Investigating the Role of Maternal Age in the Occurrence of Non-Chromosomal Congenital Anomalies

Ph.D. Thesis Booklet

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1. INTRODUCTION

1.1 What is the topic?

The focus of my research is to investigate the impact of maternal age on the occurrence of non-chromosomal congenital anomalies (NCAs) in order to identify specific age-related risk categories and improve prenatal screening protocols.

1.2 What is the problem to solve?

The issue lies in the limited evidence regarding the exact relationship between maternal age and the occurrence of NCAs. This lack of clarity makes it difficult to develop accurate prenatal screening protocols and public health strategies.

1.3 What is the importance of the topic?

The importance of this topic cannot be overstated, as congenital anomalies are frequent with 3-5% worldwide

and play a significant role in infant mortality (6% of infant death worldwide) and morbidity rates (approximately 20%) as well as result in substantial healthcare expenses. By understanding the influence of maternal age on NCAs, we can improve prenatal screening protocols and public health strategies, consequently reducing the occurrence and impact of these anomalies on families and the healthcare system.

1.4 What would be the impact of our research results?

The outcomes of our research will have significant impact by enhancing prenatal screening protocols and public health strategies. Healthcare providers can enhance the effectiveness of prenatal care by identifying maternal age groups that are at a higher risk for NCAs. Public health campaigns can be customized to provide education and assistance to age groups that are at a higher risk, ultimately decreasing the occurrence and effect of NCAs. Furthermore, our findings will provide direction for future investigations and policy choices focused on improving maternal and child health outcomes.

2. OBJECTIVES

2.1 Study I. – Investigating the Impact of Maternal Age on the Development of Non-Chromosomal Congenital Anomalies in the Hungarian Population between 1980 and 2009

The aim of this study was to use our distinct database to determine the specific 10-year period of maternal age in Hungary that has the lowest risk for NCAs. Additionally, we also wanted to compare other maternal ages to this specific period in order to offer an original perspective on the relationship between maternal age and NCAs. The reason for this approach was to enhance our comprehension of age-related vulnerabilities and provide insights for modifying prenatal screening protocols according to the maternal age.

2.2 Study II. – Investigating the Impact of Maternal Age on the Development of Non-Chromosomal Congenital Anomalies Worldwide

The objective of this study was to perform a comprehensive meta-analysis investigating the occurrence of NCAs based on maternal age. Despite thorough investigation on this subject, the full scope and characteristics of the association between maternal age and NCAs are still uncertain. The existing literature lacks a unanimous agreement on the specific particulars of this relationship. The objective of this study was to elucidate these factors and offer valuable perspectives for formulating age-specific guidelines for prenatal screening and public health strategies.

3. METHODS

3.1 Study I:

The population-based study was conducted in Hungary over a 30-year period (1980-2009) to investigate the occurrence of NCAs in relation to maternal age. The study followed the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines for observational studies. Data were sourced from the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) and live birth records from the Hungarian Central Statistical Office (KSH). Eligible cases were those reported to the HCCSCA within three months of birth or elective pregnancy termination, with the exception of cases with only mild anomalies (hip dislocation, congenital inguinal hernia, and large haemangioma) or those associated with chromosomal abnormalities. We aimed to determine high-risk maternal ages for each NCA category through a two-step approach. Instead of using predefined age categories, first, we identified the optimal ten-year maternal age range with the

lowest anomaly frequency. Second, a non-linear, non-parametric logistic regression model (restricted cubic splines) was applied to estimate risks associated with maternal age. Risk ratios (RR) for each year were determined by taking the best ten-year period as a "reference risk". All CIs were calculated at a confidence level (1-α) of 95%. This approach allowed for a detailed assessment of risk variations across maternal age groups.

3.2. Study II:

The systematic review and meta-analysis aimed to assess the association between maternal age and NCAs globally. The study followed PRISMA 2020 guidelines and adhered to the Cochrane Handbook for Systematic Reviews of Interventions. The study protocol was registered prospectively on PROSPERO (CRD42021283593), with some deviations for clarity and subgroup analysis. A comprehensive search was conducted in MEDLINE (via PubMed), Cochrane Library (CENTRAL), and Embase databases on October 19, 2021. We included population-based studies that reported NCAs by maternal age. Studies

had to provide precise NCA counts by age group; while studies with case-control or cohort designs, case series, and reports were excluded. Studies not reporting the total number of patients and the number of NCAs by age group were not eligible. Our primary outcome was the rate of all NACs combined, while the secondary outcomes were the various specific structural defects. The age group of 20- to 30-year-old mothers was used as a reference group. In defining the age groups, the ideal 10-year period was based on other studies, including our own work. We aimed to look at very young mothers (under 20 years), advanced maternal age (35 years or older, as commonly defined); and mothers over 40.

