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CLINICAL STUDY

The low birth weights of newborns conceived using assisted reproduction technology

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ABSTRACT
Couples are increasingly using assisted reproduction technology (ART) to facilitate having children. This raises the question of whether using ART leads to the same health outcomes as spontaneous conception. One of the major health outcome factors concerns the weight of the newborn. Many foreign studies have proved that newborns conceived via ART evince lower birth weights than newborns that were conceived spontaneously. The purpose of this study is to determine whether the risk of low birth weight differs according to the ART method selected (in-vitro fertilisation with fresh embryo transfer, frozen embryo transfer, oocyte receipt), and which of these methods is associated with the lowest risk of a low birth weight. Anonymised individual data on all deliveries that took place in Czechia between 2013 and 2018 was used for the analysis. The dataset was obtained from the National Registry of Reproduction Health (administered by IHIS CR). The binary logistic regression revealed that concerning many of the covariates controlled, women who underwent IVF had a higher risk (30 %) of giving birth to a child with a low birth weight than women who received frozen embryo transfer treatment (CI 1.15–1.48). Women who underwent oocyte receipt treatment were found to have an even higher (52 %, CI 1.17–1.97) risk than women who received frozen embryo transfer. This study supports existing international knowledge of the specifics of the health outcomes of women who use ART *(Tab. 1, Fig. 3, Ref. 33). Text in PDF www.elis.sk*
KEY WORDS: Low birth weight, assisted reproduction technology, in-vitro fertilisation, frozen embryo transfer, oocyte donation.

Introduction

In the context of reproductive ageing, whereby more and more women are postponing childbearing until older age, the decreasing chances of conceiving with increasing age has resulted in increased demand for treatment via assisted reproduction technology (ART). In the European context, infertility treatment using ART is easily available in Czechia, and the proportion of children born following ART is one of the highest in Europe (according to data published by ESHRE (1), children born following ART cycles performed in Czechia made up 5.4 % of all live births in the country in 2017).

With the development of the use of ART, increasing attention is being devoted to the health aspects of assisted reproduction from the point of view of both more numerous pregnancy complications and the incidence of birth outcome complications (2). A range of studies have documented the increased risk of pregnancy complications and unfavourable perinatal outcomes as a result of the use of ART (3, 4). Assisted reproduction technology is associated with a higher risk of multiple pregnancies (5), even when only one embryo is transferred, than is spontaneous conception (6). Other studies have mentioned the higher risk of premature birth in children conceived via ART (7) and the higher incidence of caesarean births (8). A higher risk of congenital developmental defects (9) and the lower birth weight of newborns (2, 9) has also been observed in children conceived via ART.

A range of studies have shown that perinatal outcomes and the risk of adverse perinatal outcomes may also differ depending on the ART method used (10, 11). For example, Maheshwari et al (11) have documented similar or better perinatal outcomes for children born in singleton pregnancies following frozen embryo transfer (FET) than for children born in singleton pregnancies following in-vitro fertilisation (IVF) cycles using fresh embryos. Differences are particularly evident in terms of lower rates of pre-term births and low birth weights (12, 13, 14, 10), and the lower risk of SGA (small for gestational age) (15) between pregnancies following FET and following IVF with fresh embryo transfer. Conversely, a number of studies have registered a higher rate of LGA (large for gestational age) for pregnancies following FET (14, 15). Forming an understanding of these differences has the potential to play a key

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role in the selection of the most appropriate ART method, which carries the minimum of risks for both the mother and the child.

