The association between preterm births and assisted reproductive technologies

Anna Stastna[1], Eva Waldaufova[1], Tomas Fait[1,2,3]

Aims. The aim of this study is to determine whether the risk of preterm births differs according to the conception method: with or without ART and according to the ART method used (in-vitro fertilisation (IVF) with fresh embryo transfer, frozen embryo transfer (FET) and oocyte receipt (OoR)).
Methods. The research is based on individualised anonymised data on deliveries in Czechia in 2013–2018 (n=651,049) obtained from the National Health Information System. We employ the survival analysis approach applying survival functions (Life tables method) and Cox regression to model the risk of preterm births according to the conception method when controlling for a set of covariates.
Results. The results revealed that the risk of preterm births in singleton pregnancies is higher for ART-treated women (1.56 to 2.06 depending on the ART method) than for non-ART-treated women. The proportion of preterm births differs according to the ART method; the highest proportion was observed for OoR mothers.
Conclusions. Overall, the differences between ART-treated mothers according to the conception method are due mainly to the structural differences between mothers. When controlling for the covariates (Cox regression model), no significant differences were observed concerning the risk of preterm births for women who underwent fresh IVF, FET and OoR.

Key words: preterm birth, assisted reproduction technology, in-vitro fertilisation, frozen embryo transfer, oocyte donation

Received: June 30, 2023; Revised: August 30, 2023; Accepted: September 20, 2023; Available online: October 3, 2023
https://doi.org/10.5507/bp.2023.039

[1]Department of Demography and Geodemography, Faculty of Science, Charles University, Prague, Czechia
[2]Department of Obstetrics and Gynaecology, Second Faculty of Medicine, Charles University, Prague, Czechia
[3]Department of Health Care Studies, College of Polytechnics Jihlava, Jihlava, Czechia
Corresponding author: Eva Waldaufova, e-mail: waldaufe@natur.cuni.cz

INTRODUCTION

Assisted reproduction technology (ART) has undergone significant development in recent years. Thanks to ART, 8.7 million babies were born worldwide following ART treatment from the first successful attempt at in-vitro fertilisation in 1978 up to 2015 (ref.[1]). While the treatment of infertility using ART offers hope to many millions of couples around the world, it has also aroused the interest of researchers in terms of the study of the health outcomes of mothers who conceive via ART and their children.

Research has shown that women who conceive using ART usually differ from women who give birth spontaneously in terms of their socio-demographic structure and health outcomes. From the sociodemographic point of view, ART mothers are more often older[2,3], are first-time mothers[4], are married, are more highly educated[5] and enjoy higher levels of financial security[4].

From the medical point of view, children born following ART treatment have a higher risk of adverse birth outcomes than their spontaneously conceived counterparts[6]. For example, children conceived via ART bear a higher risk of congenital malformations[2], are more likely to be born via caesarean section[7,8], have lower birth weights[2,9] and are more likely to be born preterm[6]. Moreover, a higher percentage of multiple pregnancies is present in ART pregnancies[10]. In terms of pregnant women's health, the higher risk of the hyperstimulation of the ovaries and ectopic pregnancy have been observed in pregnant women who conceived using ART (ref.[10]).

Many studies have focused on the differences in the birth health outcomes of mothers according to the form of ART treatment received by the mother. Such studies focus mainly on the differences between the transfer of fresh embryos and the frozen embryo transfer (FET) (ref.[11]). Concerning singleton pregnancies following single embryo transfer, frozen embryo transfer results in a lower risk of a preterm birth than fresh embryo transfer[12]. According to the available literature, no study has yet focused on the occurrence of preterm births in Czechia in connection with the use of ART.

The research of preterm births is important since this factor is the most common cause of infant mortality and the second most common direct cause of child mortality (under 5 years of age) (ref.[13]). The incidence of preterm births was estimated at 11% in 2010; however, it was seen to vary significantly according to region[13]. For example, in developed European countries approximately 5% of newborns were born preterm, whereas the proportion was 18% in some African countries[13]. According to the authors of the study, the comparison of 60 countries (selected de-

veloped countries and Latin American countries) between 1990 and 2010 revealed that the proportion of preterm births had increased slightly (from 7.5% to 8.6%). They note that this increase could have been due partly to the improved registration of extremely preterm births over the time period considered[13].

The risks of a spontaneous preterm birth include a family history of preterm births, the young or, conversely, old age of the mother, short birth intervals, multiple pregnancies, hypertension and infections[13]. The risk of a preterm birth is higher for male than female newborns, and is further related to the mother's body mass index (BMI), i.e. those with obesity (>30) or low BMIs (<18.5) have a higher risk of preterm birth[13]. However, the causes of preterm births are multifactorial and include social, biological and psychological factors[14]. A number of meta-analyses have confirmed that conception via ART also carries a higher risk of preterm birth[15].

The aim of this article is to determine whether differences exist in terms of the incidence of preterm births for women of childbearing age in Czechia according to the conception method and the type of treatment used for the transfer of the embryo (without ART, the transfer of a fresh embryo as part of an IVF cycle, frozen embryo transfer (FET) and oocyte receipt (OoR)), thereby contributing to the international knowledge of the specifics of the health outcomes of ART. This is important since identifying the medical specifics of the various assisted reproduction methods has the potential to facilitate the choice of the most suitable ART treatment for both the mother and the child.

MATERIALS AND METHODS

Data

The study of the incidence of preterm births for pregnant women in Czechia was based on the analysis of data contained in the National Register of Reproduction Health administered by the Institute of Health Information and Statistics (IHIS CR). The dataset, which comprised anonymised individual data on deliveries that took place in Czechia in the period 2013–2018, was created by linking data from the National Register of Mothers and the National Register of Assisted Reproduction, which allowed us to assign information on the probable method of conception for all deliveries that took place in Czechia in the period 1 January 2013 to 31 December 2018 as related specifically to the use of ART methods and the transfer of the embryo at the appropriate time before the birth. The resulting dataset thus contained unique information on the mothers, the birth outcome and the newborns, as well as information on the embryo transfer and the ART method used by the mothers. This allowed for the monitoring of the length of the pregnancy and the occurrence of preterm births depending on the use/non-use of ART, as well as the analysis of the impact of the ART method on the risk of the occurrence of a preterm birth.

