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MATERNAL-FETAL MEDICINE

Offspring of women following bariatric surgery and those of patients with obesity are at an increased risk for long-term pediatric endocrine morbidity

Pinhas Damti[1,2] · Michael Friger[2] · Daniella Landau[3] · Ruslan Sergienko[2] · Eyal Sheiner[1]

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Abstract

Objective To assess whether offspring of women following bariatric surgery as well as offspring of obese women are at an increased risk for long-term pediatric endocrine morbidity.

Setting This study was conducted at the university hospital.

Methods A population-based cohort study compared the incidence of long-term (up to the age of 18 years) occurrence of endocrine morbidity between offspring of mothers following bariatric surgery and obese mothers, as compared with parturients without obesity and without prior bariatric surgery.

Results During the study period 220,563 newborns met the inclusion criteria; 1001 were delivered by patients following bariatric surgery, 2275 were delivered by obese women and 217,287 were delivered by normal weight women without prior bariatric surgery. Long-term endocrine morbidity was more common in the bariatric group (2.3%) and the obesity group (1.5%) as compared with the comparison group (0.5%; $P<0.001$). Specifically, pediatric obesity was significantly more common in children of mothers following bariatric surgery (1.8%) and of mothers with obesity (1.2%) as compared with the comparison group (0.2%; $P<0.001$). Children born to women following bariatric surgery as well as obese women had higher cumulative incidence of pediatric endocrine morbidity (Log rank, $P<0.001$). The results remained significant when controlling for maternal factors, adjusted HR 6.25, 95% CI 4.10–9.50; $P<0.001$ for women following bariatric surgery and aHR 2.40 95% CI 1.69–3.40; $P<0.001$ for obese women.

Conclusion Offspring of women following bariatric surgery as well as those of obese women are at an increased risk for long-term pediatric endocrine morbidity.

Keywords Bariatric surgery · Obesity · Pediatric outcome · Long-term outcome · Endocrine · Morbidity

Introduction

Obesity, defined as body-mass-index (BMI) above 30 kg/m^2, is on the rise in reproductive-age women [1, 2]. Obesity has been related to several adverse pregnancy outcomes, such as miscarriage, preeclampsia, gestational diabetes mellitus (GDM), large for gestational age (LGA), cesarean delivery, preterm birth and stillbirth [3–8].

Bariatric surgery has shown efficiency in achieving and sustaining weight reduction, and it has also been shown as an effective intervention method for lowering obesity-comorbidities rates [9, 10]. Most bariatric surgeries are performed in female population and almost 50% of those women are in their reproductive age [11].

It has been shown that pre-pregnancy bariatric surgery resulted in reduction of many obesity-related pregnancy

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✉ Pinhas Damti
pini.damti@gmail.com

[1] Department of Obstetrics and Gynecology, Soroka University Medical Center, Ben-Gurion University of the Negev, 151 Izak Rager Ave., Beersheba 84101, Israel

[2] The Department of Public Health, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beersheba, Israel

[3] Department of Pediatrics, Soroka University Medical Center, Ben-Gurion University of the Negev, Beersheba, Israel

adverse outcomes such as preeclampsia, GDM, macrosomia and large-for-gestational-age [12–15]. Few studies have reported no additional risk for perinatal mortality rate, meconium-stained amniotic fluid, low Apgar score at 1 and 5 min and congenital malformations following bariatric surgery [13, 16]. On the contrary, an increased risk for small for gestational age (SGA) infants has been observed following bariatric surgery [12, 13, 17]. It seems that there is no difference in the effect on pregnancy outcome among the different forms of bariatric surgeries. All procedures have basically comparable perinatal outcome, meaning reduction in gestational complications such as GDM and preeclampsia [18–20].

While obstetrical outcomes and infant's short-term outcome have been widely investigated, to the best of our knowledge, the long-term impact of maternal bariatric surgery on infants' health has not been explored yet. In this study, we aim to investigate whether infants born to women after bariatric surgery or mothers with obesity are at an increased risk for long-term (up to the age of 18 years) endocrine morbidity as compared to women without obesity and without prior bariatric surgery.

Materials and methods

Setting

The study was conducted at the Soroka University Medical Center (SUMC), the sole hospital of the Negev (southern Israel) which serves the entire population in the region. Thus, the study is based on nonselective population data. The Institutional Review Board (in accordance with the declaration of Helsinki) approved the study (no. SOR-0236-13 approved November 2013).