The aim of this article is to identify whether ART is also associated with a higher risk of giving birth to a child with a low birth weight in Czechia, which has recently witnessed a relatively significant increase in terms of the use of ART (16), and which is currently one of the leading countries in Europe in this respect (1). This development is due not only to the popularity of cross-border reproductive care, but also to a steady increase in the number of domestic patients (16). In addition, the reproductive behaviour of Czech women has changed significantly over the last 20 years, especially in terms of its timing, i.e. reproduction has shifted to significantly older ages since the 1990s (17) and today almost 59 % of children are born to mothers over the age of 30 (18) and almost half of first-time mothers (45 %) were older than 30 in 2021 (18). Czech data shows that the increasing age of mothers is related, *inter alia*, to an increase in the proportion of children born with low birth weights (19, 6). The study devotes particular attention to identifying differences in this respect in terms of the ART method used. The analysis is based on anonymised individual data obtained from the National Registry of Reproduction Health administered by the Institute of Health Information and Statistics of the Czech Republic (IHIS CR).

Assisted reproduction and related changes in Czechia as a starting point for the research

As in several other developed countries, the use of ART has increased significantly in Czechia in recent years. The total number of ART cycles, as defined by the National Registry of Reproduction Health, increased more than 2.6-fold between 2007 and 2019 (16). The number of cycles aimed at achieving pregnancy, including IVF (in-vitro fertilisation), FET (frozen embryo transfer), oocyte receipt (OoR), embryo receipt (EmR) and, up to 2015, PGD (preimplantation genetic diagnosis) as a separate type of cycle (PGD has not been included as a separate ART cycle in the registry since 2016; preimplantation genetic testing (PGT) now forms a potential component of all cycles) increased 2.2-fold during the same period (16). The share of ART live births of all live births in Czechia is significant; according to estimates adjusted for the effect of the provision of cross-border reproductive care, it reached almost 4 % in 2020, at which time the share of ART fertility of total fertility rate stood at 3.4 % (20).

In tandem with the development of ART, preferences in terms of the method are also changing dynamically. International indicators have recently revealed a significant increase in the use of intracytoplasmic sperm injection (ICSI) at the expense of conventional IVF, as well as an increase in the proportion of FET cycles compared to IVF cycles with fresh embryos (1). An international comparison of European countries conducted by ESHRE (the European Society of Human Reproduction and Embryology) revealed that Czechia not only has one of the highest incidences of ART cycles per million women of reproductive age, but also one of the highest shares of FET cycles, i.e. 48.9 % (calculated as FET/(FET + ICSI + IVF)), which significantly exceeded the European FET cycles average of 35.5 % in 2018 (1). The detailed data available from IHIS CR clearly indicates a significant increase in both the number and share of FET cycles in Czechia over the last 12 years. While the number of "classic" IVF cycles remains relatively stable (12.2 thousand cycles in 2007 and 14.8 thousand cycles in 2019, when this number also included cycles that were previously allocated to preimplantation genetic diagnosis cycles), the number of FET cycles increased in the same period from 4.2 thousand to 16.2 thousand (16). This significant increase in the number of FET cycles was primarily related to a policy strategy that favours single embryo transfer (a condition for the reimbursement of the costs of up to 4 treatment cycles from the health insurance system provided that only one embryo is transferred in the first two cycles), which resulted in an increase in both the number of frozen embryos and, subsequently, the number of transferred embryos (16).

It is therefore necessary to consider whether the risk of giving birth to a child with a low birth weight differs for women who undergo ART treatment depending on the chosen procedure since these women differ significantly in terms of a number of important characteristics. The data shows, for example, that women who undergo FET in Czechia are on average 1.4 years older than women who receive IVF with fresh embryo transfer (16). Studies have also shown that comorbidities, which may result in problems with conception, risks during pregnancy and unfavourable perinatological outcomes, are more common in women who undergo oocyte receipt cycles (21).

Materials and methods

The analysis is based on a set of anonymised individual data on deliveries that took place in Czechia in the period from 1st January 2013 to 31st December 2018. This data set covers selected information on mothers as collected in the National Registry of Reproduction Health administered by the IHIS CR. By linking information from the two modules of the register – women who give birth and women who use ART – it was possible to combine unique information on the birth outcome and the characteristics and health status of the women with data on whether childbirth was preceded by ART treatment. Thus, the data allows for the highly accurate estimation of those births and children that can be classified as ART births and ART children and which followed conception without the use of ART.

