Effect of pre-gravid body mass index on outcomes of pregnancies following in vitro fertilization

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Abstract

Purpose To examine the effect of pre-gravid body mass index (BMI) on perinatal outcomes in in vitro fertilization (IVF) singleton pregnancies.

Methods Retrospective population-based cohort study. All singleton pregnancies delivered at ≥ 22 weeks' in Slovenia between 2002 and 2015 were included. Logistic regression analysis was used to examine the relationship between BMI category and outcomes, controlling for potential confounding variables. Interaction term was included to evaluate whether effects of obesity on perinatal outcomes differ in IVF vs. non-IVF pregnancies. We counted the frequencies of hypertensive disorders of pregnancy, gestational diabetes, cesarean delivery, preterm births, and small as well as large for gestational age neonates, neonatal respiratory distress syndrome, neonatal intraventricular hemorrhage, and perinatal deaths.

Results Pre-gravid overweight and obesity were associated with higher rates of hypertensive disorders, gestational diabetes, and cesarean deliveries in both IVF and non-IVF pregnancies. Pre-gravid underweight was associated with small for gestational age neonates in IVF and non-IVF pregnancies. There was a significantly lower effect of pre-gravid obesity on the incidence of hypertensive disorders (odds ratio (OR) 0.7; 95% confidence interval (CI) 0.5–0.9) and cesarean delivery (OR 0.8; 95% CI 0.7–0.99) in IVF vs. non-IVF pregnancies. The effect of pre-gravid obesity on neonatal mortality was significantly greater in IVF compared to non-IVF pregnancies (OR 4.6; 95% CI 1.4–15.8).

Conclusions Pre-gravid BMI has an important effect on perinatal outcomes in pregnancies following IVF.

Keywords In vitro fertilization · Body mass index · Overweight · Obesity · Underweight · Maternal and neonatal complications, small for gestational age neonates

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Purpose

As obesity and overweight became one of the most important threats to human health in general, they also became one of the most common medical conditions complicating pregnancy [1, 2]. Excessive amount of maternal adipose tissue has been linked to several obstetrical complications, such as gestational diabetes mellitus (GDM), preeclampsia, preterm delivery, stillbirth, cesarean section, and small as well as large for gestational age neonates [1, 2]. There is also an increased prevalence of infertility among overweight and obese women resulting in higher rates of in vitro fertilization (IVF) in this population [3].

Most of the studies on effects of maternal body mass index (BMI) on IVF focused on the impact of adiposity on ovarian responsiveness during ovarian stimulation or ovulation induction before IVF and live birth rates following IVF [4–11]. In contrast, the effects of BMI on risks of maternal and fetal adverse outcomes in pregnancies following successful IVF have not yet been adequately studied. The aim of our study was to examine the effect of pre-gravid BMI on perinatal outcomes in IVF singleton pregnancies.

Material and methods

We used data from the Slovenian National Perinatal Information System (NPIS) for the period 2002 to 2015. NPIS registers all deliveries in Slovenia at ≥ 22 weeks' gestation or when the fetus weighs ≥ 500 g. Registration is mandatory by law and more than 140 variables are entered immediately postpartum into a computerized database. Our study population comprised singleton pregnancies delivered during the period 2002 to 2015.

This retrospective study of anonymous entries did not require approval by the ethical committee.

Definitions of parameters studied

The NPIS method of registering maternal pre-gravid weight is particularly accurate and presumably without recall bias because pre-gravid data were registered very early during pregnancy. BMI was defined as the individual's body mass divided by the square of body stature (kg/m^2). The pre-gravid BMI was categorized according to the Institute of Medicine criteria as underweight ($< 18.5 \text{ kg/m}^2$), normal ($18.5\text{--}24.9 \text{ kg/m}^2$), overweight ($25\text{--}29.9 \text{ kg/m}^2$), and obese ($\geq 30 \text{ kg/m}^2$) [12].