For analysis purposes, births following ART treatment were defined as those that were preceded by embryo transfer 22–40 weeks prior to the date of the birth. If more than one ART cycle in the given range was reported, the last cycle that was administered before childbirth and not exceeding 40 weeks was considered.

The subsequent analysis considered the information on the embryo transfer via the 3 selected monitored ART cycles, the designation of which follows the terminology used in the National Registry of Reproduction Health – Assisted Reproduction (NRAR): 1) IVF cycles involving both conventional in-vitro insemination and ICSI in which a single spermatozoon is injected into the oocyte cytoplasm, 2) FET (frozen embryo transfer) cycles involving the transfer of thawed embryos preserved from a previous IVF cycle. 3) OoR (oocyte receipt) cycle, in which a woman receives oocytes from a donor to be used for reproductive purposes. According to Czech legislation, the recipient of the oocyte is always an infertile couple and if the embryos produced during the OoR cycle are frozen, the FET cycle follows[16]. According to the IHIS CR methodology and the definition of ART cycles, the analysed IVF and OoR cycles cover the transfer of fresh embryos. In the case of FET cycles, this is a data mix of own and donated oocytes, since the origin of the oocyte cannot be distinguished from the available data. According to the WHO, a preterm birth is defined as occurring before the 37th completed week of pregnancy[17]. Our analysis focused on preterm births of at least one live child, the reason for which was related primarily to the data source, i.e. stillbirths have for many years been underestimated in the IHIS CR data compared to data provided by the Czech Statistical Office[18]. However, a further factor concerned the substantive relevance of focusing only on live births since the aim was to study the impact of ART on selected fertility outcomes and not on stillbirths.

The source dataset contained information on 651,394 deliveries that took place in Czechia in the period 2013–2018. Since the aim of the analysis was to determine whether the incidence of preterm births differs depending on the conception method, the source dataset was reduced by 345 deliveries, concerning which the women conceived by methods other than those studied.

Therefore, the analytical sample of 651,049 deliveries included 629,485 deliveries without the use of ART and deliveries of ART-treated women: 12,530 deliveries following fresh embryo transfer (IVF), 8,020 deliveries following frozen embryo transfer (FET) and 1,014 deliveries following donated oocyte receipt (OoR).

Of the analytical sample, 649,279 cases related to at least one live birth: 627,785 deliveries without the use of ART methods, 12,491 deliveries following IVF with fresh embryo transfer, 7,994 following FET and 1,009 following OoR. In view of the fact that applied survival analysis (see below) allows for the censoring of stillbirths, we worked with a subset of live births only in the initial descriptive part of the study, whereas the subsequent models considered the whole dataset as defined by the conception method.

Methods

The study includes both descriptive analytical approaches and survival analysis (the life table method and Cox regression). Descriptive analyses and life tables employ the complete analytical dataset. Given the significant differentiation of preterm births observed in the descriptive analysis and survival curves concerning pregnancy frequency, the Cox model is employed to model the risk of preterm birth solely for singleton pregnancies.

Survival analysis, which allows for the monitoring of both the occurrence of an event (here a preterm live birth) and the time at which the event occurred[19], was applied for the initial analysis of the timing of births with regard to the length of the pregnancy. This study concerned pregnancies that ended in a delivery. The length of time under study is gestational age measured in weeks. The observations were censored when a) gestational age attains the 37th week of pregnancy (births after this time are concerned full-term births), or b) at the time of the birth of a stillborn child, provided it occurred before the 37th week of pregnancy. The survival functions were constructed applying the life table method, which shows the distribution of events over time in intervals of equal length[19], in this case completed weeks of pregnancy.

The Cox proportional hazard model was subsequently applied[20] since the aim of the study was to monitor the occurrence of preterm live births for mothers according to the conception method over time, while including the influence of explanatory variables in the model. Two Cox regression models were created. Firstly, all singleton births (40,302 events and 600,848 censored observations) were monitored via which it was possible to compare the risk of a preterm birth for women who received ART versus women who gave birth without the use of ART. The second model was constructed only for singleton births to women who underwent ART (2,027 events and 17,698 censored observations), and concerning whom it was possible to compare the risks of a preterm birth according to the ART method used (IVF versus FET and OoR).

The following control variables were included in model 1 for all singleton births: the conception method (without ART – *ref.*, FET, IVF, OoR), the age of the mother (≤24, 25–29, 30–34 *ref.*, 35–39, ≥40), pregnancy complications (without hypertension and diabetes – *ref.*, gestational hypertension, diabetes, hypertension and diabetes), a previous caesarean birth (no – *ref.*, yes), the birth order (first – *ref.*, second, third and higher), a previous preterm birth (no – *ref.*, yes) and the year of birth (2013–2018, *ref.* 2013). The same set of variables were included in model 2 for singleton births following ART, with the addition of a cause of infertility variable (male factor – *ref.*, not determined, female factor, both the male and female factor); in addition, the conception method variable comprised just three categories in model 2 (IVF – *ref.*, FET and OoR).

Our research strategy was focused on the collection and evaluation of high-quality papers that analysed the association between the use of assisted reproductive technologies and the health outcomes of newborns and labour (especially the occurrence of preterm birth). The search for papers was conducted primarily on Google Scholar by using keywords such as “preterm birth”, “assisted reproductive technologies”, “IVF”, “FET”, “OoR”, or “health outcomes of ART”. The priority for selection was given to recent literature (from 2010 onwards) and high-quality journals with IF.

