

Effect of bariatric surgery before pregnancy on the vascular function in the offspring: protocol of a cross-sectional follow-up study

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ABSTRACT

Background The offspring of obese pregnant women are at risk for adverse metabolic, inflammatory and cardiovascular programming. Comprehensive long-term data are lacking on the contribution of changes in maternal weight after bariatric surgery before pregnancy compared with lifestyle interventions during pregnancy on the cardiovascular programming of the offspring.

Methods EFFECTOR is designed as a cross-sectional cohort follow-up study targeting the children of different groups of women who were previously studied during their pregnancy. Four subgroups of children are identified, based on maternal weight characteristics during pregnancy: normal weight women, obese women without any intervention and obese women who underwent a lifestyle intervention during or bariatric surgery before pregnancy. Data collection is performed as a single study visit at home. Data on the sociodemographic situation, food habits and psychomotor development are obtained through questionnaires. During the home visit, extensive anthropometric and vascular assessment is performed. Information on body composition is provided by assessment of body weight and height, bioelectrical impedance analysis, skinfold measurements and ultrasound. Endothelial function is measured by non-invasive peripheral arterial tonometry (EndoPAT 2000). Biomarkers performed in blood and urinalysis conclude the data collection process.

Trial registration number NCT02992106 (Pre-results).

INTRODUCTION

According to WHO, tackling childhood obesity is one of the major global public health challenges of this century.¹ Because of a consequently rising incidence of associated diseases, for example, cardiovascular diseases and diabetes, overweight and obesity are seen to be an origin of a continuously intergenerational challenge in the healthcare of future generations.

The research field on maternal obesity is of broad and current interest since there are known adverse outcomes for the offspring both in short and long term. There is an increased risk of large for gestational age or

macrosomia, delivery by caesarean section, admission to a neonatal care unit and still-birth.^{2,3} Several hypotheses have been formulated trying to identify the in utero origin of long-term adverse metabolic effects on the offspring, including a tendency to insulin resistance, adverse body composition and lipid profile and chronic state of low-grade inflammation.⁴⁻⁹

In order to influence these in utero programming processes, the preconception period and early pregnancy are considered as a window of opportunity for healthcare providers. Consensus on the long-term effects of a lifestyle intervention during pregnancy in the offspring is conflicting since most studies use a different methodology making it difficult to draw unambiguous conclusions.¹⁰ Scarce data might point in the direction of less macrosomia and less obesity at childhood age.^{3,11,12} Furthermore, bariatric surgery is widely used when the desired weight loss cannot be obtained through a lifestyle intervention. The current evidence indicates favourable neonatal and long-term outcomes with less macrosomia and large for gestational age, less childhood obesity, favourable lipid profile and less chronic inflammation.¹³⁻¹⁵ Nevertheless, further research is needed to confirm these observed trends.

The cardiovascular effects on the offspring are often mentioned in the same sentence as the adverse metabolic effects but this research area has been studied significantly less. Endothelial cell dysfunction is the preliminary state of atherosclerosis that offers a window of opportunity for a healthcare intervention since the process is still reversible.¹⁶ Different hypotheses identify a probable fetal origin of the condition, programming the offspring of obese pregnant women for the early development of cardiovascular disease through altered fetal haemodynamics



and/or increased expression of vascular inflammation markers.^{5 9 17}

The EFFECTOR study is designed as a cross-sectional cohort follow-up study in the offspring of mothers followed in previous studies.^{11 18–23} The main outcome is the endothelial function of the offspring measured by non-invasive peripheral arterial tonometry (EndoPAT 2000). The overall objective is to compare the endothelial function of the offspring of mothers suffering from obesity; after they underwent bariatric surgery before pregnancy or a lifestyle intervention during pregnancy.

METHODS AND ANALYSIS

Study outcomes

The primary aim of the study is to compare the endothelial function (measured by peripheral arterial tonometry) in the offspring of mothers who underwent bariatric surgery before pregnancy to the endothelial function in the offspring of mothers with obesity during pregnancy.

Our secondary outcome consists of an assessment of body composition, metabolic and inflammatory profile in the offspring after bariatric surgery compared with the other subgroups.

Study design

The study is designed as a cross-sectional cohort study and the subjects are children of women that were recruited previously in different studies and have a maximum age of 11 years at the start of our study. The children are assigned to a specific subgroup based on the characteristics of their mother, but all subgroups undergo the same prospective data collection procedure. There is no randomisation or blinding procedure.

Patient and public involvement

Patients were not directly involved in the design of the study.

Study population and recruitment

The EFFECTOR study population will consist of children whose mothers were recruited in previous Flemish studies, supervised by the Ethical Committee of the University Hospital of Leuven. All of these mothers were well informed about possible follow-up studies at the time of the original study. For reasons of clarification, the children are arbitrarily assigned to a subgroup according to the characteristics of the original maternal cohort, identified as can be seen in [table 1](#).

