Maternal age as a risk factor in pregnancy and perinatal period: a retrospective cohort study.

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Abstract

Objective The main aim of the study was to assess the influence of maternal age on the incidence of significant pregnancy and childbirth complications in women with low-risk pregnancies. Design A retrospective cohort study. Setting Data collected from hospital delivery admission electronic medical records and discharge summaries of patients hospitalized in St Sophia's Hospital in 2010-2016. Population or Sample 25063 women with low-risk singleton pregnancies. We excluded all patients with known main comorbidities influencing perinatal outcome. Methods The univariate and multivariate statistical analysis was performed to estimate the impact of age on the primary endpoint. Main Outcome Measures The primary endpoint was defined as a compiled adverse pregnancy outcome, which included several components. Results Maternal age is a significant risk factor for adverse pregnancy outcomes. Each subsequent year of life increases the incidence of pregnancy and childbirth complications (OR 1,014; 95%CI 1,008–1,021). Conclusions Maternal age is an independent risk factor for some of the complications of pregnancy and childbirth. Keywords maternal age, perinatal outcome, advanced maternal age, risk factor

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Design

A retrospective cohort study.

Setting

Data collected from hospital delivery admission electronic medical records and discharge summaries of patients hospitalized in St Sophia's Hospital in 2010-2016.

Population or Sample

25063 women with low-risk singleton pregnancies. We excluded all patients with known main comorbidities influencing perinatal outcome.

Methods

The univariate and multivariate statistical analysis was performed to estimate the impact of age on the primary endpoint.

Main Outcome Measures

The primary endpoint was defined as a compiled adverse pregnancy outcome, which included several components.

Results

Maternal age is a significant risk factor for adverse pregnancy outcomes. Each subsequent year of life increases the incidence of pregnancy and childbirth complications (OR 1,014; 95%CI 1,008–1,021).

Conclusions

Maternal age is an independent risk factor for some of the complications of pregnancy and childbirth.

Keywords

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Main research article

Introduction

Over the past few decades, there has been an increase in the average age of women becoming pregnant with their first and subsequent pregnancies observed in developed countries, including Poland. According to the data presented by Eurostat in Poland, the highest fertility of women in the age group of 20-24 years moved in 1995 to the group of 25-29 years in 2015. The median age of all women giving birth increased from 26.9 years in 2005 to 29.2 in 2015 and women giving birth to the first child from 23.7 years in 2005 to 27 in 2015. A similar tendency occurs in many European countries, as illustrated in Figure 1. The reason for this phenomenon is very complex. It consists of social, cultural, economic and demographic factors [1]. People postpone reproduction to a later stage of life to pursue educational goals, professional development and financial stabilization [2-5]. Many women admit that the lack of a suitable partner is the main reason for late motherhood [6, 7].

According to current data, advanced maternal age is associated with an increased risk of some of the complications of pregnancy and childbirth [8-11]. Most frequently, these complications are associated with comorbidities, the incidence of which also increases with age. However, despite numerous studies on the subject since the 80s of the last century, maternal age has not been validated as an independent risk factor for adverse pregnancy outcomes [12-16]**.** The available literature mainly concerns Western European, Asian, Australian and North American populations. There is a lack of studies examining Central European, including Polish, population. As a result of different socioeconomic factors and ethnic structure as well as different healthcare policies, it could be possible that there are differences in the influence of maternal age on the incidence of peripartum complications.

Methods

This study is a retrospective analysis of data collected from electronic medical records of Saint Sophia Hospital in Warsaw. The study center is a mono specialist municipal tertiary referral hospital. During the study, data of all patients hospitalized from 2010-2016 were extracted from hospital delivery admission electronic medical records and discharge summaries. International Classification of Diseases, ninth revision (ICD-9) codes were also abstracted. For each woman included in the study, data from electronic medical records were available, including demographic data, risk factors of adverse pregnancy and delivery outcome diagnosed before and during the current pregnancy, data on the course of the current labour and delivery, including the occurrence of perinatal complications. Among 32332 women in singleton pregnancies who gave birth in St Sophia's Hospital in 2010-2016, 7269 met the exclusion criteria. These were: in vitro fertilization, diagnosis of hypertension or diabetes before pregnancy, and diseases complicating the current pregnancy such as hypertension diagnosed, gestational diabetes, HELLP syndrome, cholestasis, eclampsia or preeclampsia, previous cesarean section, prenatal genetic defect of the fetus. The final sample for the analyses was 25063 women in low-risk pregnancy, in which the frequency of the primary composite endpoint was assessed.