RESULTS

The proportion of preterm births in Czechia is comparable to that in other developed countries. The period 2013–2018 even saw a slight decrease in the proportion of preterm births, which can be considered a success of the Czech healthcare system. This occurred despite the fact that the mean age of mothers at births in the same period continued to increase, and despite the older age of first-time mothers is a proven risk factor in terms of preterm births; on the other hand, this period also saw a

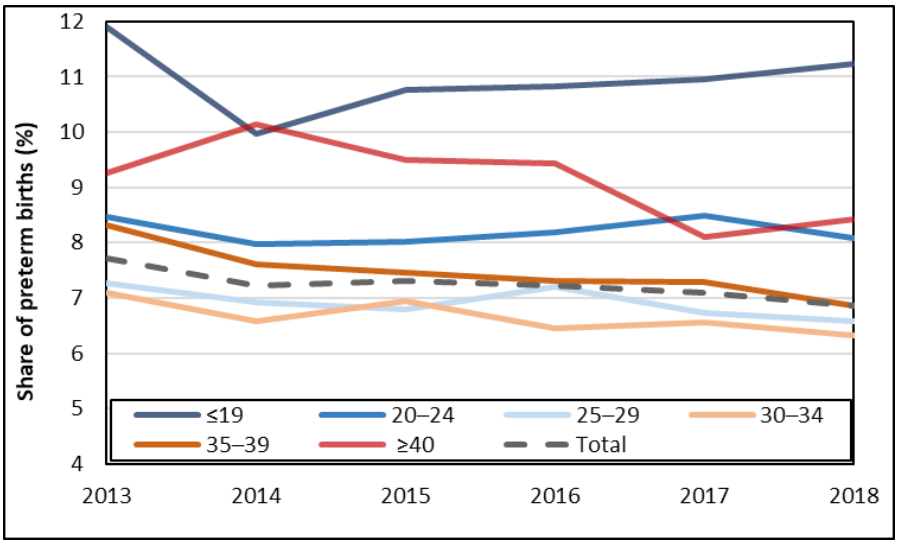

Fig. 1. Proportion of preterm births according to the age of the mother, Czechia, 2013–2018, (%).

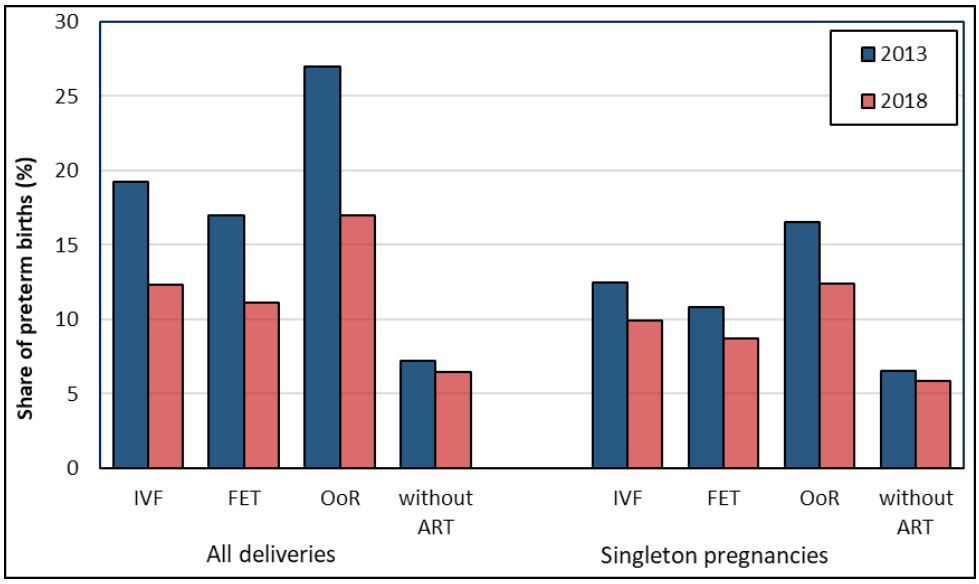

Fig. 2. Proportion of preterm births according to the conception method, all deliveries and singleton pregnancies, Czechia, 2013 and 2018, (%).

significant decline in the share of multiple pregnancies[21]. In 2013, 7.7% of women in Czechia had a preterm birth and in 2018 this figure had declined to 6.9% (Fig. 1). In terms of age, the most at-risk group of mothers comprised the youngest (under 19 years) and the oldest (40 years and older) age categories. Mothers aged 25–34 comprised the least at-risk group throughout the observed period (Fig. 1).

627,785 deliveries resulted to at least one live birth in Czechia without the use of ART methods in the period 2013–2018, 12,491 deliveries following IVF with fresh embryo transfer, 7,994 following FET and 1,009 following OoR. The incidence of preterm births varied significantly between these groups, although a decrease was observed in the proportion of preterm births for all the monitored groups of deliveries between 2013 and 2018 (Fig. 2). Women who gave birth without ART had the lowest proportion of preterm births throughout the monitored period (in 2018, 6.5% of those who did not undergo ART had a preterm birth) and, compared to the other groups, this proportion saw the lowest decrease between 2013 and 2018. ART-treated mothers were found to be significantly more at risk of a preterm birth. In 2018, 12.4% of women who gave birth following IVF, 11.1% of women following FET and 17% following OoR had a preterm birth. In 2013, however, the differences in the proportion of preterm births according to the ART method used were even more pronounced. Between 2013 and 2018, a decrease in the share of preterm births of more than 5 p.p. was observed for all women who gave birth following ART; the greatest decrease concerned those who gave birth following OoR (Fig. 2). The decrease in the proportion of preterm births for ART-treated mothers can, to a certain extent, be ascribed to the introduction of a single embryo transfer strategy, which was reflected in a significant decrease in the share of multiple pregnancies (in 2013, 13.5% of ART mothers gave birth to multiple children, in 2018 it was just 5.4% of ART mothers).

