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Original Article

The effect of body mass index (BMI) and gestational weight gain on adverse obstetrical outcomes in pregnancies following assisted reproductive technology as compared to spontaneously conceived pregnancies

Dvora Frankenthal[a], Galit Hirsh-Yechezkel[a], Valentina Boyko[a], Raoul Orvieto[b,d], Raphael Ron-El[c,d], Liat Lerner-Geva[a,d], Adel Farhi[a,*]

[a] Women and Children's Health Research Unit, Gertner Institute for Epidemiology & Health Policy Research Ltd., Tel Hashomer, Israel
[b] Department of Obstetrics and Gynecology, IVF Unit, Sheba Medical Center, Israel
[c] Department of Obstetrics and Gynecology, IVF Unit, Assaf-Harofeh Medical Center, Israel
[d] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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ABSTRACT

Objective: To compare the effect of pre-pregnancy body mass index (BMI) and inappropriate gestational weight gain (GWG) on adverse obstetrical outcomes among women undergoing assisted reproductive technology (ART) treatments as compared to spontaneously-conceived (SC) pregnancies.
Methods: This prospective cohort study included 1058 pregnant women from two medical centres; 504 women who conceived following ART treatments and 554 who conceived spontaneously. The women were recruited at 8 weeks of gestation and follow-up telephone interviews were conducted 6 weeks after delivery. Obstetrical outcomes included pregnancy hypertension, gestational diabetes (GD), low birth weight (LBW) (<2500 g) and small for gestational age (SGA). Multivariate analyses were used to assess the effect of pre-pregnancy BMI and inappropriate GWG on these obstetrical outcomes adjusted for risk factors.
Results: The effect of pre-pregnancy BMI and inappropriate GWG on adverse obstetrical outcomes did not differ between ART and SC pregnancies. Pre-pregnancy obesity was found to be associated with increased risk for pregnancy hypertension (OR = 2.16; 95%CI 1.16–4.03), GD (OR = 2.89; 95%CI 1.61–5.17), caesarian section (OR = 1.77; 95%CI 1.10–2.85) and SGA (OR = 1.91; 95%CI 1.05–3.46). GWG below recommendations was associated with increased risk for GD (OR = 1.73; 95%CI 1.06–2.82) and SGA (OR = 1.69; 95%CI 1.17–2.40) while GWG above recommendations was associated with increased risk for pregnancy hypertension (OR = 1.77; 95%CI 1.02–3.06).
Conclusions: Pre-pregnancy obesity and inappropriate GWG were associated with adverse obstetrical outcomes in both ART and SC pregnancies. Emphasis should be given on the importance of an optimal pre-pregnancy BMI and appropriate GWG during pregnancy.

Introduction

Obesity is a global epidemic and weight management before and during pregnancy represents an important issue in healthcare [1]. The impact of obesity on natural fecundity has well been demonstrated with decreased pregnancy rates, decreased live birth rates and increased miscarriages rates [1–3]. Since obesity is associated with infertility, substantial number of overweight and obese women are treated using assisted reproductive technology (ART). Such treatment has an impaired outcome among these patients [3]. In general, previous data have shown that the risk for neonatal complications in ART pregnancies is higher as compared to spontaneous pregnancies [4]. Adverse pregnancy outcomes have been linked to maternal obesity with higher rates of maternal morbidity and increased risk for neonatal complications [5–7]. Higher gesta-

* Corresponding author at: Women and Children's Health Research Unit, Gertner Institute for Epidemiology & Health Policy Research Ltd., Sheba Medical Center, Tel-Hashomer 5261, Israel.
E-mail address: dollyf@gertner.health.gov.il (A. Farhi).

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tional weight gain (GWG) has been associated with increased risks of preeclampsia, gestational diabetes, caesarean delivery and large-for-gestational-age (LGA) infants while insufficient GWG has been associated with preterm birth, low birth weight, growth restriction and prematurity [8,9].

However, little is known whether the associations between maternal body mass index (BMI) and obstetrical outcomes are different among women who conceived naturally or following ART.

Considering the high prevalence of both ART and obesity, the objective of this study was to analyse data from an Israeli prospective cohort in order to assess the effect of pre-pregnancy BMI and inappropriate GWG on the risk for adverse obstetrical outcomes among women undergoing ART treatments as compared to spontaneously-conceived (SC) pregnancies.