Study population

The study population consisted of all patients who delivered between the years 1991 and 2014 and their offspring. Multiple pregnancies, unknown gestational age, gestational age of less than 24 weeks, fetuses with congenital malformations and perinatal mortality were excluded from the study.

Study design

We conducted a population-based cohort study. The study was consisted of three groups: parturients with previous bariatric surgery, parturients with obesity and parturients without obesity and without prior bariatric surgery. A comparison was performed between children born to parturients with previous bariatric surgery, parturients with obesity and parturients without obesity and without prior bariatric surgery.

Outcomes assessed include encounters with the hospital up to the age of 18 years due to endocrine morbidity. Offspring endocrine morbidity was defined according to preexisting *International Classification of Diseases*, ninth revision codes (ICD-9), which were gathered in any encounter with the hospital regardless of decision on admission. In Soroka Medical Center, physicians document all patient diagnoses in the medical record, beyond primary diagnoses. Endocrine morbidity included diagnoses such as hypothyroidism, diabetes mellitus, hypoglycemia or obesity (supplemental Table 1). Follow-up time was defined as time to an event (related hospital encounter, or until censored). Censoring occurred in case of death (during hospitalization, other than endocrine related) or at age 18 (which was calculated for each child based on the date of birth). Follow-up terminated at any of the following: upon the first encounter with SUMC for each category of morbidity, when hospitalization resulted in death, or when the child reached 18 years of age.

Data were collected from two databases that were cross-linked and merged (merging was based on mothers' and infants' identification numbers): the computerized perinatal database of the Obstetrics and Gynecology department, and the computerized pediatric database of the Soroka University Medical Center. The perinatal database consists of information recorded immediately following delivery by an obstetrician. Skilled medical secretaries routinely review the information before entering it into the database. Coding is performed after assessing medical prenatal care records together with the routine hospital documents. These procedures assure maximal completeness and accuracy of the databases.

Statistical analysis

Statistical analysis was performed using SPSS software Version 21 (SPSS, Chicago, IL, USA). Quantitative normally distributed variables were compared by independent ANOVA, Quantitative variables with non-normal distribution were compared by Kruskal–Wallis and categorical variables were compared by Chi Square test (or Exact Fisher test as appropriated). Kaplan–Meier survival curve was used to compare cumulative incidence of endocrine morbidity events. Cox proportional hazards model analysis was used to control for variables that were significant in univariate analysis and to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for long-term risk pediatric endocrine events. A probability value < 0.05 was considered statistically significant. Weibull regression analysis was used to control for maternal clusters in addition to all variables that found significant in univariate analysis and to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for

long-term risk pediatric endocrine morbidity. A probability value < 0.05 was considered statistically significant.

Results

Between the years 1991 and 2014, 220,563 women delivered at SUMC, of which 1001 mothers were after bariatric surgery, 2275 women with obesity and 217,287 women were in the comparison group (without obesity and without bariatric surgery). During this period, 47,899 offsprings of these mothers were encountered in SUMC.

Pregnancy characteristics and delivery outcomes across study groups are detailed in Table 1. Women following bariatric surgery were older and had higher rates of preterm delivery (< 37 weeks), cesarean section, smoking, diabetes (gestational and pregestational) and hypertensive disorders of pregnancy. Women with obesity gave more births (higher parity) and had higher birth weight, macrosomia, and Apgar score < 7 in the first minute.

Table 2 summarizes the differences in long-term endocrine morbidity, between offspring of mothers after bariatric surgery, offspring of mother with obesity and offspring of mothers without obesity and without previous bariatric surgery. Long-term in-hospital diagnosed endocrine morbidity was 2.3% in the bariatric group, 1.5% in the obesity group and 0.5% in the comparison group; this difference was statistically significant ($P < 0.001$). Endocrine morbidity

Table 1 Cohort characteristics by exposure to maternal obesity and previous bariatric surgery

