

# Perinatal outcomes of multiple births conceived through in vitro fertilization compared with spontaneous multiple births

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**Abstract.** Pregnancies that occur after assisted reproduction procedures constitute high-risk pregnancies. There is a lack of sufficient epidemiologically based data on this issue in Latvia. The aim of this study was to compare the maternal and perinatal outcomes of multiple pregnancies conceived by in vitro fertilization (IVF) in comparison with spontaneous multiple pregnancies. This retrospective cohort study (2007–2014) analysed data from population-based Medical Birth Register (MBR). There is a statistically significant increase of multiple births from IVF pregnancies – an average 2% per year ( $p < 0.01$ ). Newborns of IVF multiple births have higher odds of low birth weight (OR = 1.2) and congenital anomalies (OR = 1.6). Maternity characteristics showed that mothers in the IVF group were significantly older than those in the control group ( $\geq 35$  years) (OR = 2.1) and primipara births (OR = 4.1). Multiple births conceived by IVF have similar outcomes as spontaneously conceived multiples in the perinatal period, although the rates of congenital anomalies after IVF are just slightly higher than in control group.

**Key words:** in – vitro fertilisation (IVF), multiple births, perinatal outcomes.

## 1 Introduction

The improvement of mother and child health is one of the health priorities in Latvia. Reproductive health is of particular importance due to the unfavourable demographic situation in Latvia. Although the birth rate in Latvia has been rising slightly in the recent years, it is still lower than the mortality rate, thus creating a negative natural growth [1]. In addition, a very serious medical and social problem is infertility, which affects up to 10% of couples around the world [2]. Due to the unfavourable demographic situation in Latvia, one of its objectives to improve it was the implementation of the state-funded infertility program that was launched in 2012.

However, one should take into account the health risks increased with in-vitro fertilization (IVF). Pregnancies that occur after assisted reproduction procedures constitute high-risk pregnancies. Studies have been done worldwide to analyse the outcome of IVF pregnancies [3–7]. Literature data show that the multiple births and delivery complications are much higher from IVF pregnancies than in the average [8–10].

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There is a lack of sufficient epidemiologically based data on this issue in Latvia. In Latvia IVF births increased from 147 cases in 2007 to 263 in 2014 (an average 1% from all deliveries) [11]. The aim of this study was to compare the maternal and perinatal outcomes of multiple pregnancies conceived by IVF to spontaneous multiple pregnancies.

## 2 Material and methods

This retrospective cohort study (2007–2014) analysed data from population-based Medical Birth Register (MBR). The MBR is compiled from the standardized medical record forms that are used by all maternity units across the country. The analysis includes data on 661 newborns from IVF multiple births and control group of 3607 newborns from spontaneous multiple births.

The study analysed and compared maternal and neonatal risk factors between two groups: newborns with IVF and without IVF. The analysis included factors related to the maternal age and factors characterising health status of a mother (clinical history, complications during pregnancy and childbirth), the mode of delivery and newborn's health (birth weight, congenital abnormalities).