Materials and methods

The study population consisted of participants from a prospective cohort described in detail elsewhere [10]. Briefly, the cohort comprised 509 women with singleton pregnancies following ART treatments and 587 women with SC singleton pregnancies from two medical centres (Sheba Medical Centre and Assaf Harofeh Medical Centre). All women were recruited during the period between June 2006 and December 2008.

There were 2 encounters: the first encounter was recruitment at 6–12 weeks of gestation with a short self-administered questionnaire mainly with contact information. The second encounter was a telephone interview that was conducted 6 weeks following delivery. The telephone interview included demographic characteristic (age, education), lifestyle during pregnancy (smoking, physical activity), medical history (hypertension, diabetes), obstetric history (nulliparous, number of live births with no previous abortions or with previous abortions), morbidity during pregnancy, maternal height and body weight a month prior to conception and at delivery and obstetric outcomes including complications during pregnancy and birth.

Pre-pregnancy BMI was calculated and stratified according to the World Health Organization classification as follows: underweight (BMI < 18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9) and obese (BMI $\geq$ 30) [11]. GWG was calculated as the difference between maternal weight at delivery and pre-pregnancy weight. The Israeli guidelines for GWG [12] as well as the American guidelines [13,14] recommend weight gain during pregnancy based on pre-gestational BMI: 11.5–16.0 kg if pre-gestational BMI is within the normal range, 12.5–18.0 kg if pre-gestational BMI is low (<18.5 kg/m^2), 7.0–11.5 kg if pre-gestational BMI is between 25.0–29.9 kg/m^2 and 5.0–9.0 kg if pre-gestational BMI is high (>30 kg/m^2). Gestational weight gain was calculated individually for each participant according to her pre-pregnancy BMI. GWG was then grouped into 3 categories: "below recommendations", "as recommend" and "above recommendations".

Obstetrical outcomes included pregnancy-induced hypertension (including gestational hypertension or preeclampsia), gestational diabetes and treatment (including only diabetes discovered during pregnancy), caesarean section, low birthweight (<2500 g), small for gestational age (birth weight < 10th percentile for gestational age according to gender-specific charts [15]) and large for gestational age (LGA) (birth weight > 90th percentile for gestational age according to gender-specific charts [15]).

Statistical analysis

Differences between ART and SC groups were tested using the chi-squared test or Fisher's exact test for categorical variables and the Student t-test for continuous variables. P for trend was calculated using Mantel–Haenszel Chi-square test. Interactions between pre-pregnancy BMI/GWG, mode of conception and adverse obstetrical outcomes (pregnancy hypertension, GD, caesarean section, LBW, SGA) were assessed. A statistically non-significant interaction indicates that the effect of BMI/GWG on obstetric outcomes do not differ between the ART and SC groups. Logistic regression analyses were used to assess the effect of pre-pregnancy BMI and inappropriate GWG on obstetrical outcomes among pregnancies following ART treatments as compared to SC adjusting for risk factors. Adjustment was done for maternal age and education, mode of conception, obstetric history, physical activity and smoking during pregnancy. All tests were two tailed and P-values <0.05 were considered statistically significant. Statistical analyses were performed using SAS statistical software version 9.2 (SAS Institute, Inc., Cary, NC).

Ethical approval

Approval was obtained from the two participating medical centres (Sheba Medical Centre #3657/05, 26/04/2005 and Assaf Harofeh Medical Centre #129/05, 10/11/2005).

Results

The cohort included 1096 women with singleton pregnancies, of them, 38 were excluded from the analysis because of missing BMI data. The final study population comprised 1058 women with singleton pregnancies; 504 pregnant women following ART treatments and 554 pregnant women following spontaneous conceptions.

Women in the ART group were significantly older (mean $\pm$ SD age 33.0 $\pm$ 4.9 versus 30.7 $\pm$ 4.9 years, P < 0.001) and less educated compared to the SC group (Table 1A). Medical history (hypertension and diabetes prior pregnancy) and lifestyle during pregnancy (smoking, physical activity) did not differ significantly between the two groups [10].

Pre-pregnancy obesity was higher in the ART group compared to the SC group (11.7% versus 7.6% for BMI $\geq$ 30) although not statistically significant. There were borderline significant differences (P = 0.08) in GWG between the groups with a higher proportion of women with inappropriate GWG among the ART group compared to the SC group.

The incidence rates of all adverse obstetric outcomes were higher in the ART group compared to the SC group although only pregnancy hypertension, LBW and SGA reached statistical significance (Table 1B). Treatment for GD did not differ significantly between the two groups (Pv = 0.18). Most women (73.2%) who reported GD changed their diet during pregnancy, 13.4% were treated with Insulin and 13.4% did not get any treatment.