In addition, the modules contain information on the ART cycle used by the mothers, which allowed for the analysis to take into account the most frequently selected ART cycles and their association with the risk of a low childbirth weight. The analysis focused on three types of the ART cycles distinguished by the National Registry of Reproduction Health (16): 1) IVF cycles (including both conventional in vitro insemination and ICSI in which a single spermatozoon is injected into the oocyte cytoplasm); 2) FET cycles (the transfer of thawed embryos preserved from a previous IVF cycle) and 3) OoR cycles, i.e., the receipt of a (donated) oocyte. The anonymised data set was provided by the IHIS CR to the staff of the Department of Demography and Geodemography for scientific purposes as part of a grant-supported project.

It is necessary here to point out the limits of the data used, especially concerning the potential for the reliable identification of those children born following an ART conception. The National Registry of Reproduction Health covers only treatment administered in Czechia, i.e. it does not contain any information on ART treatment received abroad. Our approach classified such conceptions/births as not involving the use of ART. However, since Czechia is classified as a destination (22) rather than a source country in terms of cross border reproductive care, we do not anticipate any significant underestimation of the number of women who gave birth as a result of successful ART treatment, nor the significant distortion of the results presented herein.

The dataset contained information on 651,221 deliveries that took place in Czechia in the period 2013–2018 for which the birth weight of the child/children was reported. Of this number, 629,315 (96.6 %) deliveries with high probability did not follow ART and 21,906 (3.4 %) deliveries of ART-treated women. Of the ART cycles defined in the National Registry of Reproduction Health, the aim of which is to achieve pregnancy, only those deliveries resulting from classic IVF treatment with fresh embryos (12,529 deliveries), FET treatment (8,018 deliveries) and oocyte receipt (1,014 deliveries) were included in the detailed analysis of the risk of low birth weight. 345 (1.6 %) deliveries following other ART cycles were not included in the analysis due to the low numbers of these treatment cycles. Thus, the descriptive analysis included a total of 650,876 deliveries that took place in Czechia in the period 2013 and 2018. The analysis focusing on ART-treated women by ART method included 21,561 deliveries from the same time period.

The binary logistic regression method was chosen for the analysis of the impact of the ART method on the occurrence of low birth weight of the newborn. In accordance with WHO (23) recommendations, the dependent variable was dichotomised into low birth weight (defined as less than 2,500 g) and normal birth weights (2,500 g and more). In the case of multiple pregnancies, the birth weight of the lighter newborn was considered since this child is more likely to be most vulnerable to potential health complications. The odds of hav2ing a low birth weight newborn were monitored primarily via the method of conception. This variable included the three most common ART methods aimed at becoming pregnant in Czechia: IVF cycles with fresh embryo transfer, FET cycles using thawed embryo transfer and OoR receipt cycles (16). The birth order was categorised in terms of three groups: first-time, second-time and third- and higher-order mothers. In view of the fact that the data also contained information on some of the health conditions of the mothers that are known to exert an impact on the birth weight of the child, e.g. hypertension, gestational diabetes (24, 25), the regression model included a pregnancy complication variable that considered the occurrence of gestational hypertension and diabetes (without hypertension and diabetes, gestational hypertension, diabetes, hypertension and diabetes). The data also provided a unique opportunity to control for other health covariates in the analysis since it allowed to control for the cause of infertility (male factor, female factor, both male and female factor, not detected). The length of pregnancy was categorised as preterm births, i.e. according to Lawn et al (26) before the 37th completed week of pregnancy, and full-term births. The frequency of pregnancies was divided into single and multiple pregnancies. The age of the mother at delivery was included in the model as a continuous variable.