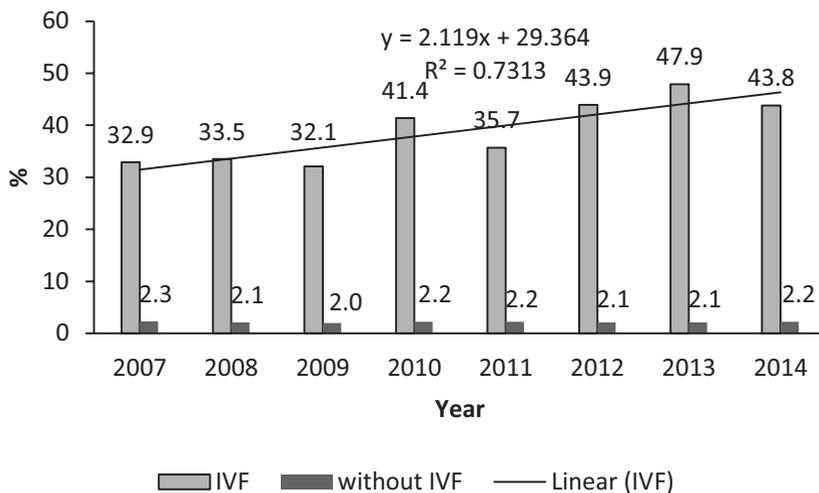
The descriptive statistics for all continuous variables are reported as median (inter-quartile range (IQR)). Mann-Whitney Test for nonparametric quantitative data and Chi-square test for comparing categorical variables were used. Categorical data are reported as percentages and 95% confidence interval (CI). The odds ratios (OR) and 95% CI were computed to measure the strength of the association between the outcome and the explanatory variables. Each factor association with the outcome was tested by univariate logistic regression analysis. Independent factors that were significantly ( $p < 0.05$ ) associated with the outcome were included in multivariate logistic regression. The regression model was adjusted for the age of mother, mode of delivery, number of birth, birth weight and congenital anomalies.

## 3 Results

The study analysed data on 4,268 multiple births during the period from 2007 to 2014. There was 51.1% ( $n = 2182$ ) of boys and 48.9% ( $n = 2086$ ) of girls of all multiple births. 2.5% ( $n = 4268/168712$ ) of all newborns (2007–2014) were born as the result of multiple deliveries. 39.5% of all IVF newborns ( $n = 661/1674$ ) were multiple pregnancy births versus 2.2% ( $n = 3607/167038$ ) from spontaneous pregnancies ( $\chi^2 = 76.9$ ;  $p < 0.001$ ). There is statistically significant increase of multiple births from IVF pregnancies – an average 2% per year ( $p < 0.01$ ) (Fig. 1).

The median age of mother in IVF group was statistically significantly higher ( $p < 0.01$ ) than without IVF, respectively 33 years (30–36) to 29 years (25–34), there is no difference by the median values of gestational week (37 (34–38)) and birth weight, respectively, from 2560 g (2170–29100) to 2600 g (2180–2930).

There were statistically significant differences in maternal and neonatal factors between two groups. The proportion of older mothers ( $\geq 35$  years) in the IVF group was significantly higher than in the control group 35.2% (95%CI 31.7–39.0) vs. 20.3% (95%CI 19.0–21.6)) ( $\chi^2 = 71.6$ ;  $p < 0.001$ ). The same situation was with mothers as primipara: 76.9% (95%CI 73.5–80.0) to 44.4% (95%CI 42.8–46.0) ( $\chi^2 = 63.5$ ;  $p < 0.001$ ) and caesarean sections for IVF group were 16.0% points higher ( $\chi^2 = 63.2$ ;  $p < 0.001$ ), respectively 48.0% (95%CI 44.2–51.8) to 32.0% (95%CI 30.5–33.5). Within the IVF multiple births, the proportion of newborns with low birth weight ( $\leq 2499$  g) was 4.0% points higher ( $\chi^2 = 3.8$ ;  $p < 0.05$ ). There were no statistically significant differences related to different maternal diseases, complications during pregnancy and deliveries, although the proportion of complications was