The incidence rate of LGA infants was very low in both groups so no further analysis according to pre-pregnancy BMI or GWG was performed. The highest differences in the crude incidence rates of most adverse obstetric outcomes were observed among women with pre-pregnancy BMI $\geq$ 30 kg/m^2 (Table 2A) especially pregnancy hypertension (20.3% for ART and 11.9% for SC pregnancies, P = 0.26), caesarean section (42.4% for ART and 26.2% for SC pregnancies, P = 0.09), LBW (20.3% for ART and 2.4% for SC pregnancies, P = 0.008) and SGA (18.6% for ART and 9.5% for SC pregnancies, P = 0.20). When GWG was analysed (Table 2B) and was above recommendations, the highest differences in the crude incidence rates of adverse obstetric outcomes were observed for GD (10.7% for ART and 6.6% for SC pregnancies, P = 0.18) and LBW (10.7% for ART and 4.2% for SC pregnancies, P = 0.02). However, when GWG was below recommendations, the crude incidence rates of all adverse obstetric outcomes were higher in the ART group compared to the SC group.

Table 1
Maternal characteristics and adverse obstetric outcomes by mode of conception.

Maternal characteristics	Assisted reproduction treatment		Spontaneous conception		P-value
	N = 504		N = 554		
	n	%	n	%	
Age, years, mean ± SD	33 ± 4.9		30.7 ± 4.9		<0.001
Education, years, n (%)					0.0004
≤12	204	40.7	168	30.3	
13+	297	59.3	386	69.7	
Obstetric history, n (%)					<0.0001
Nulliparous	204	40.5	168	30.3	
Previous livebirths, no abortions	133	26.4	223	40.2	
Previous livebirths with previous abortions	167	33.1	163	29.4	
Pre-pregnancy BMI (kg/m^2), n (%)					0.12
<18.5	38	7.5	47	8.5	
18.5–24.9	321	63.7	376	67.9	
25.0–29.9	86	17.1	89	16.0	
≥30.0	59	11.7	42	7.6	
Gestational weight gain, n (%)					0.08
Above the recommendations	168	34.0	166	30.5	
As recommendation	171	34.6	225	41.3	
Below the recommendations	155	31.4	153	28.1	

Adverse obstetric outcomes, n (%)	Assisted reproduction treatment		Spontaneous conception		n
	N = 504		N = 554		
	n	%	n	%	
Pregnancy hypertension	56	11.1	36	6.5	0.008
Gestational diabetes	60	11.9	52	9.4	0.18
Caesarean section	131	26.0	118	21.3	0.07
Low birth weight	50	9.9	33	6.5	0.01
Small for gestational age	121	24.0	106	19.1	0.048
Large for gestational age	19	3.4	15	2	0.68

BMI = body mass index.

Pre-pregnancy BMI and adverse pregnancy outcomes

In multivariate analysis for the association between pre-pregnancy BMI and adverse pregnancy outcomes adjusted for maternal age and education, mode of conception, obstetric history, physical activity and smoking during pregnancy. No interaction between mode of conception and BMI was observed and therefore the effects of pre-pregnancy BMI on obstetrical outcomes did not differ between modes of conception.

Table 3 presents the association between the different BMI categories, mode of conception and adverse obstetric outcomes for the whole study population. Pre-pregnancy overweight and obesity were found to be risk factors for pregnancy gestational diabetes (GD) (OR = 2.32; 95%CI 1.41–3.80 and OR = 2.89; 95%CI 1.61–5.17, respectively), caesarian section (OR = 1.68; 95%CI 1.15–2.47 and OR = 1.77; 95%CI 1.10–2.85, respectively) and SGA (OR = 1.64; 95%CI 1.05–2.57 and OR = 1.91; 95%CI 1.05–3.46, respectively). Obesity was also found to be a risk factor for pregnancy hypertension (OR = 2.16; 95%CI 1.16–4.03). Mode of conception was not associated with adverse pregnancy outcomes except for pregnancy hypertension. The risk for pregnancy hypertension in ART pregnancies was higher compared to SC pregnancies (OR = 1.61; 95%CI 1.00–2.59).

GWG and adverse pregnancy outcomes

In multivariate analysis for the association between GWG and adverse pregnancy outcomes (Table 4), again no interaction between mode of conception and GWG was observed.

