

Doctoral School of Clinical Medicine
Reproductive Health Program

Maternal age as an influencing factor of obstetrical and neonatal outcomes – retrospective studies in Southeastern Hungary

PhD Thesis

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INTRODUCTION

Promotion of healthy life start is an important priority all over the world. Health promoting or health damaging behaviour of mothers before conception and during pregnancy can influence the health status of their newborns, and their future life.

During the last decades, the total number of births has been decreasing in Hungary, and today, the number of deliveries is around 90.000 per year. Parallel with this change, the age composition of pregnant women has been changed; the rate of advanced aged mothers (over 40 years) has increased.

In contrast the rate of preterm deliveries has not changed for years, it is around 8–9% despite the efforts to decrease this number: extended system of health visitors, free prenatal care (insurance is not needed), antenatal steroid prophylaxis, use of surfactant, and neonatal intensive care units (NICU).

Although the rate of preterm births runs like mentioned above, the rate of infant mortality has been decreasing year-by-year (3.3 per thousand in 2021). The two main causes of infant's death are conditions that occurs in perinatal period (like prematurity) and congenital abnormalities.

The importance of maternal age is increasing in these days due to the demographical changes. Health care providers have to be prepared to manage complications, which are more common in advanced age such as gestational diabetes mellitus and preeclampsia. The frequency of Caesarean section is also higher. Considering neonatal outcome there is higher rate of low birth weight, macrosomia, prematurity, intrauterine growth retardation, congenital malformations, neonatal intensive care admission and perinatal mortality.

Furthermore, it is also important to call attention to teenage pregnancies and their perinatal outcome, such as higher rate of low birth weight, prematurity, intrauterine growth retardation, congenital malformations, neonatal intensive care admission and perinatal mortality.

It is a widely known fact that maternal age is one of the determining factors of many genetical aberrations. Therefore, screening methods consider maternal age as an important variable. Several types of screening methods are applied to determine chromosomal abnormalities: first trimester combined test (maternal age, nuchal thickness, maternal serum b-human chorionic gonadotrophin, pregnancy-associated plasma protein-A), free fetal deoxyribonucleic acid based tests, detailed ultrasound examination. If these screening tests give rise to suspicion, an invasive procedure is needed like chorionvillus sampling or amniocentesis to get correct diagnosis. Autosomal aberrations are associated with maternal age, but in case of

abnormalities of sex chromosome, there is no correlation with maternal age. Furthermore, in case of abnormalities of sex chromosome the above-mentioned screening methods are less useful as in case of autosomal trisomies.

Adequate prenatal care can help to prevent maternal and perinatal complications and can decrease the number of neonates born with any kind of chromosomal aberration.

Fetal health can be affected by several lifestyle factors. Out of these, the followings are the most important: diet, physical activity, smoking and alcohol consumption during pregnancy. Adequate nutrition is essential for fetal development and regular physical activity has many advantages for fetus and mother. Maternal smoking and alcohol consumption during pregnancy are associated with many negative outcomes. Women's knowledge of healthy lifestyle is an important factor to have healthy babies.

AIMS

The aims of this thesis are the followings:

- To determine whether teenage pregnancy is associated with adverse perinatal outcome with particular regard to congenital malformations.
- To determine the association between advanced maternal age and various adverse maternal and neonatal outcomes.
- To investigate the cases with in-utero-diagnosed trisomies of sex chromosome, and to determine the frequency of prenatal identification and outcome of these pregnancies.
- To determine the association between demographic characteristics and lifestyle factors in pregnant women.

MATERIALS AND METHODS

Two types of studies were delivered to characterize the role of mothers' age in obstetrical and perinatal outcome.

One type of studies used data collected from the medical records of the Department of Obstetrics and Gynecology, University of Szeged, Hungary. It comprised mothers' age, marital status, smoking habits, and the following obstetrical data: number of previous pregnancies (primigravida vs. multigravida), in vitro fertilization-embryo transfer technique (IVF-ET), attendance in prenatal care (it was considered adequate when the first visit was registered before 16 weeks of gestation or at least four check-ups were done during pregnancy), registered

maternal complications (gestational diabetes mellitus or preeclampsia during actual pregnancy), threatened preterm delivery, weeks of gestation, and the mode of delivery. Neonatal data included birth weight and length, congenital malformations, Apgar score at 5-minute, umbilical cord blood pH, and admission to NICU. All data were registered anonymously.