The results of binary logistic regression model were interpreted in terms of odds ratio (exp β_k):

$$\frac{\Pr\langle Y=1|x\rangle}{1-\Pr\langle Y=1|x\rangle} = \exp[logit(\Pr\langle Y=1|x\rangle)] = \exp(\beta_0+\beta_1x_1+\beta_kx_k) = \exp(\beta_0)\times\exp(\beta_1x_1)\times\ldots\times\exp(\beta_kx_k),$$

where Y is the dependent variable (Y=1 for a "low birth weight"; otherwise Y=0), x = (x_1, …. x_k)' is the vector of the explanatory variables, β_0 is the intercept parameter and β is the vector of the slope parameters.

We calculated also the probability of a low birth weight based on the regression coefficients:

$$Pr(Y=1) = \frac{\exp(\beta_0+\sum\beta_kX_k)}{1+\exp(\beta_0+\sum\beta_kX_k)}$$

Results

Of the total number of deliveries analysed (the final sample size was 650,876), 604,969 deliveries resulted in a birth of a child with a normal birth weight (i.e. 92.9 %) and 45,907 deliveries were with a low birth weight (7.1 %).

In 2018, the children of mothers who, with high probability, did not undergo ART treatment evinced higher on average birth weights (3,313 g) than all the groups of children born following ART treatment (Fig. 1). Those newborns conceived via OoR cycles had the lowest average birth weights (3,049 g), followed by IVF-conceived newborns (3,137 g). Newborns conceived via FET were observed to weigh, on average, more than 100 g more (3,259 g). Between 2013 and 2018, while increases were observed in the average birth weights of all newborns for all the groups of mothers studied, the highest average increase was observed for those born following an ART conception. The increase in the birth weights of ART-conceived newborns can be partly explained by the recent trend towards transferring a lower number of embryos, which is reflected in the lower incidence of multiple pregnancies (in 2013, the proportion of multiple births was 12 % for FET, 13 % for IVF and 24 % for OoR compared to 5 % for IVF and FET and 12 % for OoR in 2018).

The fact that the difference in the proportion of multiple pregnancies contributed to the differing birth weights of newborns was taken into account in the comparison of the average birth weight with respect only to singleton pregnancies (Fig. 1). While the differences in the average birth weight of newborns according to the conception method were lower, they still remained significant. The newborns conceived via FET evinced surprisingly high average birth weights in 2018, i.e. an average birth weight of just 7 g lower than for non-ART conceived newborns. The lowest proportion of low child birth weights were to women who gave birth without ART treatment, i.e. less than 7 % for both total pregnancies and singleton pregnancies in the monitored period. Conversely, the incidence of low child birth weights was significantly more frequent