Since the differences in the proportions of preterm births are related largely to the differing structures of the mothers, especially in terms of the pregnancy frequency, Fig. 2 shows the proportions of preterm births according to the monitored treatment method for singleton pregnancies only. While the proportions of preterm births were lower for this group of mothers in 2013 and 2018 than for all mothers (Fig. 2), differences persisted between non-ART and ART mothers and according to the ART method used (IVF, FET, OoR).

Fig. 3. presents survival curves that illustrate the proportions of pregnancies that had not yet ended in childbirth by the gestational age (completed week of pregnancy). This method allows for the monitoring of both the total shares of preterm births and their timing within the course of pregnancy. The results for all deliveries show that by the end of the 36th week of pregnancy, 93% of pregnancies without the use of ART had not yet ended in childbirth. However, the results for the ART pregnancies revealed a significantly lower proportion of ongoing pregnancies; around 85–87% of the pregnancies following IVF and FET and just 80% of pregnancies following OoR were still ongoing at the end of 36 weeks. The survival curves also reveal that women with OoR pregnancies gave birth significantly earlier than the other groups – 10% gave birth before attaining the 34th week of pregnancy and 5% of OoR mothers had extremely or very preterm births[22] up to the 31st week of pregnancy.

Since the risk and occurrence of preterm births are higher for multiple pregnancies[13], which are, moreover, more frequent for ART-treated women, Fig. 4 shows the survival curves for singleton pregnancies only. It is clear that the proportions of singleton pregnancies still ongoing at the end of the 36th week are higher than for all pregnancies and that preterm births are significantly less frequent for singleton pregnancies, as previously indicated by the descriptive results (see Fig. 2). Moreover, it is evident that the differences between the observed groups of

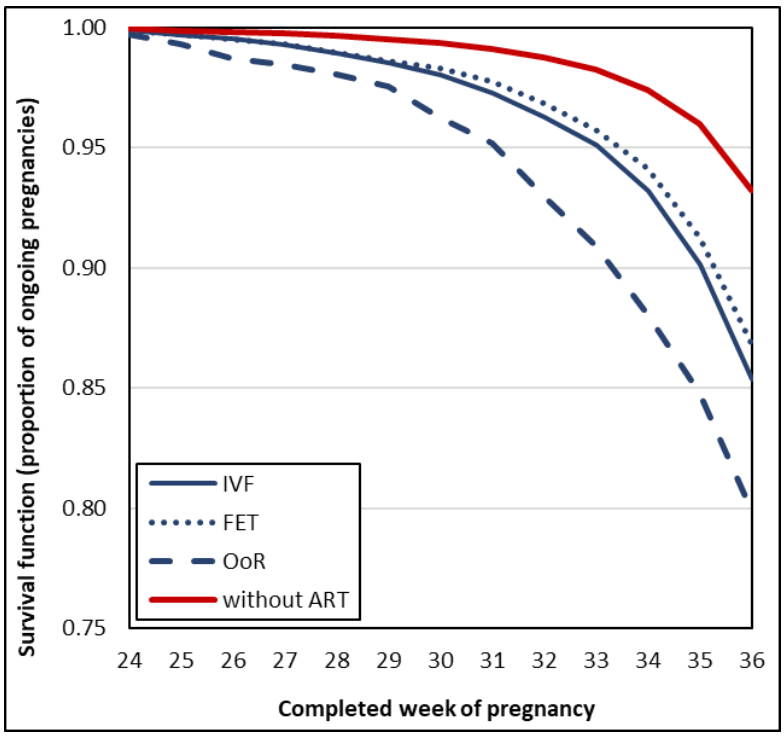

Fig. 3. Survival function of the time to delivery by the conception method, all deliveries, Czechia, 2013–2018.

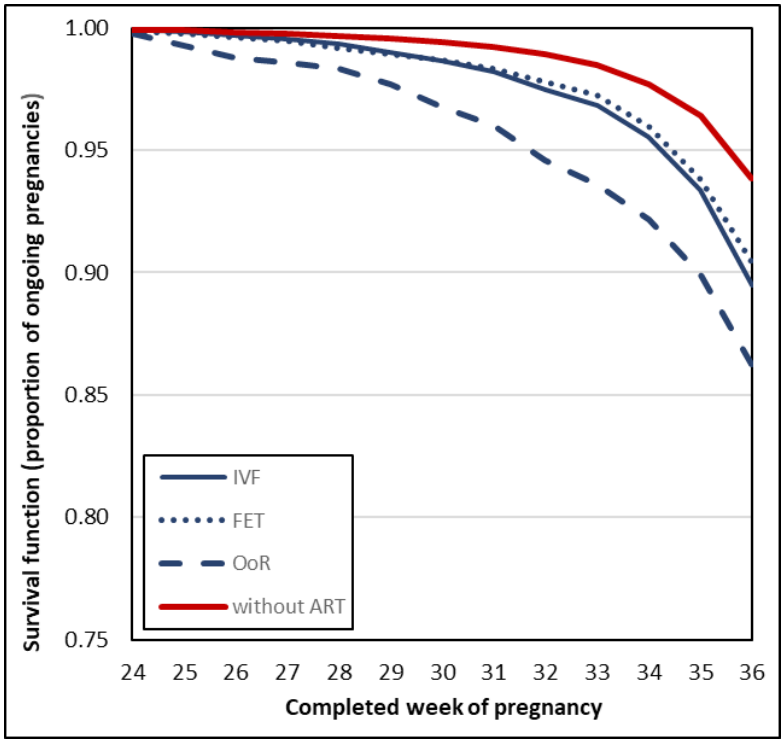

Fig. 4. Survival function of the time to delivery by the conception method, singleton pregnancies, Czechia, 2013–2018.

mothers persist even in the case of singleton pregnancies. The lowest preterm birth risk group relates to non-ART mothers (94% of pregnancies were still ongoing at the end of the 36th week) versus OoR mothers (86% of pregnancies). The proportion of pregnancies still ongoing at the end of the 36th week differed by 1 p.p. for women who received FET and IVF treatment (90% vs. 89%).