In the teenage mothers' study, we compared the data of teenage mothers (under 20 years of age) with the control group: data of all mothers who delivered in Hungary according to Hungarian Central Statistical Office during the study period.

In the study of older mothers, the advanced maternal age group (40 years or over) was compared to the control group of women aged 25–29 years who delivered during the same period and department, the controls were matched according to the number of previous gestations and previous deliveries.

In the study of sex chromosome trisomy (at the department between 2003 and 2015), twelve cases were prenatally diagnosed by cytogenetic methods at the Department of Medical Genetics, University of Szeged. The following parameters were examined: frequency of pregnancy termination, medical indications of termination, and the rate of numerical chromosome abnormalities based on fetal karyotyping and out of these the rate of sex chromosomal trisomies.

The study protocol was approved by the Regional and Institutional Human Medical Biological Research Ethics Committee of the University of Szeged, Hungary (No: 4046).

The second type of study based on a self-administered questionnaire (containing sociodemographics, lifestyle, conception, previous and current pregnancy related questions) and also health documentation (mothers' health characteristics before and during pregnancy, type of delivery, complications; and health characteristics of the newborn) to analyze the lifestyle of pregnant women in various age-groups. Participation was voluntary, and a written informed consent was obtained from each participant of the study.

The study protocol was approved by the Regional and Institutional Review Board of Human Investigation in University of Szeged, Hungary (No: 3328).

Statistical analyses were performed using STATA (StataCorp, College Station, TX, USA) 9.0 statistical software and IBM SPSS Statistics version 24 and 26. Student's t-test, chi-square test, Mann-Whitney U test, Fischer's Exact test, and logistic regression analyses were used. In case of logistic regression analyses odds ratios (OR), adjusted odds ratios (AOR) and 95% confidence intervals (CI) were calculated for each variable. Statistical significance was defined at $p < 0.05$.

RESULTS

Study of teenage mothers

During the 5-year study period, 12,845 births were recorded at the Department of Obstetrics and Gynecology, University of Szeged. The total number of teenage pregnancies was 274 (2.1%). Out of these, 273 were singleton gestations and one was twin pregnancy. In Hungary, the total number of births was 448,852, out of these 27,777 (6.2%) were teenage pregnancies.

Analysis of characteristics of teenage mothers showed that most of them (41.0%) were 19 years old and only one was under 14 years. The rate of marriage was 11.7%, but the number of single mothers and number of mothers who had a partner in life was nearly the same. Altogether 66 mothers (24.0%) reported smoking during pregnancy, 94.5% of them attended prenatal care regularly, while 2.5% of mothers never attended; 90 mothers (32.8%) had history of previous gestation(s) and 14.2% of the mothers had at least one previous delivery.

Analysis of the rate of maternal complications during pregnancy demonstrates that gestational diabetes was significantly lower (1.8%) among teenage mothers than in the control group (6.3%). The prevalence of preeclampsia was 7.6% in teenage mothers, 6.0% in the control group, there was no significant difference.

The comparison of the perinatal outcome between the control and the study group showed that the rate of premature deliveries was worse in the study group (10.2%) than the national rate (8.9%), but the difference was not significant. Frequency of spontaneous vaginal delivery and Caesarean section were similar in the two groups (66.5% vs. 65.2% and 33.5% vs. 34.8%). Intrauterine growth retardation (IUGR) occurred a little bit more often in the teenage group (9.4% vs. 8.0%). Significant difference was found in mean birth weight (3110 g vs. 3277 g), in the rate of congenital malformation (8.0% vs. 5.0%), and in the admission to NICU (12.4% vs. 8.0%).

Analysis of the types of congenital malformations registered in the study group revealed that 22 out of 275 newborns of teenage mothers had congenital malformations (8.0%), three of them had multiple malformations.

Study of advanced age mothers

During the 3-year study period, 7799 births were recorded, and the total number of elderly pregnant women was 378 (4.8%); out of these, 374 were singleton gestations and four were twin gestations.

In the study group (older women), the mean maternal age was 41.12 ± 1.39 years, the median age was 41 years (interquartile range, IQR: 42-40=2), most of the mothers (43.3%) were 40 years old, and the oldest mother was 48 years old. Among the elderly mothers, the rate of being married was 53.2%, but the number of mothers who had a life-partner was also high (37.2%). Eleven mothers (2.9%) confessed to smoking during pregnancy, and 99.2% of them attended prenatal care regularly, but 3 mothers (0.8%) never attended, and 318 mothers (85.0%) had a history of previous gestation(s).