4. RESULTS

4.1 Study I.

From 1980 to 2009, the study identified 31,128 cases of NCAs among 2,808,345 live births in Hungary. The relative frequency of NCAs in the study period was 1.1% (excluding cases with only mild anomalies and cases with concomitant chromosomal anomalies). The occurrence of NCAs in our database was lowest between 23 and 32 years of maternal age at childbirth. The relative risk (RR) of any NCA was 1.2 (95% CI 1.17-1.23) and 1.15 (95% CI 1.11-1.19) in the very young and advanced age groups, respectively. The respective results for the circulatory system were RR = 1.07 (95% CI 1.01-1.13) and RR = 1.33 (95% CI 1.24-1.42); for cleft lip and palate RR = 1.09 (95% CI 1.01-1.19) and RR = 1.45 (95% CI 1.26-1.67); for genital organs RR = 1.15 (95% CI 1.08-1.22) and RR = 1.16 (95% CI 1.04-1.29); for the musculoskeletal system RR = 1.17 (95% CI 1.12-1.23) and RR = 1.29 (95% CI 1.14-1.44); and for the digestive system RR = 1.23 (95% CI 1.14-1.31) and RR = 1.16 (95% CI 1.04-1.29).

According to our analysis, respiratory system anomalies could not be proven to be associated with maternal age.

4.2 Study II.

The meta-analysis incorporated 72 studies from 1940 to 2018, covering diverse populations globally. Maternal age >35 showed an increased overall NCA risk (RR= 1.31, CI: 1.07 -1.61), with the risk rising notably after age >40 (RR= 1.44, CI: 1.25 -1.66). The latter changes to 1.25 (CI: 1.08 -1.46) if the co-occurrence of chromosomal aberrations is excluded. Specific NCA categories such as circulatory system defects showed markedly higher risks in advanced maternal age, with nearly doubled risks for those over 40 years (RR = 1.94, CI: 1.28–2.93). Among the diseases of the circulatory system, we also specificly analyzed the group of congenital heart defects (CHD), where we also found risk-increasing effect for advanced maternal age: for the > 35 group: RR = 1.50; CI: 1.11–2.04; and for the > 40 group: RR = 1.75; CI: 1.32–2.32 was found. Cleft lip and palate (RR = 1.57, CI: 1.11–2.20) and digestive system anomalies (> 40 RR = 2.16; CI: 1.34–3.49) risks were also

elevated in advanced maternal age group. Conversely, gastroschisis was linked to mothers <20 (RR=3.08, CI: 2.74 -3.47). We could not detect an association between maternal age and congenital anomalies of the nervous system, urinary system and musculoskeletal system. The analyses highlighted substantial heterogeneity across studies, due to differences in population, study periods, and data collection methods. Despite this variability, the pattern of increased risk associated with different maternal ages was robust across multiple anomaly categories.

5. CONCLUSION

1. Both very young (< 20 years) and advanced maternal ages (> 35 years) are associated with an increased risk of non-chromosomal congenital anomalies (NCAs) in Hungarian population. The evidence pertaining to the advanced age category is more robust and valid worldwide.
2. In the Hungarian population, mothers between the ages of 23 and 32 have the lowest risk of NCAs.
3. Very young maternal age increases the risk of nervous system anomalies in the Hungarian population.
4. Eye, ear, face, and neck anomalies are associated to advanced maternal age in the Hungarian population.
5. Anomalies in the circulatory system exhibit a higher risk in advanced maternal age. This relationship remains valid even in the absence of concurrent chromosomal anomalies.
6. Congenital heart defects demonstrate higher risk at advanced (40+) maternal age and there is a suspected mild prophylactic effect in very young mothers.

7. In the case of cleft lip and palate, both very young and advanced maternal age pose an increased risk in the Hungarian population, with this association being evident worldwide above the age of 40.

8. Very young and advanced maternal age increase the risk of digestive system anomalies in the Hungarian population, while this risk is also evident worldwide above the age of 40.

9. Genital organ anomalies exhibit a heightened risk in both very young and advanced maternal age groups in the Hungarian population.

10. For urinary system anomalies, both very young and advanced maternal age increase the risk in the Hungarian population. This effect is greater in advanced maternal age group.

11. Anomalies of the musculoskeletal system are more likely to occur in both advanced and very young mothers in the Hungarian population, but the risk is higher in younger mothers.

12. Gastroschisis is associated with a threefold risk in very young mothers.

6. BIBLIOGRAPHY

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