The complex Cox regression model also allows for the control of the impact of other variables that are associated with a higher risk of preterm birth in addition to the ART method and the pregnancy frequency, i.e. demographic (age, birth order) and, importantly, health characteristics (cause of infertility, pregnancy complications, a previous caesarean delivery, previous preterm birth).

The risk of a preterm birth for ART mothers compared to non-ART mothers

Aimed at revealing the risk of preterm birth according to the conception method, the Cox regression method was used to construct model 1, which included all singleton deliveries in Czechia in the period 2013–2018. The control of all the considered covariates (Table 1) revealed

that the risks of a preterm birth for ART-treated mothers are higher than for non-ART mothers (i.e. 56% higher for FET mothers, 72% for IVF mothers and 2 times higher for OoR mothers).

The covariates further indicated that a higher risk of preterm birth is associated with mothers who experience pregnancy complications (gestational hypertension and diabetes). A higher risk of preterm birth was also detected for mothers who had a previous preterm birth (a 5.8 times higher risk) and those who had previously given birth via caesarean section (a 1.2 times higher risk of a preterm birth). Conversely, the risk of a preterm birth was lower for higher-order than for first-order births. In terms of age, the youngest age group of mothers (up to 19 years of age – 33% higher risk) and the oldest age group (over 40 years of age – 27% higher risk) were observed to be more at risk of a preterm birth than mothers in the most numerous age group (30–34 years). The overall risk of a preterm birth decreased by 12% between 2013 and 2018 (see Table 1).

Comparison of the risks of a preterm birth for ART mothers according to the ART method

Model 1 revealed that ART mothers have a higher risk of a preterm birth than non-ART mothers. A further aim of the article was to determine whether the risk also differs according to the ART method (IVF, FET or OoR) used and to identify the method that poses the lowest risk when controlling for socio-demographic and health characteristics. Thus, only the singleton births of ART-treated women with the three most common ART methods were included in model 2 (Table 2). When taking into account the differences between the mothers in terms of the demographic and health structures, the differences with respect

Table 1. Risk of a preterm birth (Exp(β)) for singleton pregnancies (model 1), Czechia, 2013–2018.

Variable	*P*	Exp(B)	95% confidence interval	
Type of conception				
without ART (ref.)		1		
IVF	<0.001	1.72	1.62	1.82
FET	<0.001	1.56	1.45	1.68
OoR	<0.001	2.06	1.71	2.48
Age				
≤24	<0.001	1.33	1.29	1.37
25–29	<0.001	1.04	1.02	1.07
30–34 (ref.)		1		
35–39	<0.001	1.08	1.05	1.11
≥40	<0.001	1.27	1.21	1.34
Pregnancy complications				
without hypertension and diabetes (ref.)		1		
gestational hypertension	<0.001	1.42	1.34	1.51
diabetes	<0.001	1.20	1.15	1.25
hypertension and diabetes	<0.001	1.84	1.65	2.06
Previous CS birth				
no (ref.)		1		
yes	<0.001	1.19	1.15	1.23
Birth order				
first (ref.)		1		
second	<0.001	0.61	0.60	0.63
third and more	<0.001	0.72	0.70	0.74
Previous preterm birth				
no (ref.)		1		
yes	<0.001	5.82	5.63	6.02
Year				
2013 (ref.)		1		
2014	<0.001	0.94	0.91	0.97
2015	<0.001	0.95	0.92	0.98
2016	<0.001	0.93	0.90	0.96
2017	<0.001	0.92	0.88	0.95
2018	<0.001	0.89	0.86	0.92
Number of observations	641,150			
number of events	40,302			
number of censored events	600,848			

Table 2. Risk of a preterm birth (Exp(β)) for ART mothers with singleton pregnancies (model 2), Czechia, 2013–2018.

Variable	*P*	Exp(B)	95% confidence interval	
Type of conception				
IVF (ref.)		1		
FET	0.17	0.94	0.85	1.03
OoR	0.10	1.18	0.97	1.45
Age				
≤24	0.13	1.32	0.92	1.89
25–29	0.09	1.12	0.98	1.28
30–34 (ref.)		1		
35–39	0.12	0.92	0.83	1.02
≥40	0.07	1.15	0.99	1.33
Cause of infertility				
the male factor (ref.)		1		
not detected	0.27	1.12	0.92	1.35
the female factor	<0.001	1.48	1.30	1.68
the female and male factor	<0.001	1.32	1.16	1.50
Pregnancy complications				
without hypertension and diabetes (ref.)		1		
gestational hypertension	<0.01	1.38	1.09	1.73
diabetes	0.13	1.13	0.96	1.32
hypertension and diabetes	0.08	1.41	0.96	2.06
Previous CS birth				
no (ref.)		1		
yes	0.02	1.21	1.03	1.43
Birth order				
first (ref.)		1		
second	<0.001	0.64	0.57	0.73
third and more	<0.001	0.61	0.49	0.75
Previous preterm birth				
no (ref.)		1		
yes	<0.001	5.81	4.84	6.98
Year				
2013 (ref.)		1		
2014	0.08	0.87	0.75	1.01
2015	0.04	0.85	0.73	0.99
2016	<0.001	0.80	0.68	0.93
2017	<0.001	0.79	0.68	0.93
2018	<0.001	0.78	0.67	0.91
Number of observations	19,725			
number of events	2,027			
number of censored events	17,698			

to the risk of a preterm birth between those who used IVF and OoR with the transfer of a fresh embryo, and FET were not proved to be statistically significant.