The primary composite endpoint of the study was defined as the occurrence of any of the complications of pregnancy or delivery: macrosomia, intrauterine fetal growth restriction, polyhydramnios, oligohydramnios, intrauterine fetal death, fetal distress, labour dystocia, oxytocin augmentation, obstetric haemorrhage, third or fourth-degree perineal lacerations, placental abruption, placenta previa, unplanned cesarean section, premature delivery, instrumental delivery.

The univariate statistical analysis of the results was carried out using the Statistica 12 program. The distribution of qualitative variables is presented by the absolute number of the subjects and the percentage share in the studied population or group. Quantitative variables are presented as mean values, standard deviation (SD) and median and the smallest and largest values. The Chi-square Pearson test was used to compare groups for qualitative variables (with the Yates continuity correction if the number of subgroups required it). For discrete variables, the Mann-Whitney U test was used (a non-parametric test for the transparency of the analysis was consistently applied). Each time, a p-value of <0.05 was considered a statistically significant result of comparisons between defined groups.

Multivariate statistical analysis was performed using the Medcalc 14 program to determine the influence of age on the occurrence of study endpoints. In multivariate analysis, logistic regression models were built using the ascending method - the following inclusion parameters were used for the model: for inclusion of the variable $p < 0.05$, for switching off the variable $p > 0.1$. The significance of the models was determined by the value of $p < 0.05$ for the model.

Results

In 2010 - 2016, a total of 32 332 women gave birth in the study center. The exclusion criteria met 6,958 women. Finally, 25,063 women were included in the analysis. The average age of women in the study was 31.07 + 4.23 years (the youngest woman was 15 years old, and the oldest was 48 years old). Figure 2 presents the distribution of the study group by age. The mean gestational age in the study group was 39.15 weeks, in children, the predominant gender was male (51.1%), and the average birth weight was 3440.76 g. The primary composite endpoint occurred in 10,578 (42.2%) women. Among the components of the primary endpoint, the most common was oxytocin augmentation (17%) and unplanned caesarean section (13.8%), the most rarely intrauterine fetal death (0.1%), third or fourth-degree perineal lacerations (0.1%) and forceps delivery (0.1%). There was a significant difference between women characteristics in which the primary endpoint occurred and the others. A comparison of the subgroups examined depending on the occurrence of the primary endpoint is presented in Table 2. Age is an important risk factor for the primary endpoint in the whole study group. Its significance is unevenly distributed in the population - with the age of a woman, every subsequent year of life increases the risk of pregnancy and childbirth complications. In the subgroup of women after 20 or 25 years of age, the risk of a primary endpoint (respectively OR = 1.016 [95% CI 1.009-1.023] and 1.023 [95% CI 1.014-1.031]) with each year of life increases to a much lesser extent than in the subset of women over 35 years of age. (OR = 1.079 [95% CI 1.041-1.117]). The relationship between the age of women and the risk of the primary composite endpoint is shown in Figure 3.

Discussion

Main Findings

This study shows that age is an independent risk factor for pregnancy and delivery complications. The risk of complications increases with age in low-risk women. In the entire study population, regardless of the age of the woman, a statistically significant increase in the risk of the primary composite endpoint was observed (OR 1.012, 95% CI 1.005-1.01. The risk increased in subsequent age groups.

Strengths and Limitations

A homogeneous group of patients was selected from women giving birth to the first or subsequent child in a public tertiary hospital with one of the largest number of deliveries per year in Poland.