In the control group, the mean maternal age was 27.51 ± 1.33 years; most of the mothers were 29 years old (32.0%). The rate of women who were married or had a life partner was over 90% (54.8% and 40.7%). In the control group, nine mothers smoked during pregnancy (2.4%), every mother attended prenatal care regularly, and 55.0% of them had previous gestation(s).

The frequency of gestational diabetes mellitus and preeclampsia was significantly higher in the study group than in the control group (16.8% vs. 6.9% and 17.9% vs. 1.6%, respectively). The frequency of threatened preterm delivery (5.6% vs. 1.8%) and the use of IVF-ET (4.5% vs. 0.0%) were significantly higher in the study group.

Mean gestational age (38.22 ± 2.30 vs. 38.85 ± 1.49 weeks) was significantly lower, while the number of Caesarean sections (58.6% vs. 29.4%) was significantly higher in the study group.

The data of perinatal outcome showed that the frequencies of preterm birth and low birth weight were significantly higher in the study group compared to the control group (11.8% vs. 6.9% and 11.2% vs. 5.2%, respectively). The rate of fetal macrosomia was higher in the study group (12.8% vs. 8.6%), although the difference was not significant. However, a significant difference was found in the admissions to NICU (9.4% vs. 5.0%). The frequency of registered congenital malformations (mainly heart defects and urogenital defects) was similar (5.6% vs. 6.9%) in both groups. There was no significant difference in the Apgar score at 5-min < 7 (1.1% vs. 0.0%), whereas the frequency of low umbilical cord blood pH (< 7.1) was significantly lower in the study group (2.8% vs. 5.9%).

According to the logistic regression analysis, age had a significant effect on various maternal outcomes. The odds of gestational diabetes (OR: 2.74; AOR: 2.81), preeclampsia (OR: 13.53; AOR: 13.05), threatened preterm delivery (OR: 3.15; AOR: 3.62), and Caesarean section (OR: 3.40; AOR: 3.31) were significantly higher in older than younger mothers in unadjusted and adjusted models as well.

The odds of adverse neonatal outcomes, such as low birth weight (OR: 2.30; AOR: 2.56) and admission to NICU (OR: 1.95; AOR: 2.03), were significantly higher in older vs. younger mothers in both models. The odds of preterm birth (OR: 1.80; AOR: 1.67) and low level of

umbilical cord blood pH (OR: 0.46, AOR: 0.70) were significant in the unadjusted models, but these relationships were no longer statistically significant after the adjustment for marital status, smoking status, primigravity, IVF-ET, and attendance of prenatal care. There was no significant effect of maternal age on the frequency of fetal macrosomia and congenital malformations.

Study of sex chromosome trisomy

During the study period (2003–2015) 31,287 birth and 14,990 terminations were registered at the Department of Obstetrics and Gynecology, University of Szeged. Out of these 12 cases (0.026%) were diagnosed with sex chromosome trisomy prenatally. No new case was identified during the 3–5-day long observation after birth. 481 termination (3.2%) were performed according to medical indication, out of these 140 cases (0.9%) were numerical chromosome abnormality. Out of these 140 terminations, six were trisomies of sex chromosome (three Klinefelter syndrome and three triple X syndrome) and there were six prenatally diagnosed cases, which resulted in delivery according to parents' choice. Out of the six live newborns, two have Klinefelter syndrome, two have Jacob syndrome and two have triple X syndrome. In the in utero diagnosed cases mosaic cell line was not detected by FISH (fluorescence in situ hybridization) (Department of Medical Genetics, University of Szeged).

The average age of the 12 pregnant women was 38,7 years, the youngest was 35 years old, the oldest was 47 years old. The indication of fetal karyotyping was maternal age in all (12) prenatally diagnosed cases, and increased fetal nuchal translucency thickness were observed in two cases as well.

The average age of the six pregnant women deciding for delivery was 36.3 years. Fetal karyotyping was performed during amniocentesis in all six cases; the mean gestational age was 17.5 weeks at the time of procedure. The number of previous pregnancies was 1.2; the number of previous deliveries was 0.8. All six pregnancies resulted in delivery between 37th and 41st weeks of gestation (mean gestational age: 37.8 weeks). The mean birth weight of newborns was 3015.7 g.