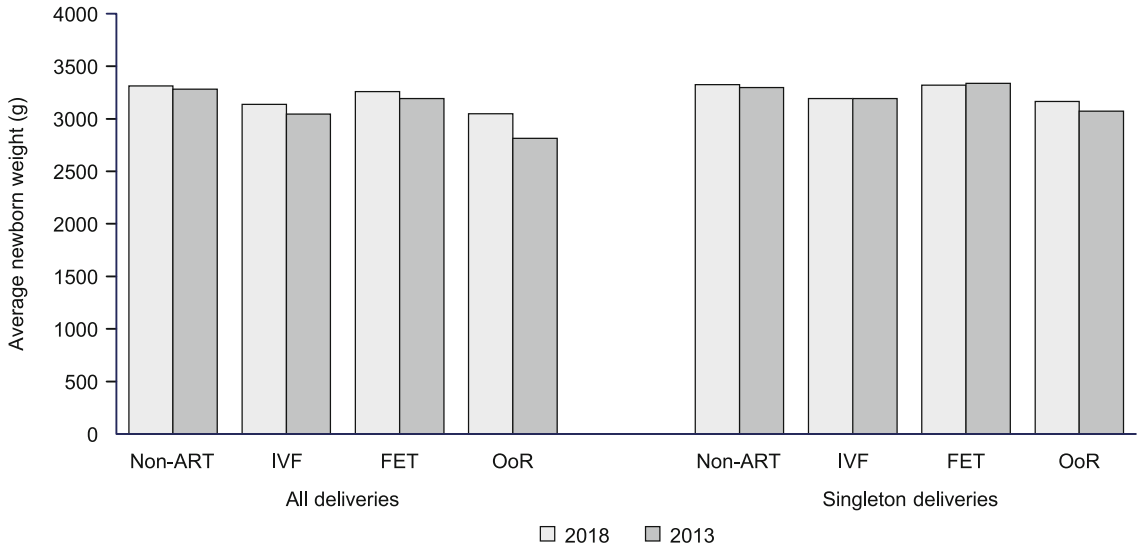

Fig. 1. Average newborn weight: according to the conception method; all deliveries and singleton deliveries, 2013 and 2018, (g). Concerning multiple pregnancies, the birth weight of the child with the lowest weight was considered. Source: NHIS 2013, 2018.

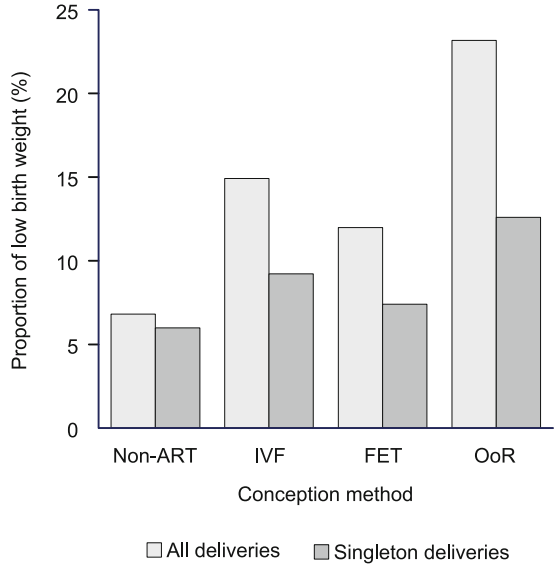

Fig. 2. Proportion of low birth weight newborns according to the conception method; all deliveries and singleton deliveries, 2013–2018 (%). Source: NHIS 2013–2018.

for ART-conceived births concerning both total (12 % for FET, 15 % for IVF and 23 % for OoR) and singleton births. Despite taking into account the differing incidence of multiple pregnancies in the various groups of mothers, the proportions of low childbirth weights for mothers with singleton newborns differed according to the selected ART method. While in the case of singleton pregnancies, the proportion of low weight births for mothers who received FET was almost comparable to mothers who did not receive ART (7 %), 9 % of mothers who underwent IVF gave birth to low birth weight newborns and 13% of mothers who received oocytes from a donor (OoR cycle) (Fig. 2).

The subsequent logistic regression analysis focused on the differences in the incidence of low birth weight identified within the group of ART-treated women. The odds of having a low birth weight (< 2,500 g) child were found to be 30 % higher for mothers who underwent IVF with fresh embryo transfer than for those who received FET (Tab. 1). The highest risk was identified for women who gave birth following OoR treatment (52 % higher than for FET), after controlling for other covariates, e.g. the pregnancy frequency, birth order, premature birth, age and health status of the mother, including whether the cause of infertility was the female factor or not. Thus, cycles involving the transfer of fresh embryos (IVF cycle and OoR cycle) appear to involve a greater risk of a low birth weight than cycles involving the transfer of a thawed embryo, regardless of the other covariates that are associated with the risk of a low birth weight and health complications that are more commonly observed for ART-treated women.

Mothers who gave birth prematurely, had multiple pregnancies or experienced problems with infertility (the cause was exclusively the female factor or concerned both partners) also evinced a significantly higher odds of a low birth weight. Conversely, the odds of a low birth weight were seen to decrease with the birth order. Moreover, the odds of a low birth weight were lower for mothers diagnosed with diabetes than for those without pregnancy complications (gestational hypertension and diabetes). When the range of covariates were included, the differences regarding the odds of a low birth weight newborn in terms of the mother's age were found to be insignificant.