**Fig. 1.** Prevalence of multiple births, %.

**Table 1.** Perinatal and maternal characteristics for multiple births with and without IVF.

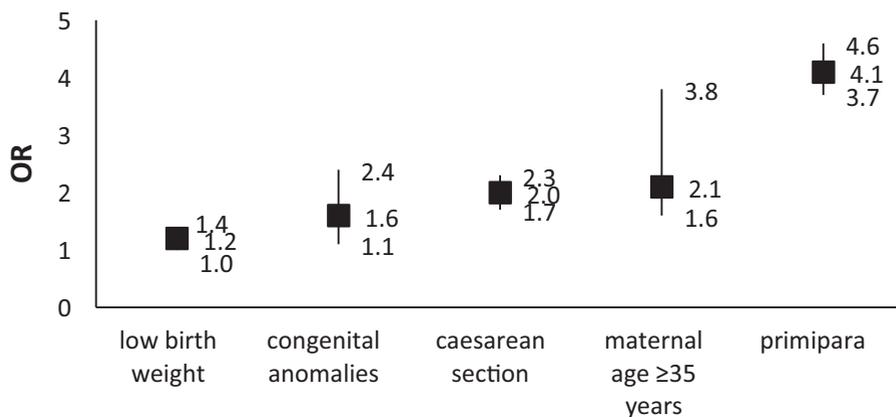
Characteristics	without IVF (n = 3607)	IVF (n = 661)	p value
Mean maternal age <sup>1</sup>	29 (IQR 9)	33 (IQR 6)	<0.001
Mean birth weight (g) <sup>1</sup>	2600 (IQR 750)	2560 (IQR 740)	NS
Maternal age group <sup>2</sup> :			
≤ 24 years	23.0 (828)	1.8 (12)	<0.001
25–34 years	56.8 (2046)	62.9 (416)	<0.01
≥ 35 years	20.3 (731)	35.2 (233)	<0.001
Parity <sup>2</sup> :			
Primipara	44.4 (1602)	76.9 (508)	<0.001
2nd delivery	35.5 (1281)	20.7 (137)	<0.001
3rd delivery	20.1 (724)	2.4 (16)	<0.001
Caesarean section <sup>2</sup>	32.0 (1153)	48.0 (317)	<0.001
Low birth weight <sup>2</sup>	42.1 (1517)	46.1 (305)	<0.05
Maternal diseases in anamnesis <sup>2</sup>	32.1 (1159)	33.9 (224)	NS
Complications during pregnancy <sup>2</sup>	44.6 (1607)	45.7 (302)	NS
Complications during delivery <sup>2</sup>	59.4 (2142)	61.9 (409)	NS

<sup>1</sup>Represents median (interquartile range (IQR)) and Mann-Whitney U test is used.

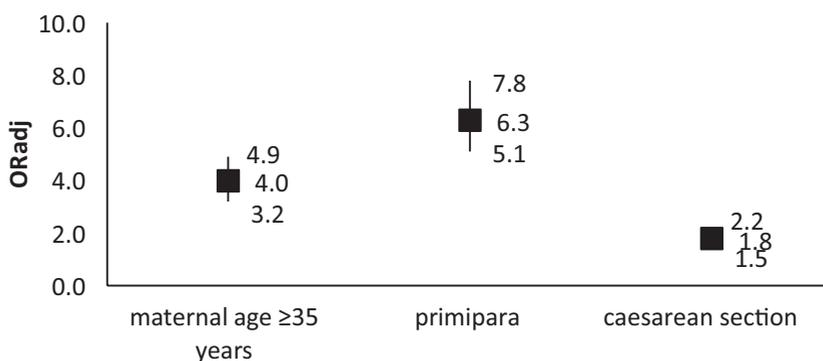
<sup>2</sup>Represents % (n) and Chi square test is used; NS: Not Significant.

slightly higher to IVF multiple births. Characterization of parameters with and without IVF is shown in the Table 1.

Multiple births with IVF showed the higher odds of low birth weight (OR = 1.2; 95%CI 1.0–1.4;  $p < 0.05$ ) and congenital anomalies (OR = 1.6; 95%CI 1.1–2.4;  $p < 0.05$ ). IVF multiple births 2 times increased caesarean section rate (OR = 2.0; 95% CI 1.7–2.3;  $p < 0.05$ ). Maternity characteristics showed that mothers in the IVF group were significantly older than those in the control group ( $\geq 35$  years) (OR = 2.1; 95% CI 3.8–2.6;  $p < 0.001$ ) and primipara births (OR = 4.1; 95% CI 3.7–4.6;  $p < 0.001$ ) (Fig. 2).