Table 4 presents the association between the GWG categories and adverse obstetric outcomes for the whole study population. GWG below recommendations was associated with increased risk for GD (OR = 1.73; 95%CI 1.06–2.82), SGA (OR = 1.69; 95%CI 1.17–2.40) and lower risk for caesarean section (OR = 0.55; 95%CI 0.36–0.85). GWG above recommendations was significantly associated with increased risk for pregnancy hypertension (OR = 1.77; 95%CI 1.02–3.06). Mode of conception was not associated with adverse pregnancy outcomes.

Discussion

The present study demonstrated that the effect of pre-pregnancy BMI and inappropriate GWG on adverse obstetrical outcomes did not differ between ART and SC pregnancies. To our knowledge, this is the first prospective study in Israel that describes the association between pre-pregnancy BMI, inappropriate GWG and obstetrical outcomes among pregnancies following ART treatments as compared to SC pregnancies. In Israel, ART is funded in the framework of the national health insurance for the first two children, with no limitations on the number of treatment cycles for women up to the age of 45 and with no specific restrictions. Pre-pregnancy obesity was associated with pregnancy hypertension, GD, caesarean section and SGA. The results of this study are comparable with the results of previous studies. Dokras et al. [16] investigated the effects of obesity on obstetric outcomes after IVF treatment in 1293 women. Among the women who delivered, there was a significant linear trend for risk of preeclampsia, gestational diabetes, and caesarean delivery with increasing BMI. A recent retrospective hospital based cohort study by Machtinger et al. [17] reported that the odds of adverse obstetrical outcomes were not significantly greater in IVF singleton pregnancies compared with those conceived spontaneously as BMI increased. The study compared 464 ART and 1171 SC singleton pregnancies within categories of maternal BMI. Among overweight women following

Table 2A
Obstetric outcomes by mode of conception and pre-pregnancy body mass index (BMI).

Obstetric outcome by BMI category	Assisted reproduction treatment		Spontaneous conception		P-value*
	N = 504		N = 554		
	$n/N_{\text{of the BMI group}}$	%	$n/N_{\text{of the BMI group}}$	%	
Pregnancy hypertension by BMI category					
BMI < 18.5	0/38	0	2/47	4.3	0.49
BMI 18.5–24.9	32/321	10.0	22/376	5.8	0.04
BMI 25.0–29.9	12/86	13.9	7/89	7.9	0.19
BMI ≥ 30	12/59	20.3	5/42	11.9	0.26
	$P_{\text{for trend}} = 0.0012$		$P_{\text{for trend}} = 0.16$		
Gestational diabetes by BMI category					
BMI < 18.5	5/38	13.1	2/47	4.3	0.23
BMI 18.5–24.9	27/321	8.4	26/376	6.9	0.45
BMI 25.0–29.9	15/89	17.4	15/86	16.8	0.91
BMI ≥ 30	13/59	22.0	9/42	21.4	0.94
	$P_{\text{for trend}} = 0.054$		$P_{\text{for trend}} = 0.0012$		
Caesarean section by BMI category					
BMI < 18.5	8/38	21.0	7/47	14.9	0.45
BMI 18.5–24.9	71/320	22.0	72/376	19.1	0.32
BMI 25.0–29.9	27/89	31.4	28/86	31.4	0.99
BMI ≥ 30	25/59	42.4	11/42	26.2	0.09
	$P_{\text{for trend}} = 0.007$		$P_{\text{for trend}} = 0.03$		
Low birth weight by BMI category					
BMI < 18.5	2/38	5.3	5/47	10.6	0.45
BMI 18.5–24.9	30/320	9.4	24/376	6.4	0.14
BMI 25.0–29.9	6/89	7.0	3/86	3.4	0.32
BMI ≥ 30	12/59	20.3	1/42	2.4	0.008
	$P_{\text{for trend}} = 0.055$		$P_{\text{for trend}} = 0.05$		
Small for gestational age by BMI category					
BMI < 18.5	12/38	31.6	9/47	19.1	0.19
BMI 18.5–24.9	85/320	26.6	78/376	20.7	0.07
BMI 25.0–29.9	13/89	15.1	15/36	16.8	0.75
BMI ≥ 30	11/59	18.6	4/42	9.5	0.20
	$P_{\text{for trend}} = 0.032$		$P_{\text{for trend}} = 0.31$		

P for trend was calculated using Mantel–Haenszel Chi-square test.
* Chi-squared test or Fisher's exact test P value, between ART and SC group in each BMI category.