The odds of a low birth weight was found to be higher for preterm than for full-term newborns; however, the odds differed significantly according to the frequency of pregnancy, as evidenced by the significant interaction of these variables in model 1 (Tab. 1).

Tab. 1. Model 1 – Odds ratio Exp(β) of a low birth weight delivery for ART-treated mothers, Czechia, 2013–2018.

Variable	Odds ratio estimate	95% confidence interval	
Type of conception			
FET (ref.)	1		
IVF	1.30	1.15	1.48
OoR	1.52	1.17	1.97
Birth order			
first (ref.)	1		
second	0.66	0.58	0.76
third and more	0.49	0.37	0.63
Age	1.00	0.98	1.01
Pregnancy complications			
without hypertension and diabetes (ref.)	1		
gestational hypertension	1.36	0.99	1.87
diabetes	0.76	0.61	0.94
hypertension and diabetes	1.91	1.13	3.24
Cause of infertility			
male factor (ref.)	1		
not detected	1.25	0.98	1.60
female factor	1.34	1.14	1.58
both male and female factor	1.24	1.05	1.47
Preterm birth			
no (ref.)	1		
yes	64.43	56.48	73.51
Pregnancy frequency			
single (ref.)	1		
multiple	35.14	29.54	41.79
Interaction of preterm births and pregnancy rate			
preterm birth * multiple pregnancy	0.28	0.20	0.38
Constant	0.02		
Number of observations	21 561		
Nagelkerke coefficient	63.0		
Proportion of successfully classified cases (%)	92.6		

Source: NHIS 2013–2018

After recalculating the odds of having a low birth weight newborn into probabilities (Fig. 3), it is evident that full/post-term singleton pregnancies have the lowest probability (2 %) of the birth of a low birth weight newborn. Conversely, mothers with multiple pregnancies who gave birth prematurely are most at risk, with a 93 % probability of giving birth to a child with a low birth weight. Moreover, multiple pregnancies were also found to be risky from the point of view of low birth weight even for full-term deliveries; the probability of a low birth weight for at least one of the children was determined at 43 %. Again, these values take into account the covariates considered in the model and thus highlight the importance of the strategy that encourages the transfer of just one embryo per ART cycle.

Discussion

The aim of this article was to determine whether any differences exist in terms of the risk of giving birth to a child with a low birth weight depending on the type of ART methods (IVF, FET or OoR) in Czechia. The strength of the study lies in the use of a unique data set that provides a range of information on all deliveries that took place in Czechia, i.e. information on the course of the pregnancy, childbirth and the newborn(s), including information on the probable conception method used, over a period of 6 years (2013–2018). Thanks to the relatively long time series, it is also possible to include the numerically less popular OoR method in the analysis.

A range of foreign studies have been devoted to the health outcomes of the births of newborns conceived via ART. According to a meta-study by Maheshwari et al (27), pregnancies following FET have a lower risk of a constitutionally small foetus, low birth weight and preterm birth than IVF. The results of our analysis correspond to those of a meta-study by Zhao et al (28), in which the authors, *inter alia*, compared the risk of a low birth weight newborn following IVF/ICSI and FET in singleton pregnancies. The authors studied the results of 12 studies and confirmed that the IVF/ICSI method is associated with a higher risk of a low birth weight child than FET. The authors suggest that the better birth weight results for FET are due, for example, to the fact that frozen embryo transfer requires no, or only slight stimulation of the ovaries; thus, the uterus is in the natural state, which exerts a positive impact on both the acceptance of the embryo and the subsequent growth of the foetus (28). Conversely, the stimulation of the ovaries leads to the desynchronisation of the state of the uterus and the embryo, which has a negative effect on the development of the embryo. In addition, the freezing and thawing of the embryo ensures that only the "best quality" embryos survive and, consequently, show better clinical results (28).