It is worthy of note that the risk of a preterm birth differed depending on which of the partners was the cause of infertility. ART-treated mothers for whom the cause of infertility was identified as being exclusively female factor or combination of female and male factor evinced a 48% and 32%, respectively higher risk of preterm birth compared to mothers for whom the cause of infertility was found to be on the side of their partner. The higher risk of a preterm birth was also associated with other health aspects such as gestational hypertension (a 38% higher risk than for women without gestational hypertension and diabetes). Mothers who had a previous caesarean birth or a previous preterm birth were also more at risk of a preterm birth (21% and 5.8 times higher, respectively). Conversely, the risk decreased with the birth order and also over time. The risk of having a preterm birth in 2018 was 29% lower for ART mothers than in 2013 (Table 2) – the risk therefore decreased more rapidly during the monitored period for ART mothers than for non-ART mothers (compare Model 1 and Table 1).

DISCUSSION

Infertility treatment via the use of ART offers hope to many couples who are unable to conceive naturally. However, it is necessary that users fully understand the health consequences of ART, which may affect the health of both mothers and their newborns. Having a preterm birth, one of the most fundamental causes of child mortality, also comprises one of the most significant ART-related health risks[23].

A large number of studies have been devoted to the health aspects of ART. The results of the analysis presented in our study correspond with those of studies that have indicated the elevated risk of a preterm birth for mothers who conceive using ART (ref.[15]). However, the reasons for the higher risk of a preterm birth following ART are not easy to determine. While some studies suggest that the risk is associated with the ART method itself, other studies have linked the risk to infertility rather than the ART method[15].

No unequivocal agreement has been reached in previous studies on the dependency of a preterm birth on the specific ART method. A review[24] of the results of 11 studies that compared the incidence of a preterm birth for IVF/ICSI and FET pregnancies shows a higher risk (1.14 times) of a preterm birth for IVF/ICSI than for FET pregnancies. Of the 11 monitored studies, however, only 5 studies confirmed the significantly higher risk of a preterm birth for IVF/ICSI. A further 5 studies concluded that there is no difference in terms of this risk between IVF/ICSI and FET births, while the authors of one study determined the opposite results, i.e. that FET results in a higher risk of a preterm birth. The results of our study are, therefore, consistent with studies that failed to determine a statistically significant difference in the risk of a preterm birth between IVF/ICSI and FET when controlling for the relevant covariates.

A meta-study[25] compared the risk of a preterm birth for IVF/ICSI and OoR mothers. Four of the six studies compared indicated the higher risk of a preterm birth for OoR mothers, whereas the other two studies revealed no difference in the risk of a preterm birth between IVF/ICSI and OoR. OoR is, however, associated with a higher risk of perinatological complications according to the analysis of 35 studies conducted in the period 1982–2016 both for singleton and multiple pregnancies[26].

Our article monitored in detail only singleton pregnancies since the representation of multiple births decreased within the monitored period and, moreover, differed between the monitored groups of women. The data indicated the more frequent occurrence of multiple pregnancies for ART mothers compared to non-ART mothers, as well as differences according to the ART treatment method, i.e. the highest frequency of multiple pregnancies related to the OoR method (18% compared to 9% following IVF and 7% following FET).

The analysis of singleton pregnancies did not reveal any significant differences in terms of the risk of a preterm birth between IVF, FET and OoR mothers in Czechia when controlling for covariates. Thus, it appears that the overall differences in the incidence of preterm births (Fig. 2) according to the ART method used (IVF, FET or OoR) are due mainly to the differing structure of the mothers and, in particular, to the differences in the proportions of multiple pregnancies. This finding confirms the justification of the one-embryo transfer strategy in the ART treatment of infertility.

The aim of this article was to present the occurrence of preterm births for pregnant women in Czechia according to the probable conception method and to determine whether the differing proportions of preterm births according to the ART method are due to the differing structures of the women (in terms of both socio-demographic variables such as age, the birth order and the pregnancy frequency, and health complications) or other factors.

According to a Czech study[27] there is a strong risk of a preterm birth for mothers with a previous preterm birth or abortion in the second trimester of pregnancy. Other risk factors comprise being in the young (<20) or older (>40) age categories, chronic medical conditions (e.g. diabetes, hypertension and obesity), infections and multiple pregnancies. The potential influence of the mother's immunity and microbiota on the incidence of preterm births is also studied[28].

While the influence of many of these factors was confirmed by our analysis, the study presented herein further serves to expand current knowledge via the linking of the risk of a preterm birth with ART and the various ART methods used, as well as, for example, the influence of which partner in the couple is the bearer of infertility. As far as the available Czech literature is concerned, no other studies have been conducted that monitored the occurrence of preterm births in connection with the use of ART. Furthermore, a knowledge of the health consequences of ART is crucial in the context of the postponement of motherhood to older ages, the increasing use of ART, and changes in the use of the various ART methods available in Czechia. According to Řežábek[29], the number of IVF and OoR cycles performed in Czechia increased only slightly between 2007 and 2017. The growth in the number of OoR cycles was, presumably, limited primarily by the number of female donors. Conversely, there has been a marked increase in the use of the FET method, which is probably due, at least partly, to the trend towards the transfer of just one embryo, as a result of which the unused embryos are frozen in the case of a subsequent conception attempt should the first transfer be unsuccessful[16]. However, frozen embryos can also be used by women who have already given birth and wish to conceive again[29].

