

Offspring born after maternal bariatric surgery

PhD thesis presented online on the 16th of December 2020 in a joint PhD project VUB-KUL

Karolien Van De Maele^{a,b,c,e}

Promoters: Inge Gies^{a,c}, Roland Devlieger^{b,d}

^a Division of Pediatric Endocrinology, Department of Pediatrics, University Hospital Brussels, Jette, Belgium

^b Research unit Organ Systems, Department of Development and Regeneration, Catholic University of Leuven, Leuven, Belgium

^c Research unit GRON, Free University of Brussels, Jette, Belgium

^d Department of Obstetrics and Gynecology, University Hospital of Leuven, Leuven, Belgium

^e University of Antwerp, Antwerp University Hospital, Department of Pediatrics

Karolien.vandemaele@uza.be

Keywords

Maternal obesity, maternal bariatric surgery, childhood obesity

The main topic of this thesis revolves around a better understanding of the long-term effects on the offspring of women who underwent bariatric surgery before their pregnancy. Pregnant women with obesity (BMI ≥ 30 kg/m² at start of the pregnancy) have been a growing population of interest because their offspring is at risk for development of childhood obesity, an adverse metabolic and inflammatory profile and possible premature cardiovascular morbidity. Since bariatric procedures have been relatively "new", there is still a lack of scientific data on the long-term outcomes in the offspring. However, the management of obesity and its associated comorbidities (such as diabetes and cardiovascular diseases) and a better understanding of the intergenerational programming circle remain a huge challenge for current health care systems around the world.

To gain insight in the topic, the first aim was to review the existing literature and knowledge. Since the offspring of women with obesity during their pregnancy have been exposed to an altered intra-uterine environment, a subsequent influence on the cardiovascular development during fetal life is assumed (1). Based on animal studies, different contributing mechanisms have been hypothesized. Insulin resistance, increased levels of leptin, chronic inflammatory state, perturbation of sympathetic tone and epigenetic modifications contribute to a suboptimal nutrient environment and changed hemodynamics. The ensuing aberrant cardiomyocyte development, impaired endothelial cell relaxation and atherogenic lipid profile put the children of mothers with obesity during pregnancy at risk for the development of endothelial cell dysfunction. Increasing possibilities for the early detection of this preliminary stage of atherosclerotic disease and the proven reversibility of this condition make it an excellent prevention and treatment target.

Since many questions remain unanswered about the actual endothelial cell function in the offspring of mothers with obesity, we designed the EFFECTOR-study as a cross-sectional cohort study (children aged 4 -12 years old) (2). We compared the offspring born after maternal bariatric surgery to the offspring of a group of women with overweight or obesity during pregnancy and the offspring of a group of women with normal weight during pregnancy. A prospective data collection was performed to gain insight in the body composition, metabolic and inflammatory state as well as the vascular function (measured by peripheral arterial tonometry) of the children. In the following paragraphs, we elaborate on the outcomes of the EFFECTOR-study per topic.

Non-therapeutic research and especially long-term follow-up studies are characterized by challenging inclusion processes. Therefore, the second aim of this PhD research was to develop a study framework to maximize the

participation of the children. All study documents and measurements were assembled into a superhero framework, to make the study attractive and as child-friendly as possible. Children received age-appropriate information before the study visit by a visually attractive assent and a short superhero video. During the study visit, the investigator used a sticker diploma and provided a superhero-cape for the toddlers. The children were actively involved during the study visit. 294 eligible subjects were contacted by mail and subsequently by phone. One hundred and seven children were lost- to-follow-up because of changed postal address or phone number (5 to 11 years gap between original and follow-up study). From the 187 remaining subjects another 44 parents refused to participate. Resulting in an overall participation rate of 143 out of 294 eligible study subjects (48%) or 143 out of 187 subjects reached by phone (76.5%) (3).

As a first topic, we studied the body composition and psychomotor development of the children born after maternal bariatric surgery. In order to have comparable subgroups, the children of the bariatric surgery group (BS) were matched based on pre-pregnancy body mass index (BMI) to children from mothers that had overweight or obesity during pregnancy (OW/OB). A third control group consisted of children whose mothers had a normal weight during pregnancy (NW). The children born after bariatric surgery (n = 36) presented with the highest body weight SD (standard deviation) score, BMI SD scores, excess in body fat percentage and waist circumference SD score in comparison to the matched OW/OB offspring (n = 36) or NW offspring (n = 35) (figure). Despite a comparable school career, the parents of the BS group reported more behavior problems. The Strength and Difficulties Questionnaire revealed a higher amount of overall problems in the BS offspring as well as higher Externalizing score at the Child Behavior Checklist (4).