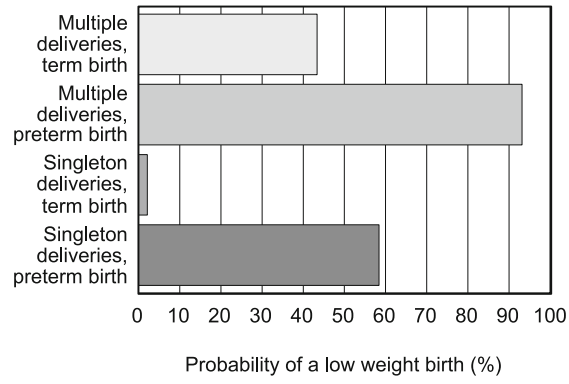

Fig. 3. Probability of a low weight birth according to the frequency of pregnancy and gestational age, Czechia, 2013–2018 (%). Source: NHIS 2013–2018.

A meta-analysis by Mascarenhas et al (29), on the other hand, focused on the comparison of birth outcomes following donated oocyte receipt or the receipt of the woman's own oocyte (fresh or frozen). Several studies have confirmed that the risk of a low birth weight in pregnancies following donor oocyte transfer is higher than that following autologous oocyte transfer (29).

The results of the analysis presented herein do not fully correspond to the results of a study by Ainsworth et al (30) who indicated that the birth weight of newborns following fresh and frozen embryo transfer does not differ when considering the child's gender and gestational age. However, the authors approached the analysis in a different way and rather than monitoring the incidence of low birth weights, considered the average birth weight of newborns. According to Ainsworth et al (30), although the average birth weight of newborns following FET is higher than that following fresh embryo transfer, the average weight or the body mass index (BMI) of newborns following fresh and frozen embryo transfer does not differ in childhood. Thus, we suggest the application of a longitudinal approach to the study of the postpartum outcomes of newborns as an innovative way to further understanding the health implications of assisted reproduction technology.

Very little attention has been devoted to date to the study of health differences following births conceived via ART in the Czech environment (31). However, the specifics of caring for children born following ART treatment have been discussed with concern to some of the negative impacts of ART on the health and quality of life of ART-treated mothers and their children as identified in international epidemiological and clinical studies (32). A descriptive study by Kocourková et al (33) that compared only newborns from singleton births observed the effect of the mother's age on the child's birth weight and demonstrated higher incidence of low birth weights for newborns that were, with high probability, conceived via IVF than for newborns most likely conceived spontaneously.

This study allowed for the analysis of all deliveries that took place in Czechia over a relatively long period of time (2013–2018); thus, it is not a case study. Moreover, the linking of data from the National Registry of Mothers and the National Registry of Reproduction Health allowed for the monitoring of the odds of giving birth to a low-birth-weight newborn according to the method of conception and other selected characteristics of the mothers in addition to the cause of infertility, a factor that has only rarely been monitored in foreign studies.

The study has a number of limitations. In addition to the constraints resulting from the method used to determine births that occurred following ART (as discussed in the description of the data set), certain limits can be identified concerning some of the other variables, which, from a substantive point of view, it would have been appropriate to include in the model since they also relate to the risk of a low birth weight and the need to undergo ART but are not monitored in the National Registry of Reproduction Health. This mainly concerns the inability to control for the mother's BMI variable, which is usually included in foreign studies when considering ART-related issues and the birth weight of newborns (30).

Conclusion

This study proved the elevated odds of giving birth to a low birth weight newborn in deliveries following IVF with fresh embryo transfer and oocyte receipt compared to FET, after controlling for covariates such as the frequency and length of the pregnancy, medical complications, the cause of infertility, the birth order, etc. Thus, it served to reinforce the recognition of differences in the birth outcomes of ART-treated mothers in Czechia and provided a valuable contribution to the international discussion on the birth outcomes of ART. It is hoped that the results of this discussion will assist in the evaluation of the risks and benefits of the various ART methods available and facilitate the selection of the most appropriate approach to conception.

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