The average age of the six women who chose termination was 41.3 years. Fetal karyotyping was performed during amniocentesis (three cases, mean gestational age: 18.3 weeks) and chorionvillus sampling (three cases, mean gestational age: 13.6 weeks). The mean gestational age was 20.3 weeks at the date of termination. In one case there was a major congenital malformation (cystic adenomatoid malformation) described by pathological examination (and it was identified by prenatal ultrasound examination, too). The number of previous pregnancies was 3.5, the number of previous deliveries was 2.7.

Increased fetal nuchal translucency thickness were observed in two cases (1-1 case in both group). Both cases were similar to each other: the fetal nuchal translucency thickness was 4.1 mm and Triple X syndrome was diagnosed. The pathological examination did not describe any kind of malformation which could have been identified by ultrasound examination during pregnancy (except cystic adenomatoid malformation mentioned before). Other screening methods as extended ultrasound diagnostics, maternal serum markers and free fetal deoxyribonucleic acid (DNA) based tests (noninvasive prenatal tests, NIPT) were not forgone by these affected pregnant women.

Study of lifestyle factors

Comparisons of the basic demographic characteristics of women and the frequency of the different components of lifestyle show that most of the mothers had daily fruit (78.5%) and vegetable (63.8%) consumption, but they eat fish less frequently than once per week (60.8%), while majority of mothers eat sweets regularly (80.3%). Each lifestyle field had given points. Assessing the points of dietary habits 41.3% of included women had healthy diet, 9.0% were physically active and attended special pregnancy exercise classes, 84.4% did not drink alcohol and 93.5% were not smoking during present pregnancy.

There were associations between the different components of healthy lifestyle and maternal age and marital status. Healthy diet was more prevalent among older women. Regular physical activity was more frequent among mothers aged from 25 and 34 years old. Smoking during pregnancy was significantly associated with younger maternal age. Younger mothers consumed significantly less alcohol during pregnancy. Marital status can affect a pregnant woman's lifestyle; healthy diet and nonsmoking behavior were significantly frequent in partnership.

DISCUSSION

The aim of this thesis was to characterize the association between mother's age and adverse maternal, perinatal and neonatal outcomes. To solve this aim we analyzed the relationship between teenage pregnancy and adverse perinatal outcome (congenital malformations), advanced maternal age and various adverse maternal and neonatal outcomes, and the association between demographic factors and lifestyle factors in pregnant women. Additionally, we investigated the cases with in-utero-diagnosed trisomies of sex chromosome.

Our results showed that younger maternal age was significantly associated with lower mean birth weight, higher risk of congenital malformations and increased admission rate to NICU.

Older maternal age was significantly associated with maternal complications, higher frequency of using IVF-ET, higher rate of Caesarean section, prematurity and increased admission rate to NICU. We expected significantly higher rate of congenital malformations in the study group, but our results showed that advanced maternal age was not associated with higher rate of birth defects.

From the point of the lifestyle of the mothers during pregnancy, our results showed significant association between maternal age and health behaviour. With the exception of alcohol consumption older mothers showed healthier lifestyle (healthy diet, regular physical activity, non-smoking).

In Hungary, infant mortality has decreased in recent years, but among the causes of infant deaths, the rate of congenital malformations is the same (25%). It is a notable number, which should not be ignored. Today, health care providers pay more attention to older mothers because of the risks of advanced age, but our results showed that the early detection of congenital malformations may be important in every age group.

Considering our results, it should be important to inform women about the consequences of delayed childbearing. Older mothers may need more attention during an adequate prenatal care program provided by obstetricians, midwives, and health visitors, and they are recommended to deliver in a regional centre to decrease adverse perinatal outcomes.

The prenatal diagnosis of sex chromosome trisomies is not as efficient as of the autosomal trisomies.

At the beginning of the 1990s, when the nuchal thickness had been introduced as an ultrasound marker, prenatal genetics started on its journey by screening for Down syndrome. Without any doubt it is unquestionable that the problem caused by 21 trisomy is one of the greatest professional challenges in these days, but it has to be stated that prenatal genetics consists of more than screening for Down syndrome only.

The frequency of prenatal recognition of sex chromosome trisomies lags behind autosomal trisomies. The causes are the following: low sensitivity of the screening methods used in the investigated period and the various clinical appearance of sex chromosome trisomies. The real frequencies of diseases are underestimated by most of the studies because they are not paired with as serious clinical symptoms as autosomal trisomies. Much of them do not get diagnosed immediately after birth, and some of the people suffering from Klinefelter syndrome do not get diagnosed even in their whole lifetime.