**Fig. 2.** Odds ratio of selected risk factors for IVF multiple births, based on univariate analysis.



**Fig. 3.** Adjusted Odds ratio of selected risk factors for IVF multiple births.

Adjusted higher odds for IVF multiple births were observed just for three factors: maternal age (OR = 4.0; 95% CI 3.2–4.9;  $p < 0.001$ ), primipara (OR = 6.3; 95% CI 5.1–7.8;  $p < 0.001$ ) and caesarean section (OR = 1.8; 95% CI 1.5–2.2;  $p < 0.05$ ). There are no differences found by congenital anomalies and low birth weight between the groups after factor adjustment (Fig. 3).

## 4 Discussion

In Latvia, spread of IVF occurred during 2007–2014, the average of 1.0%, which is slightly less than in the countries such as Sweden 2–3% [6], Japan about 2% [12], the USA [13] and the Netherlands about 1.5% [14]. In Latvia, a slightly smaller rate of IVF births than in the world can be explained by not so big experience applying the Assisted Reproductive Technology in comparison with other countries [6, 11, 15]. In addition, taking into account different socio-economic processes in the country and the high cost of fertility treatments [16], this service has not been available for a long time to the part of the society.

The number of births with IVF has begun to increase since 2012, when it was included in the national list of state paid services [17]. The financial support of the state for in-vitro fertilization procedures significantly increases every year, consequently, making it more accessible to the public, which may have also influenced the growth of rate positively [18]. However, the MBR data cannot be selected by state-funded IVF treatments.

Multiple births after assisted reproductive technology procedures are common [6, 8–10, 19, 20] as several embryos are often implanted. In addition, this study showed that the multiple births increased in the IVF group – on average by 2% per year or from 32.9% in 2007 to 43.8% in 2014.

This study is highly important because the effects of in-vitro fertilization on the newborn's health condition have been studied for several decades worldwide, but in Latvia, no epidemiological studies have been conducted in this field so far.

Being aware of the perinatal risks related to multiple pregnancies, there are several matters under discussion in the world concerning the determination of the number of embryos to transfer and the legislation setting restrictions on the use of transfers in each country, as well as linking embryo implantation conditions with cost-effectiveness in the near and distant future [8, 21–24].

The scientific literature also mentions other reasons of perinatal outcomes related to IVF like low birth weight, premature birth risk, congenital anomalies [3, 4, 12, 14, 25]. Worse IVF perinatal outcomes in newborns have been associated also with multiple pregnancies [6, 26].

This study reveal that IVF multiple births newborns had lower birth weight, were born by Caesarean section and with an increased risk of congenital malformations in comparison with multiple births in control group, other studies also noted these outcomes [6, 26, 27]. Sometimes as an important cause of congenital anomalies, the age of woman is mentioned [4] or different perinatal conditions (for example, small gestational age) rather than the IVF procedure [28]. This study results also confirmed that the IVF group had a higher proportion of women aged from 35 years, as well as primipara, which is also referred to in other studies [6, 29].

There are a few studies that analyze the different perinatal outcomes in relation to the type of IVF [3, 6, 9, 12]. As the total number of IVF children born in Latvia is not relatively large, and detailed breakdown by type is available only since 2013, separate perinatal conditions were not analyzed in comparison to IVF methods. In the future having accumulated more data and the amount of information about children born as a result of IVF, it will be possible to explore different perinatal outcomes and the risk of congenital malformations in connection to in-vitro fertilization method.

The results of this study can serve as an evidence-based proposal for the planning and implementation of additional effective policies in Latvia for the sustainability, development, and improvement of maternal and child health programs.

## 5 Conclusions

Multiple births conceived by IVF have similar outcomes as spontaneously conceived multiples in the perinatal period, although the rates of congenital anomalies and low birth weight after IVF are just slightly higher than in the control group. Maternity characteristics showed that mothers in the IVF group were significantly older than those in the control group ( $\geq 35$  years) and primipara births.

Special attention is needed to monitor these high-risk pregnancies. More studies are needed to investigate assisted reproduction policy in the country, including the number of embryo transfers. To avoid multiple pregnancies after IVF is a challenge in assisted reproduction.

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