exomphalos cases.

Studying the impact of maternal age on the gender split for cases of isolated congenital abnormalities did not produce many results. It was only for cleft lip ± palate cases (which already has a higher ratio of boys (0.64)) that a significant increase for pregnant women in the 25-29 age group (0.69) was found, while the ratio of boys significantly decreased (0.56) in the group of pregnant women aged 35 or older.

6. Acknowledgments

I would like to thank Associate Professor Béla Veszprémi, who approached my work with patience, friendship and profound expertise. I would also like to extend many thanks to Professor Czeizel for providing me with access to the database and the very helpful instructions which made it possible for me to prepare this essay. I would also like to express my gratitude to the researchers who analyzed the statistics for the patience with which they assisted me in understanding the essence of the each of the tests used. Finally, I would also like to thank the staff of the Rózsakert Medical Center for their cooperation, without which I could not have carried out this work.

7. Publications

Gyula Csermely, Éva Susánszky, Andrew E. Czeizel:
Association of young and advanced age of pregnant women with the risk of isolated congenital abnormalities in Hungary – A population-based case-matched control study
JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE 28:(4) pp. 436-442. (2015)
IF: 1,208

Gyula Csermely, Éva Susánszky, Andrew E. Czeizel, Béla Veszprémi:
Possible association of first and high birth order of pregnant women with the risk of isolated congenital abnormalities in Hungary – A population-based case-matched control study
EUROPEAN JOURNAL OF OBSTETRICS GYNECOLOGY AND REPRODUCTIVE BIOLOGY 179: pp. 181-186. (2014)
IF: 1,627

Gyula Csermely, Andrew E. Czeizel, Béla Veszprémi:
Distribution of maternal age and birth order groups in cases with unclassified multiple congenital abnormalities according to the number of component congenital abnormalities. - A population-based case-matched control study
BIRTH DEFECTS RESEARCH PART A-CLINICAL AND MOLECULAR TERATOLOGY 103:(2) pp. 67-75. (2015)
IF: 2,211

Gyula Csermely, Robert Urban, Andrew E. Czeizel, Béla Veszprémi:
Sex ratio of isolated congenital abnormalities in the function of maternal age. - A population-based case-matched control study
CONGENITAL ANOMALIES 55:(2) pp. 85-91. (2015)
IF: 0,783

Csermely Gyula, Elekes Tibor, Molnár László, Hozsdora Andrea, Gullai Nóra, Keszthelyi Gábor:
Az első trimeszteri kiterjesztett szűrés jelentősége és metodikája *[Significance and methodology of extended first-trimester screenings]*
(MAGYAR NŐORVOSOK LAPJA, 2015)