ART, only LBW was significantly increased. For obese women, there were no differences between IVF and SC pregnancies in placental ischemic disorders, preeclampsia, SGA, GD, preterm delivery, caesarean section, gestational age at delivery, and birthweight <2500 g and >4000 g.

Another recent Norwegian registry-based study [18] compared the association between pre-pregnancy BMI and adverse perinatal and maternal outcomes in 6760 singleton pregnancies following ART treatments and 221,005 singleton SC pregnancies. A high maternal pre-pregnancy BMI was associated with a higher risk of preterm birth, SGA, large for gestational age (LGA), perinatal death, hypertensive disorders, GD, induction of delivery and caesarean section in pregnancies following both SC and ART. Due to their substantial sample size, the authors also demonstrated that the absolute risks of all outcomes were higher after ART conception compared to SC pregnancies. However, these studies [17,18] did not compare the effect of inappropriate GWG on adverse obstetric outcomes.

The present study demonstrated a higher risk for pregnancy hypertension (although marginally significant) in ART pregnancies as compared to SC pregnancies, as was also suggested by others [19,20]. Similar findings were also described in a systematic review and meta-analysis [21] that demonstrated a statistically increased risk of hypertensive disorders in singleton ART pregnancies when compared with singletons from spontaneous conception. With regard to the association between inappropriate GWG and obstetrical outcomes, the present study is among the first to examine this relationship in the ART population. The present study demonstrated that GWG below recommendations was associated with GD and SGA and with lower risk for caesarean section. GWG above recommendations was associated with increased risk of pregnancy hypertension.

Most studies examined inappropriate GWG in the obese population. A recent systematic review [22] that included six cohort studies demonstrated that insufficient GWG in obese women according to the 2009 Institute of Medicine recommendations (IOM) guidelines was associated with higher odds of SGA. Another study [8] showed that insufficient weight gain in obese women was associated with twofold greater odds of LBW infants while excessive weight gain was associated with doubled odds of gestational hypertension or preeclampsia. Also the odds of SGA were greater for women who lost than gained excessive weight. This is in accordance to the findings of the present study that included women from all BMI categories. Another population-based cohort study of 120,251 pregnant obese women [23] delivering full-term and singleton infants demonstrated that GWG less than recommended was associated with a significantly lower risk of preeclampsia, caesarean delivery, and LGA birth and higher risk of SGA.

The present study showed that GWG below recommendations was associated with GD. To date, investigations have found that

Table 2B
Obstetric outcomes by mode of conception and gestational weight gain (GWG).

Obstetric outcome by BMI category	Assisted reproduction treatment		Spontaneous conception		P-value*
	N = 504		N = 554		
	$n/N_{of\ the\ BMI\ group}$	%	$n/N_{of\ the\ BMI\ group}$	%	
Pregnancy hypertension by GWG category					
Below recommendation	17/155	11.0	5/153	3.3	0.009
As recommended	18/171	10.5	10/225	4.4	0.02
Above recommendation	21/168	12.5	21/166	12.6	0.96
Gestational diabetes by GWG category					
Below recommendation	26/155	16.7	19/153	12.4	0.28
As recommended	15/171	8.7	21/225	9.3	0.84
Above recommendation	18/168	10.7	11/166	6.6	0.18
Caesarean section by GWG category					
Below recommendation	39/154	25.3	21/153	13.7	0.01
As recommended	42/171	24.5	50/225	22.2	0.58
Above recommendation	47/168	28.0	47/166	28.3	0.94
Low birth weight by GWG category					
Below recommendation	17/154	11.0	12/153	7.8	0.33
As recommended	15/171	8.7	14/225	6.2	0.33
Above recommendation	18/168	10.7	7/166	4.2	0.02
Small for gestational age by GWG category					
Below recommendation	49/154	31.8	18/153	24.8	0.17
As recommended	41/171	24.0	39/225	17.3	0.10
Above recommendation	30/168	17.8	28/166	16.8	0.81

* Chi-squared test or Fisher's exact test P value, between ART and SC group in each GWG category.

Table 3
Adjusted odds ratios (OR) for the association between pre-pregnancy body mass index (BMI) and adverse obstetric outcomes.