Applying the survival curves method, our article demonstrates differences in the incidence of preterm births for women with singleton pregnancies who, most probably, conceived without ART and those who used ART (IVF, FET, OoR). After controlling for a series of risk factors that are associated with preterm births (e.g. a previous preterm birth, the maternal age, hypertension, diabetes, parity, etc.), differences in terms of the risk of a preterm birth according to the conception method were demonstrated only between ART and non-ART mothers rather than between the 3 considered ART treatments (IVF,

FET, OoR). The strength of the study lies in the use of a unique and extensive dataset, which allowed for both the comparison of mothers according to the conception method and the consideration of the roles of a number of variables that are usually associated with the occurrence of preterm births.

However, the study also has a number of limitations. The dataset considers only women who received ART treatment in Czechia; therefore, women who were treated for infertility abroad were identified as non-ART mothers. Given that Czechia is, however, considered to be a major target country for reproductive tourism[30], no significant underestimation of the number of women who gave birth using ART in Czechia can be expected. Despite the potential for the inclusion of a range of significant preterm birth predictors in the Cox regression model, it was not possible to control for certain other important risk factors, e.g. the BMI and infections[28]. Thus, the consideration of their influence on the occurrence of preterm births according to the conception method could well form the subject of future research. In the case of FET cycles, the data did not allow us to distinguish between own and donor oocytes, which could potentially affect the results due to the different structure of women undergoing different ART cycles. However, we reduce this risk mainly by including and controlling for the main differential characteristics (age, parity, causes of infertility and selected pregnancy complications) in the model. Further research is needed to further analyse possible differences in the risk of preterm birth between own and donor oocytes in FET cycles, which is currently preferred in clinical practice as it eliminates the need for the uneasy synchronisation of donor and recipient cycles[31].

A detailed knowledge of the risk factors surrounding preterm births could help to identify those women who have a higher risk of a preterm birth and to establish effective preventive measures. According to Flood and Malone[14], a distinction can be made between primary prevention (for women who are or are not yet pregnant, with the aim of reducing the risk of preterm birth) and secondary prevention (for women who already have a higher risk of a preterm birth). Examples of pre-conception prevention approaches include, for example, leading a healthy lifestyle (no smoking or alcohol use, a normal BMI etc.). Examples of prevention measures for already pregnant women at risk of a preterm birth include the use of progesterone or cervical cerclage[32].

CONCLUSION

The incidence of preterm births differs not only between women who give birth with/without ART, but also according to the ART method used. The detailed analysis of singleton pregnancies revealed that when controlling for factors that are traditionally associated with the risk of a preterm birth, the risk of such a birth differs between ART and non-ART women. When controlling for selected health factors and sociodemographic characteristics (age, parity, etc.), however, the analysis did not reveal any statistically significant differences between the risk of a preterm birth between the three monitored ART treatments (IVF, FET and OoR).

Acknowledgments: This paper was supported by the Czech Science Foundation (No. 21–31691S), the "Demographic consequences of assisted reproduction in Czechia" project.

Author contributions: AS, EW: conceptualization and design of the research, methodology; formal analysis and interpretation of data, writing – original draft preparation; EW: data preparation; TF: writing – reviewing and editing; All authors read and approved the final manuscript.

Conflict of interest statement: The authors state that there are no conflicts of interest regarding the publication of this article.

REFERENCES

1. Adamson GD, De Mouzon J, Chambers, Zegers-Hochschild F, Mansour R, Ishihara O, Banker M, Dyer S. International Committee for Monitoring Assisted Reproductive Technology: World Report on Assisted Reproductive Technology, 2015 (preliminary) [online]. Available from: https://secureservercdn.net/198.71.233.206/3nz.654.myftpupload.com/ wp-content/uploads/ICMART-ESHRE-WR2015-FINAL-20200901.pdf.
2. Lv H, Diao F, Du J, Chen T, Meng Q, Ling X, Li H, Song C, Xi Q, Jiang Y, Xu Y, Tao S, Huang L, Wen M, Peng M, Liu C, Lu Q, He Y, Yin Y, Liu X, Xu B, Han X, Zhou K, Jiang T, Zhao Y, Ma H, G Jin, Xia Y, Liu J, Lin Y, Hu Z, Shen H. Assisted reproductive technology and birth defects in a Chinese birth cohort study. Lancet Reg Health West Pac 2021;7:1-9. doi: 10.1016/j.lanwpc.2020.100090
3. Kocourková J, Šťastná, A, Burcin B. The influence of the increasing use of assisted reproduction technologies on the recent growth in fertility in Czechia. Sci Rep 2023;13(1):10854. doi: 10.1038/s41598-023-37071-7
4. Goisis A, Håberg SE, Hanevik HI, Magnus MCh, Kravdal Ø. The demographics of assisted reproductive technology births in a Nordic country. Hum Reprod 2020;35(6):1441-50. doi: 10.1093/humrep/deaa055
5. Barbuscia A, Myrskylä M, Goisis A. The psychosocial health of children born after medically assisted reproduction: evidence from the UK Millennium Cohort Study. SSM Popul Health 2019;7:100355. doi: 10.1016/j.ssmph.2019.100355
6. Goisis A, Remes H, Martikainen P, Klemetti R, Myrskylä M. Medically assisted reproduction and birth outcomes: a within-family analysis using Finnish population registers. Lancet 2019;393(10177):1225-32. doi: 10.1016/S0140-6736(18)31863-4
7. Waldaufová E, Šťastná A. Role reprodukčního stárnutí v nárůstu porodů císařským řezem v Česku. Demografie 2022;64(2):91-105. (In Czech)
8. Fait T, Šťastná A, Kocourková J, Waldaufová E, Šídlo L, Kníže M. Has the cesarean epidemic in Czechia been reversed despite fertility postponement? BMC Pregnancy Childbirth 2022;22(1):469. doi: 10.1186/s12884-022-04781-1
9. Waldaufová E, Šťastná A, Fait T. The low birth weights of newborns conceived using assisted reproduction technology. Bratisl Lek Listy 2024;125(2):137-43. doi: 10.4149/BLL_2024_023
10. Řežábek K. Asistovaná reprodukce. 3. aktualizované a doplněné vydání. Praha: Maxdorf. Farmakoterapie pro praxi 2018. (In Czech)
11. Maheshwari A, Pandey S, Shetty A, Hamilton M, Bhattacharya S. Obstetric and perinatal outcomes in singleton pregnancies resulting from the transfer of frozen thawed versus fresh embryos generated through in vitro fertilization treatment: a systematic review and meta-analysis. Fertil Steril 2012;98(2):368-77. doi: 10.1016/j.fertnstert.2012.05.019
12. Ishihara O, Araki R, Kuwahara A, Itakura A, Saito H, Adamson GD. Impact of frozen-thawed single-blastocyst transfer on maternal and