Gestational age was derived from the day of embryo transfer for IVF pregnancies and from the last menstrual period, confirmed or modified by first trimester ultrasound for non-IVF pregnancies. Pregnancies following controlled hyperovulation and intrauterine insemination were not included in the analysis.

Preeclampsia was defined as the presence of hypertension (blood pressure $\geq 140/90$ mmHg) and proteinuria or end-organ dysfunction after 20 weeks' of gestation. Gestational hypertension was defined as the presence of hypertension measured for the first time in the current pregnancy after 20 weeks' gestation without significant proteinuria or end-organ dysfunction. Chronic hypertension was defined as the presence of hypertension before 20 weeks' gestation.

National guidelines for screening and diagnosing GDM changed during the study period. Until 2012, GDM was diagnosed in Slovenia using the two-step approach: screening with 50 g oral glucose load and, when indicated, performing a 100 g oral glucose tolerance test (OGTT) using the Carpenter and Coustan criteria [13]. Since 2012, we diagnose GDM using the one-step approach by a 75-g OGTT according to the 2010 International Association of Diabetes and Pregnancy Study Groups Consensus [14].

Neonatal intraventricular hemorrhage (IVH) grade III or IV was diagnosed by ultrasound according to Papile's criteria [15]. IVH is graded according to this classification as: grade I (the mildest form of IVH in which bleeding is limited to the lining of the ventricles), grade II (the blood spilled into the ventricles, but there is no enlargement or swelling), grade III (the ventricles had become enlarged and are full of blood), and grade IV (blood spilled out from the ventricles into the surrounding brain). Neonatal respiratory distress syndrome (RDS) was defined as one or more signs of increased work of breathing, such as tachypnea, nasal flaring, chest retractions, or grunting [16]. Stillbirths were defined as fetal deaths of at least 500 g birth weight or at least 22 weeks' gestation [17].

Statistical analysis

For comparison between BMI groups chi-square test was used. Comparisons were performed for IVF and non-IVF pregnancies separately.

In order to determine whether BMI is an independent predictor of pregnancy outcome, logistic regression analysis was used to examine the relationship between BMI category and outcomes, controlling for the effect of potential confounding variables (maternal age, parity, chronic hypertension, maternal height, and gestational age). Interaction term was included into logistic regression to evaluate whether effects of obesity on perinatal outcomes differ in IVF vs. non-IVF pregnancies.

For all tests, a p value ≤ 0.05 was considered statistically significant. The software used for statistical analysis was IBM SPSS Statistics for Windows Version 21.0 (Armonk, NY: IBM Corp.).

Results

A total of 271,913 singleton pregnancies were included in the study: 6028 (2%) IVF and 265,885 (98%) non-IVF (1093 (0.4%), of these were pregnancies following ovulation induction).

Tables 1 and 2 present comparisons of perinatal outcomes between different BMI groups in IVF and non-IVF pregnancies, respectively. Significant differences were found between women with different BMIs before pregnancy following IVF in all outcomes studied, except in incidences of stillbirth ($p = 0.4$) and neonatal IVH ($p = 0.2$). In non-IVF pregnancies, only rates of IVH did not differ significantly between BMI groups ($p = 0.7$).

Comparisons of perinatal outcomes in different pre-gravid BMI groups compared to the reference group with normal pre-gravid BMI are presented in Table 3 (for IVF pregnancies) and Table 4 (in non-IVF pregnancies).

Pre-gravid BMI in the overweight or obese range was associated with higher rates of hypertensive disorders (pre-eclampsia, gestational hypertension, and chronic hypertension with superimposed preeclampsia), GDM, and cesarean

deliveries in both IVF and non-IVF pregnancies. Underweight pre-gravid BMI, on the other hand, was associated with lower neonatal birth weight and higher incidence of SGA neonates (neonates with birth weight < 10th percentile for gestational age) in IVF and non-IVF pregnancies. Logistic regression analysis did not show statistically significant differences in adverse neonatal outcomes between different BMI groups in women who conceived following IVF, except for a significantly higher rate of neonatal mortality in women with pre-gravid obesity.