The limitation of the study may be its one-center character. However, the use of electronic medical records

allowed for high reliability and credibility of the research material collected in the center. The period of the study, covering 6 years, does not preclude a possible change in the standard of conduct in the course of the study, which may affect the results of the analysis. However, it allowed the recruitment of a large number of patients to the study. The studied group included 394 patients were over 40 years of age which amounted to 1.5% of the population. Probably, for this reason, no logistic regression model was built, in which age would be a significant risk factor in this subgroup of patients. The interpretation of the results for women over 40 years of age should be cautious. Patients who had experienced the study endpoint in the previous pregnancy were not excluded from the study group. There was no sufficient data on the course of previous pregnancies and deliveries, except for previous cesarean section; thus, the results should be interpreted with caution. Due to the lack of data, the socioeconomic status, educational level, height and body mass index were not evaluated. The authors are aware of a potential correlation between the above factors and the risk of adverse perinatal outcome [17, 18]. The use of nicotine and alcohol is not taken into account; however, according to the available data, this should not interfere with the results of the study [19, 20]. Advanced maternal age is not associated with more frequent smoking. On the contrary, nicotinism is more common in pregnant women under 20 years of age [16].

Interpretation

In the majority of literature on the subject, the assessment of the influence of mother's age on the course of pregnancy and delivery is based on a comparative assessment of complications occurring in different age groups. The most frequently compared groups are 35-39 and over 40 years, and the control group is composed of younger patients, also in the age groups 20-24, 25-29, 20-34 years. Grouping by age certainly facilitates the interpretation and presentation of results. Data averaging in the 5-year range (most frequently used in the literature) may, however, it harms the accuracy of the study and the strength of scientific evidence [21-24]. Age as a discrete variable allows a more precise determination of its impact on the risk of the endpoint.

Despite many studies confirming the adverse effect of increasing pregnant age on the incidence of specific complications of the course of pregnancy and delivery and perinatal failures, the standard of prenatal and perinatal care was not introduced into the clinical practice in an increasing number of patients over 35 years of age. There are limited reports that include age as a discrete variable in which attempts were made to find a safe limit regardless of age group, but the results suggest a linear increase in adverse perinatal outcomes. Importantly, in subsequent publications, a coherent threshold with significantly increased risk of obstetric complications was not specified, which confirms the thesis about the relevance of the methodology of statistical analysis adopted in this study [8, 25, 26]. Determining the exact age at which the risk of complications significantly increases is difficult. According to some researchers, a statistically significant difference in the percentage of complications occurs after 35 years of age [27, 28], according to others only after 40 years of age [29]. Some studies suggest that the risk of complications increases with age, and this increase is linear, not threshold [8, 25]. Kenny et al. suggest such dependence; however, in their study, the group was divided into 5-year age ranges, which makes it difficult to confirm this hypothesis [8]. In a similarly constructed study, Joseph et al. reported an increase in the risk of perinatal morbidity and mortality in the 35-39 group (OR 1.46, 95% CI 1.11-1.92, p = 0.007) and at least 40 years (OR 1.95, 95% CI 1.13-3.35, p = 0.02) compared to 20-24 years [30]. In turn, Ezra et al. compared perinatal results in patients over 40 years of age with patients aged 35-40. They found a similar perinatal risk in both groups, nulliparous and multiparous women [31].

In this study, showing the significant increase in the risk of a primary endpoint in the entire population (treating age as a discrete variable, without the division of subjects into age groups), the importance of age as a risk factor was confirmed. It was possible due to the inclusion of a large group of women in the analysis, which distinguishes the study.

It should be emphasized that the importance of a woman's age in obstetric prognosis changes in the subsequent years of her life. Patients included in the study were a group of patients with low risk of complications of pregnancy and delivery. Nevertheless, the risk of the primary endpoint with each year increased more and more with the age of the patients. The importance of age as a risk factor changes over time, as illustrated

in the graph in Figure 3.

Conclusion

Based on the conducted research, age is an independent risk factor for significant complications of the course of pregnancy and delivery in low-risk patients. The correlation between age and the risk of significant complications of the course of pregnancy and delivery is not linear and increases with age. The presented results justify the need to consider the implementation of solutions aimed at reducing the overall perinatal risk in the constantly growing group of advanced maternal age.

Disclosure of interests

None. Completed disclosure of interests forms are available to view online as supporting information.