The mean interval between surgery and pregnancy was almost 4 years; 22% of the women got pregnant within the first year after the weight-loss procedure. The majority of the women underwent a Gastric Bypass Surgery (n=24; 66.7%), the others underwent a laparoscopic adjustable gastric banding (LABG) (n=10; 27.8%) or a Scopinaro Procedure (n=2; 5.6%). The difference in maternal BMI (pre-surgery to pre-pregnancy) was comparable in all studied BS women. However, since a Gastric Sleeve is currently the most performed intervention in women of a childbearing age; future research should aim to include these women as well and compare the different weight-loss interventions.

A second studied topic was the eating habits and meal pattern of the BS children. Since we know that women after bariatric surgery can have worrisome eating habits, we were interested in the eating habits of their

children. For these outcomes we did not perform a matching since we did not focus on neonatal outcomes (total n = 142; BS n = 36; OW/OB n = 71; NW n = 35). Meal-skipping behavior was comparable between the groups. We did not find any difference in fruit and vegetable consumption. We did find that the BS group consumed more low-calorie sweetened beverages compared to the NW group but less fruit juice compared to the NW and OW/OB groups. We hypothesized that these results may indicate a sugar-avoiding behavior in children of the BS group, fitting dietary maternal habits in a strategy to prevent dumping syndrome (5).

A third topic revolved around the vascular function of the BS children, measured by a non-invasive manner by peripheral arterial tonometry (PAT). Since the feasibility and discomfort related to this technique has mainly been studied in adults and adolescents, we collected Faces Pain Scale (FPS-R) data in 109 children. We compared the reported discomfort and pain after PAT measurement to calliper and ultrasound examination of peripheral skinfolds. We found that the proportion of higher FPS-R after PAT was significantly higher than the pain experienced after calliper measurements of peripheral skinfolds. 59 of the 109 children (54.1%) did not experience any pain. The reactive hyperemia index (RHI) could be calculated in 111 out of 142 performed PAT measurements (success rate of 78.2% in a group of children with a median age of 10.5 years old). The most frequently reported error messages by the software was a signal that was "too noisy" and/or "poor quality". The success rate was higher in children aged older than 6 years (83.1% versus 44.4%; $p < 0.001$).

Since we hypothesized that bariatric surgery before pregnancy might influence the endothelial function in the offspring, we wanted to study this with the PAT measurements. Children of the BS group had a higher diastolic blood pressure SDS and a lower RHI compared to the children of the OW/OB and NW group. After log transforming the data and correcting it for the child's age, the weight SDS, the BMI SDS, body fat percentage and diastolic blood pressure SDS, RHI was comparable between the groups. Therefore, we were not able to demonstrate a disturbed endothelial function in pre-pubertal BS children, when their increased diastolic blood pressure and degree of adiposity was taken into account (6).

All of these above-mentioned findings stress the vulnerability of the offspring born after maternal bariatric surgery. The different findings presented in this thesis underline the susceptibility of certain families for an intergenerational, vicious circle of obesity and oblige us to view this disease as a multifactorial entity. The presented data support the idea that bariatric surgery can not be perceived as "a holy grail" solving everything for these women and all their future generations. Therefore, we urge health care workers across different specialties to bundle forces in order to prevent obesity in women of childbearing age and provide a stable and accessible environment for health care without stigmatizing. Emphasis should be made on performing pre-conceptual counseling before surgery, improving the lifestyle of women after bariatric surgery and giving advice to postpone a pregnancy until two years after surgery. In addition, future research and clinical practice should aim to provide a regular, prospective follow-up for the children born after maternal pre-pregnancy bariatric surgery.

REFERENCES:

1. Van De Maele K, Devlieger R, Gies I. In utero programming and early detection of cardiovascular disease in the offspring of mothers with obesity. *Atherosclerosis*. 2018;275:182-95.
2. Van De Maele K, Gies I, Devlieger R. Effect of bariatric surgery before pregnancy on the vascular function in the offspring: protocol of a cross-sectional follow-up study. *BMJ Paediatr Open*. 2019;3(1):e000405.
3. Van De Maele K, Devlieger R, Gies I. How to Maximize Children's Involvement in Non-therapeutic Research-Lessons Learnt From EFFECTOR. *Front Pediatr*. 2020;8:47.
4. Van De Maele K, Bogaerts A, De Schepper J, Provyn S, Ceulemans D, Guelinckx I, et al. Adiposity, psychomotor and behaviour outcomes of children born after maternal bariatric surgery. *Pediatr Obes*. 2020:e12749.
5. Van De Maele K, De Geyter C, Vandenplas Y, Gies I, Devlieger R. Eating Habits of Children Born after Maternal Bariatric Surgery. *Nutrients*. 2020;12(9).
6. Van De Maele K, Devlieger R, De Schepper J, Gies I. Endothelial function and its determinants in children born after maternal bariatric surgery. *Pediatr Res*. 2021 Apr 9. doi: 10.1038/s41390-021-01500-y. Online ahead of print.

Figure : Comparison of adiposity profile of children born after maternal bariatric surgery to offspring of obese/overweight women and normal weight women