When comparing the effects of pre-gravid BMI on perinatal outcomes in IVF vs. non-IVF pregnancies using interaction term, we found a significantly lower effect of pre-gravid obesity on incidences of hypertensive disorders (odds ratio (OR) 0.7; 95% confidence interval (CI) 0.5–0.9) and cesarean delivery (OR 0.8; 95% CI 0.7–1.0) in IVF pregnancies. Effects of pre-gravid obesity were similar in IVF compared to non-IVF pregnancies in terms of GDM (OR 1.2; 95% CI 0.9–1.5), SGA (OR 1.0; 95% CI 0.7–1.5), LGA (neonates with birth weight > 90th percentile for gestational age) (OR 1.1; 95% CI 0.8–1.5), RDS (OR 1.00; 95% CI 0.6–1.6), IVH (OR 0.8; 95% CI 0.3–2.2), and stillbirth (OR 0.4; 95% CI 0.1–1.1).

Table 1 Effect of pre-gravid body mass index (BMI) on outcomes in in vitro fertilization singleton pregnancies. Data are presented as number (N) (%)

	Pre-gravid BMI				<i>p</i>
	Underweight (<i>N</i> = 237)	Normal (<i>N</i> = 4022)	Overweight (<i>N</i> = 1167)	Obese (<i>N</i> = 602)	
Chronic hypertension*	1 (0.4)	13 (0.3)	28 (2.4)	29 (4.8)	< 0.001
Hypertensive disorders*	7 (3.0)	145 (3.6)	100 (8.6)	97 (16.1)	< 0.001
GDM*	5 (2.1)	241 (6.0)	147 (12.6)	153 (25.4)	< 0.001
Cesarean births*	52 (21.9)	1076 (26.8)	413 (35.4)	234 (38.9)	< 0.001
Gestational age*					0.02
> 36	211 (89.0)	3611 (89.8)	1055 (90.4)	512 (85.0)	
33–36	23 (9.7)	289 (7.2)	75 (6.4)	62 (10.3)	
28–32	2 (0.8)	73 (1.8)	18 (1.5)	15 (2.5)	
< 28	1 (0.4)	49 (1.2)	19 (1.6)	13 (2.2)	
Birth weight*					< 0.001
≥ 4000	7 (3.0)	320 (8.0)	122 (10.5)	90 (15.0)	
2500–3999	205 (86.5)	3363 (83.6)	954 (81.7)	448 (74.2)	
1500–2499	22 (9.3)	241 (6.0)	55 (4.7)	48 (8.0)	
< 1500	3 (1.3)	98 (2.4)	36 (3.1)	16 (2.7)	
SGA (10th%tile)*	30 (12.7)	234 (5.8)	65 (5.6)	33 (5.5)	0.001
LGA (90th%tile)*	4 (1.7)	202 (5.0)	79 (6.8)	66 (11.0)	< 0.001
RDS*	6 (2.5)	115 (2.9)	48 (4.1)	27 (4.5)	0.05
IVH grade III or IV	0 (0)	30 (0.7)	14 (1.2)	5 (0.8)	0.23
Stillbirth	0 (0)	34 (0.8)	6 (0.5)	4 (0.7)	0.35
Neonatal death*	0 (0)	8 (0.2)	5 (0.4)	6 (1.0)	0.01

GDM gestational diabetes mellitus, SGA small for gestational age, LGA large for gestational age, RDS respiratory distress syndrome, IVH intraventricular hemorrhage

*Presents statistical significance ($p \leq 0.05$)

Table 2 Effect of pre-gravid body mass index (BMI) on outcomes in singleton pregnancies following non-IVF conception. Data are presented as number (*N*) (%)