Characteristics	Bariatric surgery, $n = 1001$	Patients with obesity, $n = 2275$	Comparison, $n = 217{,}287$	P value
Maternal age, years, mean ± SD	31.4 ± 5.8	30.1 ± 5.8	28.2 ± 5.8	< 0.001
Parity (%)				< 0.001
1	23.0	21.1	24.6	
2–4	67.0	47.7	51.7	
≥ 5	10.1	31.2	23.7	
Maternal diabetes (gestational and pregestational) (%)	10.3	8.0	5.4	< 0.001
Hypertensive disorders of pregnancy (%)	10.9	8.6	5.2	< 0.001
Smoking (%)	5.7	1.1	1.1	< 0.001
Cesarean section (%)	35.8	33.0	13.7	< 0.001
Gestational age at birth, weeks, mean ± SD	38.7 ± 1.8	39.2 ± 1.8	39.1 ± 1.8	< 0.001
Preterm < 37 weeks (%)	8.6	5.7	6.7	< 0.05
Preterm < 34 weeks (%)	1.2	0.9	1.2	0.47
Gender of offspring (%)				0.87
Male	51.0	51.4	50.9	
Female	49	48.6	49.1	
Birth weight (g, mean ± SD)	3164.1 ± 514.8	3434.4 ± 517.9	3211.9 ± 503.9	< 0.001
Low birthweight (< 2500 g, %)	8.5%	3.2%	6.5%	< 0.001
Very low birthweight (< 1500 g, %)	0.3%	0.5%	0.5%	0.775
Apgar score < 7 in 1 min (%)	6.3	7.4	4.9	< 0.001
Apgar score < 7 in 5 min (%)	1.3	1.7	1.9	0.445
Macrosomia (%)	4.0	11.9	4.7	< 0.001

Data are presented as % (n) or mean ± SD; significance for differences was measured using Chi-squared test, Kruskal–Wallis and ANOVA

Table 2 Long-term pediatric endocrine morbidity by exposure to maternal obesity and previous bariatric surgery

	Bariatric surgery, $n = 1001$ (%)	Patients with obesity, $n = 2275$ (%)	Comparison, $n = 217{,}287$ (%)	P value
Total endocrine morbidity ($n = 1074$)	2.3	1.5	0.5	< 0.001
Thyroid disease	0.1	0.1	0.0	0.386
Diabetes mellitus	0.1	0.3	0.1	0.105
Hypoglycemia	0.2	0.0	0.1	0.165
Obesity	1.8	1.2	0.2	0.001

sub-categories analysis has revealed statistically significant difference between study groups for obesity diagnosis ($P < 0.001$).

Figure 1 presents a Kaplan–Meier curve for the cumulative incidence of long-term total endocrine morbidity in each study group (obesity group, post-bariatric surgery group and comparison group). Children born to women with obesity and women with previous bariatric surgery had higher cumulative incidence of endocrine hospitalization. The cumulative incidence was higher in post-bariatric surgery group as compared to the obesity group.

We used Cox proportional hazards model to control for maternal age, gravidity, gestational week, ethnicity, smoking, low Apgar score at 5 min, cesarean section, diabetes mellitus (gestational and pregestaional), hypertensive disorders of pregnancy. Bariatric surgery and obesity were found as independent risk factors for long-term endocrine hospitalization of the offspring (Table 3). Further analysis, controlling for maternal clusters, utilizing Weibull regression and adjusting for same variables used in the above-specified COX regression showed similar results (Table 4).

Discussion

The major finding of the current study was that offspring of mothers with obesity as well as of mothers following bariatric surgery are at an independent risk for long-term endocrine morbidity, and especially obesity. Though, a greater impact on the risk for offspring endocrine morbidity has been shown in the group of mothers following bariatric surgery. To our knowledge, this is the first large-sized