neonatal outcome: an analysis of 277,042 single-embryo transfer cycles from 2008 to 2010 in Japan. Fertil Steril 2014;101(1):128-33. doi: 10.1016/j.fertnstert.2013.09.025
13. Blencowe H, Cousens S, Oestergaard M, Chou D, Moller A, Narwal R, Adler A, Garcia CV, Rohde S, Say L, Lawn JE. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012:9;379(9832):2162-72.
14. Flood K, Malone FD. Prevention of preterm birth. Seminars in Fetal and Neonatal Med 2012;17(1):58-63.
15. Blickstein I. Does assisted reproduction technology, per se, increase the risk of preterm birth? BJOG: Int J Obstet Gynaecol 2006;113:68-71.
16. ÚZIS ČR 2021. Asistovaná reprodukce v ČR 2018-2019. Praha. ÚZIS ČR. Available from: https://www.uzis.cz/res/f/008365/asistreprodukce2018-2019.pdf (In Czech)
17. Howson CP, Kinney MV, Lawn JE. March of Dimes, PMNCH, Save the children, WHO. Born too soon: the global action report on preterm birth. Geneva: World Health Organization 2012. Available from: http://www.who.int/pmnch/media/news/2012/201204_borntoosoon-report.pdf
18. ÚZIS ČR. Rodička a novorozenec 2016–2021. Ústav zdravotnických informací a statistiky, 2023. Available from: https://www.uzis.cz/res/f/008423/rodnov2016-2021.pdf (In Czech)
19. Tekle FB, Vermunt JK. Event history analysis. In: Cooper H, Camic PM, Long DL, Panter AT, Rindkopf KJ (eds). APA handbook of research methods in psychology. 3rd ed. Washington, DC, US: American Psychological Association 2012:267-90. Available from: https://jeroenvermunt.nl/tekle2010.pdf
20. Reisnerová, S. Analýza přežití a Coxův model pro diskretní čas. Robust 2004;13:339-46. (In Czech)
21. ČSÚ 2021. Vývoj obyvatelstva České republiky 2020. Praha: ČSÚ. Available from: https://www.czso.cz/csu/czso/vyvoj-obyvatelstva-ceske-republiky-2020 (In Czech)
22. Lawn JE, Gravett MG, Nunes TM, Rubens CE, Stanton C, GAPPS Review Group. Global report on preterm birth and stillbirth (1 of 7): definitions, description of the burden and opportunities to improve data. BMC Pregnancy Childbirth 2010;10(1):1-22. doi: 10.1186/1471-2393-10-S1-S1
23. Giouleka S, Tsakiridis I, Kostakis N, Koutsouki G, Kalogiannidis I, Mamopoulos A, Athanasiadis A, Dagklis T. Preterm Labor: A Comprehensive Review of Guidelines on Diagnosis, Management, Prediction and Prevention. Obstet Gynecol Surv 2022;77(5):302-17. doi: 10.1097/OGX.0000000000001023
24. Zhao J, Xu B, Zhang Q, Li YP. Which one has a better obstetric and perinatal outcome in singleton pregnancy, IVF/ICSI or FET? a systematic review and meta-analysis. Reprod Biol Endocrinol 2016;14:1-7.
25. Mascarenhas M, Sunkara SK, Antonisamy B, Kamath MS. Higher risk of preterm birth and low birth weight following oocyte donation: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol 2017;218:60-7.
26. Storgaard M, Loft A, Bergh C, Wennerholm UB, Söderström-Anttila V, Romundstad LB, Aittomaki K, Oldereid N, Forman N, Pinborg A. Obstetric and neonatal complications in pregnancies conceived after oocyte donation: a systematic review and meta-analysis. BJOG 2017;124(4):561-72.
27. Dudášová J, Šimjak P, Koucký M, Pařízek A. Současné možnosti predikce předčasného porodu. Ceska Gynekol 2019;84(5):355-60. (In Czech)
28. Koucký M, Malíčková K, Hrdý J, Černý A, Hrbáčková H, Šimják P, Pařízek A. Úloha mateřské imunity a mikrobiomu ženy v patogenezi předčasného porodu. Ceska Gynekol 2017;82(5):407-10. (In Czech)
29. Řežábek K. Trendy v asistované reprodukci v datech Národního registru asistované reprodukce České republiky v letech 2007–2017. Ceska Gynekol 2020;85(1):4-10. (In Czech)
30. Volejníková A, Kocourková J. Asistovaná reprodukce v Česku z pohledu přeshraniční reprodukční péče. Demografie 2022;64(2):159-74. (In Czech)
31. Glujovsky D, Pesce R, Sueldo C, Retamar AMQ, Hart RJ, Ciapponi. Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes. Cochrane Database Syst Rev 2010;(1):CD006359. doi: 10.1002/14651858.CD006359.pub2. Update in: Cochrane Database Syst Rev 2020;10:CD006359.
32. Shennan A, Story L, Jacobsson B, Grobman WA; FIGO Working Group for Preterm Birth. FIGO good practice recommendations on cervical cerclage for prevention of preterm birth. Int J Gynaecol Obstet 2021;155(1):19-22.