	Pre-gravid BMI				<i>p</i>
	Underweight (<i>N</i> = 13,665)	Normal (<i>N</i> = 183,084)	Overweight (<i>N</i> = 47,357)	Obese (<i>N</i> = 21,779)	
Chronic hypertension*	39 (0.3)	946 (0.5)	591 (1.2)	876 (4.0)	< 0.001
Hypertensive disorders*	177 (1.3)	4692 (2.6)	2757 (5.8)	3093 (14.2)	< 0.001
GDM*	281 (2.1)	5972 (3.3)	3255 (6.9)	2921 (13.4)	< 0.001
Cesarean births*	1748 (12.8)	26,545 (14.5)	9071 (19.1)	5501 (25.2)	< 0.001
Gestational age*					< 0.001
> 36	12,642 (92.5)	173,062 (94.5)	44,833 (94.6)	20,487 (94.0)	
33–36	800 (5.9)	7732 (4.2)	1971 (4.2)	978 (4.5)	
28–32	146 (1.1)	1502 (0.8)	400 (0.8)	222 (1.0)	
< 28	77 (0.6)	782 (0.4)	207 (0.4)	117 (0.5)	
Birth weight *					< 0.001
≥ 4000	499 (3.7)	16,217 (8.9)	6617 (14.0)	3742 (17.2)	
2500–3999	12,167 (89.0)	158,715 (86.7)	38,891 (82.0)	17,127 (78.6)	
1500–2499	838 (6.1)	6506 (3.6)	1476 (3.1)	679 (3.1)	
< 1500	160 (1.2)	1624 (0.9)	424 (0.9)	254 (1.2)	
SGA (10th%tile)*	1143 (8.4)	8640 (4.7)	1771 (3.7)	822 (3.8)	< 0.001
LGA (90th%tile)*	281 (2.1)	9161 (5.0)	4088 (8.6)	2366 (10.9)	< 0.001
RDS*	271 (2.0)	3028 (1.7)	937 (2.0)	468 (2.1)	< 0.001
IVH grade III or IV	0 (0)	10 (0)	1 (0)	1 (0)	0.66
Stillbirth*	60 (0.4)	887 (0.5)	240 (0.5)	149 (0.7)	0.001
Neonatal death*	31 (0.2)	232 (0.1)	57 (0.1)	27 (0.1)	0.02

GDM gestational diabetes mellitus, *SGA* small for gestational age, *LGA* large for gestational age, *RDS* respiratory distress syndrome, *IVH* intraventricular hemorrhage

*Presents statistical significance ($p \leq 0.05$)

Table 3 Regression analysis results (odds ratios with 95% confidence intervals) for perinatal outcomes according to pre-gravid body mass index (BMI) in in-vitro fertilization singleton pregnancies. Adjusted for maternal age, parity, chronic hypertension, and maternal height. Neonatal outcomes are also adjusted for gestational age

	Pre-gravid BMI			
	Underweight (<i>N</i> = 237)	Normal* (<i>N</i> = 4022)	Overweight (<i>N</i> = 1167)	Obese (<i>N</i> = 602)
Hypertensive disorders	0.8 (0.4–1.8)	1	2.2 (1.7–2.9)	4.4 (3.3–5.8)
GDM	0.4 (0.2–0.9)	1	2.2 (1.7–2.7)	5.4 (4.3–6.7)
Cesarean births	0.8 (0.6–1.1)	1	1.4 (1.3–1.7)	1.7 (1.4–2.0)
Gestational age				
> 36	1	1	1	1
33–36	1.4 (0.9–2.2)	1	0.9 (0.7–1.1)	1.5 (1.1–2.0)
28–32	0.5 (0.1–2.1)	1	0.7 (0.4–1.3)	1.2 (0.7–2.2)
< 28	0.4 (0.1–2.8)	1	1.2 (0.7–2.1)	1.6 (0.9–3.1)
Birth weight				
≥ 4000	1	1	1	1
2500–3999	3.0 (1.4–6.5)	1	0.7 (0.6–0.9)	0.5 (0.3–0.6)
1500–2499	4.7 (1.9–11.2)	1	0.6 (0.4–0.8)	0.6 (0.4–1.00)
< 1500	1.7 (0.4–6.6)	1	0.8 (0.5–1.2)	0.4 (0.2–0.8)
SGA (10th%tile)	2.5 (1.7–3.7)	1	0.9 (0.7–1.2)	0.9 (0.6–1.3)
LGA (90th%tile)	0.3 (0.1–0.8)	1	1.4 (1.1–1.8)	2.4 (1.8–3.2)
RDS	1.1 (0.5–2.8)	1	1.6 (1.1–2.4)	1.2 (0.7–2.0)
IVH grade III or IV		1	1.6 (0.8–3.3)	0.7 (0.2–1.9)
Stillbirth		1	0.5 (0.2–1.4)	0.5 (0.2–1.6)
Neonatal death		1	2.0 (0.6–7.0)	3.8 (1.1–12.8)