The decision concerning the fate of the pregnancy is a much more difficult challenge for parents in case of sex chromosome trisomy than in case of autosomal trisomy. The parents can

only make their decision based on extensive information given by a multidisciplinary team (consisting of a clinical genetician, obstetrician, pediatrician, endocrinologist, and professionals of developing treatments).

Sex chromosome trisomies are identified most commonly by amniocentesis performed in consequence of maternal age. It can be expected that the efficiency of prenatal recognition of sex chromosome trisomies will increase measurably in Hungary thanks to the spreading of free fetal DNA based tests (NIPT). This tendency increases the importance of medical teams specialized in these trisomies.

The lifestyle of the mothers during pregnancy can strongly determine their and their infant's health. Beside healthy diet and physical activity, avoidance of smoking and alcohol consumption is also an important criteria of appropriate health behaviour. From the point of the prevention, the fulfilment of the four health behaviour components is the best solution. The differences between age groups may suggest further promotion and improvement of pregnancy planning and pregnancy care among younger women.

Summary of findings

- Younger maternal age was significantly associated with lower mean birth weight, higher risk of congenital malformations and increased admission rate to NICU. Teenage mothers should be informed about the potential complications during an adequate prenatal care program and recommended to deliver in a regional centre to avoid adverse perinatal outcome.
- Our data suggest that older maternal age was significantly associated with maternal complications, higher frequency of using IVF-ET, higher rate of Caesarean section, prematurity and increased admission rate to NICU. We expected significantly higher rate of congenital malformations in the older mothers' group, but our results showed that advanced maternal age was not associated with higher rate of birth defects. It may prove that adequate prenatal care and modern genetic diagnostic methods are able to screen congenital anomalies, thereby much fewer neonates are born with severe congenital defects.
- Today, health care providers pay more attention to older mothers because of the risks of advanced age, but our results showed that the early detection of congenital malformations may be important in every age group, especially in the teenage mothers. It is important to inform women about the consequences of delayed childbearing. Older mothers may need more attention during an adequate prenatal care program provided by obstetricians,

midwives, and health visitors, and they are recommended to deliver in a regional centre to decrease adverse perinatal outcomes.

- The indication of fetal karyotyping was advanced maternal age in all prenatally diagnosed cases; maternal age is an independent factor in case of sex chromosome trisomy. However, importance of early diagnosis followed by treatment should always be emphasised to reach a better quality of life.
- The lifestyle of the mothers during pregnancy can strongly determine their own and their infant's health. From the point of prevention, the fulfilment of the four health behaviour components – healthy diet and physical activity, avoidance of smoking and alcohol consumption – is the best solution. The differences between age groups may suggest further promotion and improvement of pregnancy planning and pregnancy care among younger women.

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LIST OF SCIENTIFIC PUBLICATIONS

Publications related to the subject of this thesis

- I. **Karai A**, Gyurkovits Z, Nyári TA, Sári T, Németh G, Orvos H. Adverse perinatal outcome in teenage pregnancies: an analysis of a 5-year period in Southeastern Hungary. *J MATERN FETAL NEONATAL MED* 32(14):2376-2379. (2019). **IF: 1.737.**
- II. **Karai A**, Orvos H, Paulik E, Pap É, Gyurkovits Z, Horváth E, Németh G, Sikovanyecz J. A nemi kromoszómákat érintő triszómiák in utero felismerésének gyakorisága a Szegedi Tudományegyetem Szülészeti és Nőgyógyászati Klinika beteganyagában 2003-2015. között. *MAGYAR NŐORVOSOK LAPJA* 83(2):90-94. (2020)
- III. **Karai A**, Gyurkovits Z, Németh G, Orvos H, Paulik E. Adverse maternal and perinatal outcome of women aged 40 years or over: A retrospective study. *INTERNATIONAL JOURNAL of CHILDBIRTH* Volume 12, Issue 3:139-145 (2022)
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List of other publications

- I. Boros Á, Raáb M, Károly É, **Karai A**, Kátai A, Bolba N, Pankovics P, Reuter G. A cluster of salivirus A1 (Picornaviridae) infections among newborn babies with acute gastroenteritis in a neonatal hospital unit in Hungary. *ARCHIVES OF VIROLOGY* 161(6):1671-1677. (2016). **IF: 2.058**
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