Adjusted[a] model for:	Mode of conception		BMI (kg/m^2)			
	ART OR (95%CI)	SC	<18.5 OR (95%CI)	18.5 ≤ 25	25 ≤ 30 OR (95%CI)	30+ OR (95%CI)
Pregnancy hypertension	1.61 (1.00–2.59)	1.0 (Ref)	0.27 (0.06–1.14)	1.0 (Ref)	1.53 (0.87–2.69)	2.16 (1.16–4.03)
Gestational diabetes	1.10 (0.71–1.69)	1.0 (Ref)	1.06 (0.46–2.44)	1.0 (Ref)	2.32 (1.41–3.80)	2.89 (1.61–5.17)
Caesarean section	0.98 (0.72–1.36)	1.0 (Ref)	0.79 (0.42–1.47)	1.0 (Ref)	1.68 (1.15–2.47)	1.77 (1.10–2.85)
Low birth weight	1.40 (0.86–2.29)	1.0 (Ref)	0.87 (0.36–2.12)	1.0 (Ref)	0.70 (0.34–1.42)	1.42 (0.72–2.78)
Small for gestational age	0.78 (0.57–1.07)	1.0 (Ref)	0.96 (0.56–1.65)	1.0 (Ref)	1.64 (1.05–2.57)	1.91 (1.05–3.46)

[a] Adjusted also for: maternal age, education, obstetric history, physical activity and smoking during pregnancy.

Table 4
Adjusted odds ratios (OR) and their 95% confidence intervals (CI) for the association between gestational weight gain (GWG) and adverse obstetric outcomes.[a]

Adjusted[a] model for:	Mode of conception		Gestational weight gain		
	ART OR (95%CI)	SC	Below recommendation OR (95%CI)	As recommended	Above recommendation OR (95%CI)
Pregnancy hypertension	1.47 (0.89–2.43)	1.0 (Ref)	0.96 (0.50–1.84)	1.0 (Ref)	1.77 (1.02–3.06)
Gestational diabetes	1.12 (0.72–1.74)	1.0 (Ref)	1.73 (1.06–2.82)	1.0 (Ref)	0.82 (0.48–1.43)
Caesarean section	0.89 (0.63–1.25)	1.0 (Ref)	0.55 (0.36–0.85)	1.0 (Ref)	1.30 (0.90–1.87)
Low birth weight	1.15 (0.57–2.33)	1.0 (Ref)	1.12 (0.47–2.63)	1.0 (Ref)	1.37 (0.62–3.0)
Small for gestational age	1.25 (0.89–1.74)	1.0 (Ref)	1.69 (1.17–2.40)	1.0 (Ref)	0.77 (0.51–1.14)

[a] Adjusted also for: maternal age, education, obstetric history, physical activity and smoking during pregnancy. Preterm pregnancies were excluded from the model.

both excess and low weight gain were associated with GD [24–26]. Studies that investigated total weight gain until delivery have found that women with GD gained on average less weight than controls primarily because of higher pre-pregnancy weight [25]. In the present study, 73.2% of women who were diagnosed with GD changed their diet. We believe that the association between GWG below recommendations and GD that was found in the present study is due to the fact that women who are diagnosed with GD and learn about the risks of GD, might change their diet and gain less weight during pregnancy.

When interpreting this study's findings, the following limitations should be considered.

First, the study population was recruited from only 2 medical centres so the generalisability of the results may be affected. However, both hospitals represent heterogeneous population. Second, data were collected from self-reported interviews and may be underestimated. Third, interview responses were not validated

except for gestational age at birth and infant's birth weight that were validated through national live birth registry. The major strength of this study is the prospective follow up of women who conceived following ART with an appropriate control group of women conceiving spontaneously, thus allowing us to compare parameters such as adverse obstetric outcomes simultaneously.

In conclusion, pre-pregnancy obesity and inappropriate GWG were associated with adverse obstetrical outcomes in both ART and SC pregnancies; overall the effect did not differ between modes of conception. ART pregnancies demonstrated a higher risk for pregnancy hypertension as compared to SC pregnancies. Emphasis should be given on the importance of an optimal pre-pregnancy BMI and appropriate weight gain during pregnancy in general. Larger sample size will enable us to further assess specific categories of BMI and GWG.

Declarations of interest

None.

Ethical statement

On behalf of all authors I state that:

1. Ethical approval for this study was obtained from the two participating medical centres (Sheba Medical Centre #3657/05, 26/04/2005 and Assaf Harofeh Medical Centre #129/05, 10/11/2005).
2. We declare that this study was conducted in accordance with the Declaration of Helsinki.

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