GDM gestational diabetes mellitus, *SGA* small for gestational age, *LGA* large for gestational age, *RDS* respiratory distress syndrome, *IVH* intraventricular hemorrhage

* Reference group

Table 4 Regression analysis results (odds ratios with 95% confidence intervals) for perinatal outcomes according to pre-gravid body mass index (BMI) in singleton pregnancies following non-IVF conception. Adjusted for maternal age, parity, chronic hypertension, and maternal height. Neonatal outcomes are also adjusted for gestational age

	Pre-gravid BMI			
	Underweight (N = 13,665)	Normal ⁺ (N = 183,084)	Overweight (N = 47,357)	Obese (N = 21,779)
Hypertensive disorders	0.5 (0.4–0.6)	1	2.3 (2.2–2.5)	6.3 (6.0–6.6)
GDM	0.6 (0.6–0.7)	1	2.2 (2.1–2.3)	4.6 (4.4–4.8)
Cesarean births	0.9 (0.8–0.9)	1	1.4 (1.4–1.4)	2.0 (1.9–2.1)
Gestational age				
> 36	1	1	1	1
33–36	1.4 (1.3–1.5)	1	1.0 (0.9–1.0)	1.1 (1.0–1.1)
28–32	1.3 (1.1–1.6)	1	1.0 (0.9–1.1)	1.2 (1.1–1.4)
< 28	1.3 (1.1–1.7)	1	1.0 (0.9–1.2)	1.3 (1.0–1.5)
Birth weight				
≥ 4000	1	1	1	1
2500–3999	2.5 (2.3–2.7)	1	0.6 (0.6–0.6)	0.5 (0.5–0.5)
1500–2499	4.2 (3.7–4.7)	1	0.6 (0.5–0.6)	0.5 (0.4–0.5)
< 1500	3.2 (2.7–3.9)	1	0.6 (0.6–0.7)	0.7 (0.6–0.8)
SGA (10th%tile)	1.8 (1.7–2.0)	1	0.8 (0.7–0.8)	0.8 (0.7–0.9)
LGA (90th%tile)	0.4 (0.4–0.5)	1	1.8 (1.7–1.9)	2.3 (2.2–2.4)
RDS	1.0 (0.9–1.1)	1	1.2 (1.1–1.3)	1.2 (1.1–1.3)
IVH grade III or IV	1.1 (0.8–1.5)	1	1.1 (0.9–1.4)	0.9 (0.7–1.2)
Stillbirth	0.7 (0.5–0.9)	1	1.0 (0.9–1.2)	1.3 (1.1–1.6)
Neonatal death	1.5 (1.0–2.2)	1	0.9 (0.7–1.3)	0.8 (0.6–1.3)

GDM gestational diabetes mellitus, SGA small for gestational age, LGA large for gestational age, RDS respiratory distress syndrome, IVH intraventricular hemorrhage

⁺ Reference group

The effect of pre-gravid obesity on neonatal mortality was significantly greater in IVF compared to non-IVF pregnancies (OR 4.6; 95% CI 1.3–15.8).