Contribution to authorship

LP, EDG, AK and AC conceived the study concept and design. LP and AK collected and controlled the data. AC completed the analysis, including quality assurance and control, with the assistance of LP and AK. LP wrote the manuscript under the supervision of EDG. All authors aided in the design of the study, in the interpretation of the data and critical revision of the manuscript for valuable intellectual content, and all authors approved the final version.

Details of ethics approval

The study was approved at a meeting of the Bioethics Committee at the Warsaw Medical University under the chairmanship of Prof. dr hab. n. med. Zbigniew Wierzbicki on 7 March 2017 (decision No. AKBE / 39/17).

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References

1. Tough, S., et al., *What do women know about the risks of delayed childbearing?* Can J Public Health, 2006. **97** (4): p. 330-4.

2. Daniluk, J.C. and E. Koert, *Childless Canadian men's and women's childbearing intentions, attitudes towards and willingness to use assisted human reproduction.* Hum Reprod, 2012. **27** (8): p. 2405-12.

3. Lawson, G. and R. Fletcher, *Delayed fatherhood.* J Fam Plann Reprod Health Care, 2014. **40** (4): p. 283-8.

4. Mills, M., et al., *Why do people postpone parenthood? Reasons and social policy incentives.* Hum Reprod Update, 2011. **17** (6): p. 848-60.

5. Tough, S., et al., *Factors influencing childbearing decisions and knowledge of perinatal risks among Canadian men and women.* Matern Child Health J, 2007. **11** (2): p. 189-98.

6. Hammarberg, K. and V.E. Clarke, *Reasons for delaying childbearing–a survey of women aged over 35 years seeking assisted reproductive technology.* Aust Fam Physician, 2005. **34** (3): p. 187-8, 206.

7. Holton, S., H. Rowe, and J. Fisher, *Women's health and their childbearing expectations and outcomes: a population-based survey from Victoria, Australia.* Womens Health Issues, 2011. **21** (5): p. 366-73.

8. Kenny, L.C., et al., *Advanced maternal age and adverse pregnancy outcome: evidence from a large contemporary cohort.* PLoS One, 2013. **8** (2): p. e56583.

9. Hsieh, T.T., et al., *Advanced maternal age and adverse perinatal outcomes in an Asian population.* Eur J Obstet Gynecol Reprod Biol, 2010. **148** (1): p. 21-6.

10. Carolan, M.C., et al., *Very advanced maternal age and morbidity in Victoria, Australia: a population based study.* BMC Pregnancy Childbirth, 2013. **13** : p. 80.

11. Blomberg, M., R. Birch Tyrberg, and P. Kjolhede, *Impact of maternal age on obstetric and neonatal outcome with emphasis on primiparous adolescents and older women: a Swedish Medical Birth Register Study.* BMJ Open, 2014. **4** (11): p. e005840.

12. Berkowitz, G.S., et al., *Delayed childbearing and the outcome of pregnancy.* N Engl J Med, 1990. **322** (10): p. 659-64.

13. Buehler, J.W., et al., *Maternal mortality in women aged 35 years or older: United States.* JAMA, 1986. **255** (1): p. 53-7.

14. Ales, K.L., M.L. Druzin, and D.L. Santini, *Impact of advanced maternal age on the outcome of pregnancy.* Surg Gynecol Obstet, 1990.**171** (3): p. 209-16.

15. Spellacy, W.N., S.J. Miller, and A. Winegar, *Pregnancy after 40 years of age.* Obstet Gynecol, 1986. **68** (4): p. 452-4.

16. Dildy, G.A., et al., *Very advanced maternal age: pregnancy after age 45.* Am J Obstet Gynecol, 1996. **175** (3 Pt 1): p. 668-74.

17. Lao, T.T., et al., *Advanced maternal age and postpartum hemorrhage - risk factor or red herring?* J Matern Fetal Neonatal Med, 2014. **27** (3): p. 243-6.

18. Silver, R.M., *Fetal death.* Obstet Gynecol, 2007.**109** (1): p. 153-67.

19. Bahtiyar, M.O., et al., *Stillbirth at term in women of advanced maternal age in the United States: when could the antenatal testing be initiated?* Am J Perinatol, 2008. **25** (5): p. 301-4.

20. Sirvinskiene, G., et al., *smoking during pregnancy in association with maternal emotional well-being.* Medicina (Kaunas), 2016. **52** (2): p. 132-8.