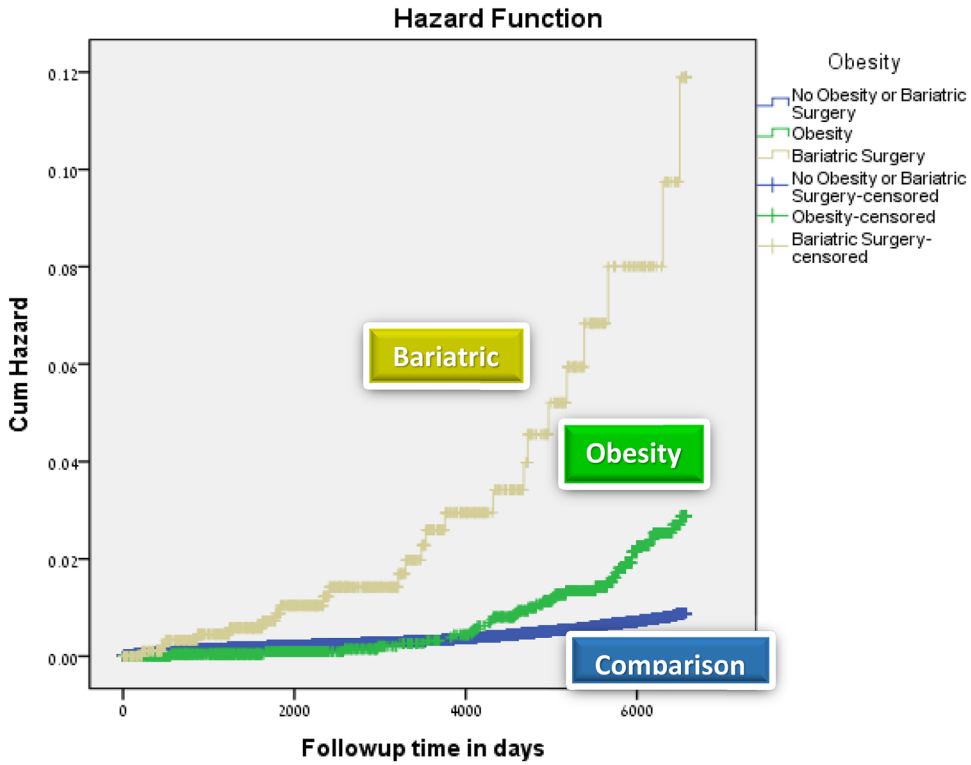

Fig. 1 Cumulative incidence of endocrine morbidity in offspring born to mothers after bariatric surgery, mothers with obesity and mother without obesity and without previous bariatric surgery

Table 3 Cox proportional hazards model of endocrine morbidity in offspring to mothers after bariatric surgery, mothers with obesity and mother without obesity and without previous bariatric surgery

Variables	Adjusted HR	95% CI	*P* value
Bariatric surgery	6.25	4.10–9.50	< 0.001
Obesity	2.40	1.69–3.40	< 0.001
Gestational age at birth, weeks	0.94	0.91–0.97	< 0.001
Diabetes mellitus (gestational and pregestational)	1.67	1.37–2.05	< 0.001
Hypertensive disorders (gestational hypertension, preeclampsia and chronic hypertension)	1.25	1.00–1.56	< 0.05

CI confidence interval, *HR* hazard ratio; the model controlled, in addition, to maternal age, gravidity, ethnicity, Apgar scores, mode of delivery and smoking

Table 4 Weibull regression model of endocrine morbidity in offspring to mothers after bariatric surgery, mothers with obesity and mother without obesity and without previous bariatric surgery

Variables	Adjusted HR	95% CI	*P* value
Bariatric surgery	5.31	3.46–8.14	< 0.001
Obesity	2.18	1.48–3.23	< 0.001
Gestational age at birth, weeks	0.96	0.92–0.99	< 0.05
Diabetes mellitus (gestational and pregestational)	1.70	1.38–2.08	< 0.001
Hypertensive disorders (gestational hypertension, preeclampsia and chronic hypertension)	1.26	1.00–1.58	< 0.05

CI confidence interval, *HR* hazard ratio; the model controlled, in addition, to maternal age, gravidity, ethnicity, Apgar scores, mode of delivery and smoking

study to examine the effects of maternal bariatric intervention and maternal obesity on pediatric long-term endocrine morbidity of the offspring.