Figure 1 presents OR and 95% CI for various pregnancy outcomes in different BMI categories in IVF compared to non-IVF pregnancies.

Discussions

Pre-IVF overweight and obesity increase the risks for several pregnancy complications, such as preeclampsia and GDM. Cesarean delivery is also more common in women, who were obese before successful IVF. They also have more LGA neonates. Their neonates develop RDS more frequently and are at increased risk of neonatal death. On the other hand, SGA neonates were more common in women who were underweight before IVF.

The association between higher pre-gravid BMI and hypertensive disorders of pregnancy, GDM, cesarean delivery, and increased neonatal birth weight has been well described in previous studies [1, 2, 18, 19]. The same is true for the association between pre-gravid underweight and SGA [20]. However, the effects of pre-IVF BMI on these outcomes have

not been fully clarified. Our results suggest similar associations between pre-gravid BMI and pregnancy outcomes in women conceiving by IVF compared to those conceiving without IVF. There are, however, some important differences. The effects of increased pre-gravid BMI on cesarean delivery and preeclampsia do not seem to be as profound in IVF as compared to non-IVF pregnancies. This may be explained by the fact that both preeclampsia and cesarean delivery are more common in IVF pregnancies in general, reducing the impact of pre-gravid maternal BMI on these outcomes. Higher cesarean delivery rates have already been reported in subfertile women which is in accordance with higher rates of cesarean delivery in all BMI groups following IVF treatment in the present study [21]. Similarly, the effect of pre-pregnancy BMI on stillbirth was only significant in the non-IVF as compared to IVF group. This could also be explained by slightly higher rate of stillbirth in IVF vs. non-IVF pregnancies (0.7 vs. 0.5%), but more probably by significantly lower absolute number of stillbirths in IVF vs. non-IVF group (44 vs. 1336) leading to type I or type II error. Rates of RDS were higher in neonates born to mothers with higher BMI in both IVF and non-IVF groups. This could be the result of increasing cesarean delivery rates with increasing BMI, since elective cesarean delivery has been associated with higher RDS rates also at

Fig. 1 Odds ratios and 95% confidence intervals for various pregnancy outcomes by body mass index (BMI) category in in vitro fertilization (IVF) compared to non-IVF pregnancies

term [22]. We also found a significantly larger increased risk of neonatal mortality with pre-gravid obesity in IVF pregnancies compared to non-IVF pregnancies. Further studies are needed to confirm these results, since they could be important for obese mothers following IVF. Nevertheless, our results can be used for counseling women with higher BMI category before IVF about different risks during pregnancy and for alerting care-givers about risks during pregnancy in these women.

The main weakness of the study is its retrospective observational nature, which does not allow accounting for all potential confounders on the effects of pre-gravid BMI on perinatal outcomes. For example, NPIS data do not permit accurate assessing of the impact of socioeconomic maternal characteristics on outcomes. They also do not allow analysis of all different forms of infertility treatments and specific medications used. Although we did not include pregnancies following controlled hyperovulation and intra-uterine insemination in the analysis, some women in the

non-IVF group conceived following other infertility treatments, e.g., surgical treatment of tubo peritoneal factors, making this a non-absolutely “clean” group of spontaneous pregnancies. These pregnancies, however, constitute a minority of all non-IVF pregnancies and do not influence the results significantly. Another limitation of the study is that pre-pregnancy weight was recorded retrospectively in the first trimester. It is, therefore, impossible to be absolutely certain about the accuracy of pre-pregnancy weight using retrospective data and some recall bias might exist as in all studies using this methodology. Nevertheless, we believe that our observations add important information to the existing literature on pre-gravid BMI. High as well as low BMI before IVF are independent risk factors for many adverse maternal and neonatal outcomes. Therefore, dietary and life style counseling intended to achieve optimal body weight prior to IVF is recommended in order to improve not only IVF pregnancy rates but also chances of uncomplicated pregnancy, childbirth, and postnatal period.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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