21. Chen, H., P. Cohen, and S. Chen, *Biased odds ratios from dichotomization of age.* Stat Med, 2007. **26** (18): p. 3487-97.

22. Greenland, S., *Avoiding power loss associated with categorization and ordinal scores in dose-response and trend analysis.*Epidemiology, 1995. **6** (4): p. 450-4.

23. Royston, P., G. Ambler, and W. Sauerbrei, *The use of fractional polynomials to model continuous risk variables in epidemiology.* Int J Epidemiol, 1999. **28** (5): p. 964-74.

24. Zhao, L.P. and L.N. Kolonel, *Efficiency loss from categorizing quantitative exposures into qualitative exposures in case-control studies.* Am J Epidemiol, 1992. **136** (4): p. 464-74.

25. Cleary-Goldman, J., et al., *impact of maternal age on obstetric outcome.* Obstet Gynecol, 2005. **105** (5 Pt 1): p. 983-90.

26. de Vienne, C.M., C. Creveuil, and M. Dreyfus, *Does young maternal age increase the risk of adverse obstetric, fetal and neonatal outcomes: a cohort study.* Eur J Obstet Gynecol Reprod Biol, 2009.**147** (2): p. 151-6.

27. Delbaere, I., et al., *Pregnancy outcome in primiparae of advanced maternal age.* Eur J Obstet Gynecol Reprod Biol, 2007.**135** (1): p. 41-6.

28. Cnattingius, S., et al., *Delayed childbearing and risk of adverse perinatal outcome. A population-based study.* JAMA, 1992.**268** (7): p. 886-90.

29. Nybo Andersen, A.M., et al., *Maternal age and fetal loss: population based register linkage study.* BMJ, 2000. **320** (7251): p. 1708-12.

30. Joseph, K.S., et al., *The perinatal effects of delayed childbearing.* Obstet Gynecol, 2005. **105** (6): p. 1410-8.

31. Ezra, Y., P. McParland, and D. Farine, *High delivery intervention rates in nulliparous women over age 35.* Eur J Obstet Gynecol Reprod Biol, 1995. **62** (2): p. 203-7.

	Primary endpoint	**Primary endpoint**	**Primary endpoint**
	Occured in 10 578 women N, %* av. + SD* median (Min – Max)*	**Did not occured in 14 485 women N, %* av. + SD* median (Min – Max)***	**p U-MW or Chi^2**
Age (year)	30,8 + 4,3 31 (15 – 47)	31,2 + 4,2 31 (15 – 48)	< 0,0001
Nullipara	6 706 (63,4)	6 431 (44,4)	< 0,0001
Number of previous pregnancies	0,57 + 0,95 0 (0 – 10)	0,88 + 1,06 1 (0 – 10)	< 0,0001
Number of previous deliveries	0,36 + 0,72 0 (0 – 9)	0,66 + 0,84 0 (0 – 10)	< 0,0001
Week of gestation	38,88 + 2,07 39 (22 – 44)	39,34 + 1,03 39 (37 – 42)	< 0,0001
Hospital stay (days)	5,33 + 4,11 4,21 (0,27 – 97,3)	3,96 + 2,29 3,13 (0,16 – 53,8)	< 0,0001
Male infant	5 543 (52,4)	7 271 (50,2)	< 0,0005
Birthweight	3 410,56 + 610,43 3 440 (141 – 5 590)	3 462,65 + 370,34 3 450 (2 160 – 4 620)	< 0,0001
*SD – standard deviation, Min – minimal value, Max – maximal value, p – value of statistical significance, U-MW – U Mann-Whitney test; *if applicable.*	*SD – standard deviation, Min – minimal value, Max – maximal value, p – value of statistical significance, U-MW – U Mann-Whitney test; *if applicable.*	*SD – standard deviation, Min – minimal value, Max – maximal value, p – value of statistical significance, U-MW – U Mann-Whitney test; *if applicable.*	*SD – standard deviation, Min – minimal value, Max – maximal value, p – value of statistical significance, U-MW – U Mann-Whitney test; *if applicable.*

Table 1. Comparison of subgroups examined depending on the occurrence of the primary composite endpoint.

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