Obesity is a known risk factor for numerous diseases such as type 2 diabetes (T2D), heart disease, stroke, malignancy (breast, colon, uterus), osteoarthritis, etc. [21–23]. The risk of developing these complications increases with weight gain. Hence, methods for weight reduction, and specifically bariatric surgery, have gained interest among physicians to reduce the burden of obesity-related morbidity. So far, bariatric surgery has been shown to produce significant long-term weight loss and reduction in obesity-related diseases and may reverse T2D mellitus [9]. In addition, bariatric surgery among women in fertility ages was shown to be associated with risk reduction of gestational complications such as gestational diabetes, preeclampsia, macrosomia and hypertensive disorder [20, 24]. Therefore, it would have been expected that bariatric surgery will result also in long-term risk reduction of obesity morbidity of the offspring, especially obesity. On the contrary, in the current study offspring of mother following bariatric surgery had a higher risk of pediatric long-term endocrine morbidity, specifically overweight obesity. This interesting finding may be related to the fact that females who underwent bariatric surgery were morbidly obese and suggests that obesity are traits which inheritance cannot be attenuated by weight reduction techniques. It should be emphasized that bariatric procedures are reserved to patients with morbid obesity, and accordingly women who are selected for bariatric surgery may be the more extreme cases. Indeed, most women following bariatric surgery in our population are still suffering from obesity [16, 18]. Even though intrauterine exposures influenced by weight during pregnancy are of major importance, we need to keep in mind that there are other factors such as maternal lifestyle, genetics and epi-genetics that can also contribute to the long-term risk of the child [25]. Also, bariatric surgery was associated with several pregnancy complications that were previously associated with endocrine morbidity of the offspring such as diabetes, preeclampsia and prematurity [26–28]. Specifically, it is well established that exposure to gestational diabetes mellitus is a risk factor for long-term endocrine morbidity in the offspring [26, 27].

Nevertheless, to address possible confounding factors related to the mother's characteristics, we included in all models prior maternal-related comorbidities, such as diabetes mellitus, gestational age and hypertensive disorders of pregnancy. Controlling for these factors and others, an independent and significant association between bariatric surgery of the mothers and long-term endocrine morbidity of the offspring was noted.

Indeed, qualification for bariatric surgery in our population as well as in most areas includes morbid obesity, i.e., BMI ≥ 40, or BMI ≥ 35 and at least two obesity-related comorbidities such as T2D mellitus, hypertension, sleep apnea and other respiratory disorders, non-alcoholic fatty liver disease, lipid abnormalities, gastrointestinal disorders, or heart disease [20, 24].

The increased long-term endocrine morbidity risk in offspring to mothers who underwent bariatric surgery may be explained by several theories. These include genetic or epigenetic predisposition leading to inter-generational passage of metabolic risk following exposure to maternal obesity (these women undoubtedly weighted more than women in the obesity group), metabolic and physiological differences in the intrauterine environment, and environmental factors [29–31]. Maternal obesity and hyperglycemia may contribute to in utero over-nutrition and metabolic changes including fetal hyperinsulinemia [30, 31]. Exposure to the adverse in utero environment may result in epigenetic changes resulting in altered structure and function of a range of organs and control systems in the offspring. This may contribute toward the increased long-term endocrine disease of the offspring such as obesity, glucose intolerance, and dyslipidemia [31]. Furthermore, some fraction of the women who underwent bariatric surgery may also be either irresponsive to intervention or, despite weight loss, still suffer from significant obesity; thus, their offspring will be affected similarly to women with obesity and without previous bariatric surgery.

Study limitations

The main strength of the study lies in the fact that our hospital serves the entire population of southern Israel. Our hospital provides both maternity services and pediatric services. Therefore, as long as a mother and child live in this area, they would be treated in this hospital. However, our study has several limitations. Those endocrine conditions can be diagnosed and treated in the community and, thus, the ascertainment of children who were never treated in the hospital at one time or another could not be accomplished. Children who in fact had a diagnosis of endocrine morbidity but did not encounter the hospital for any reason during the follow-up were missed, leading to an underestimation of the prevalence of endocrine morbidity. In any case, there seems to be no reason to suspect differential rates of such cases between the study groups.

While better estimates of the morbidities could be found in community clinics specializing in each condition, the regional hospital database is still the most comprehensive database for covering both the entire population of southern Israel and this variety of conditions. The conditions included in the study could be accompanied by comorbidities and, therefore, are likely to necessitate hospital encounter at one time or another. Furthermore, it is common practice that physicians add any chronic condition that has been diagnosed in the community to the medical chart, even when the primary indication for hospitalization is not due to an endocrine condition. Other limitations of our study are unavailability of data regarding BMI, time since the procedure and other important characteristics such as maternal weight trajectory following bariatric intervention, cholesterol and blood glucose levels.

Conclusions

In this large population-based study, offspring of mothers with obesity as well as of mothers with previous bariatric surgery were found to be in an independent increased risk for pediatric long-term endocrine morbidity. Further studies should focus on bariatric surgery of mothers while investigating the actual BMI influence on long-term endocrine morbidity of offspring.

Compliance with ethical standards

Conflict of interest The authors have no commercial associations that might be a conflict of interest in relation to this article.

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