The mothers will be contacted by letter or email, including an information brochure. Afterwards, they will be contacted by phone by an investigator to inform them thoroughly and answer all their questions. The inclusion process will start with the eldest children, going gradually down to the youngest ones.

Power calculation and statistics

The main primary outcome for the endothelial cell function is the Reactive Hyperaemia Index (RHI) measured by the EndoPAT device: a continuous variable, possibly not normally distributed. The power calculation is based on the existing literature and the subgroups where we expect the largest difference.^{9 24} Assuming a mean of 1.6 in the offspring of obese mothers without intervention compared with 1.9 in the normal weight group, with an SD of 0.05, assuming a participation rate of one in three (35%), that is, 45 children of obese mothers without intervention and 58 children in the control group, we have a power of 0.82 to demonstrate a statistically significant difference between the two groups (two-sided significance level <0.05, Mann-Whitney U test). If the actual difference in RHI would be larger, for example, 0.5 (1.4 vs 1.9), then the power of the test increases to 0.99.

A participation rate of 35% is feasible, based on reported response rates in literature and a high response rate (almost 50%) in a follow-up study that is actually

Table 1 Overview of original maternal cohorts and characteristics during pregnancy

Maternal pregnancy characteristics	Original cohort	Women in cohort	Recruitment
Bariatric surgery before pregnancy	Pregnancy after bariatric surgery cohort ²⁰	N=49	Five Flemish hospitals Inclusion before 15 weeks of gestation
	Bariatric surgery registration in women of reproductive age cohort ²²	Aim 200 (still recruiting)	Eight Flemish hospitals Inclusion before bariatric surgery
Normal weight	Bogaerts <i>et al</i> ¹⁸	N=156	Three regional Belgian hospitals
Overweight or obesity during pregnancy	Guelinckx <i>et al</i> ²¹	N=65	University Hospital of Leuven
	Bogaerts <i>et al</i> ¹⁸	N=63	Three regional Belgian hospitals
Overweight or obesity with lifestyle intervention during pregnancy	DALI cohort ^{23 29}	N=100	University Hospital of Leuven, part of European randomised controlled trial
	Guelinckx <i>et al</i> ²¹	N=130	University Hospital of Leuven

ongoing on the children of one of the original cohorts. With a participation rate of 35%, we subsequently have 80 children of obese mothers with lifestyle intervention and 87 children of mothers after bariatric surgery, so in total 270 children. Comparing the other subgroups will be exploratory, no formal hypotheses are available in the literature.

The statistical analysis will be performed by using an intention-to-treat principle. The statistical software package IBM SPSS V.24 will be used for the analyses. Descriptive statistics will be used for the description of the study population at baseline. RHI will be assessed as continuous variable. Linear regression will be used if the Gauss-Markov assumptions can be met. Otherwise, quantile regression will be used. The association between continuous explanatory variables and the outcome RHI will be assessed using splines or loess smoothers. Explanatory variables are at least the four groups (obese no intervention, obese lifestyle intervention, bariatric and control), children's age, children's body mass index (BMI), children's metabolic profile, children's eating behaviour, sociodemographic characteristics.

Data collection process

Secondary data analysis

After obtaining a written informed consent, this section of data collection will ensue by collecting available data from the previous studies. The collection of these data took place in a prospective manner at the time of the previous studies. The collection of these data will give us the opportunity to set a point of origin for all the children that will participate in our study.

The secondary data consist of the following data: maternal prepregnancy weight, pregnancy weight gain, pregnancy and birth outcomes such as pregnancy duration and birth weight, relevant medical (and obstetric) history (previous bariatric surgery, identification of any pregnancy lifestyle intervention, pre-eclampsia); biochemical data (white cell count, glucose metabolism screening and C reactive protein (CRP) at time of delivery).

Prospective data collection

Data will be obtained by performing a single home visit for approximately 90 min to gather additional data independently from the age of the child at that time (depends on the year when the mother was included in the previous study). An overview of the study intervention can be seen in [figure 1](#). This intervention is identical for all the subgroups of the cohort and will contain the following parts:

Peripheral arterial tonometry

Pulse wave amplitude will be measured by using a finger plethysmograph (peripheral arterial tonometry) by using the EndoPAT device from Itamar Medical. Briefly explained, both index fingers of the patient are placed in the pneumatic probes. First, the device performs 5 min

of baseline measurement and thereafter a blood pressure cuff occludes the arterial flow of the arm for 5 min. After a rapid deflation of the cuff, a reactive hyperaemia takes place, which is a measure for the arterial endothelial function. There is a concomitant software package. Children on growth hormone treatment will be excluded for the test with the EndoPAT, since this drug influences the test result.²⁵ If there is an infection ongoing, the examination will be postponed for 2 weeks. Since taking a blood sample can influence the test results as well, the blood sample will be done after the test with the EndoPAT device.²⁵

Anthropometric data

The anthropometric data will consist of weight and height, four site skinfold measurement, neck, waist and hip circumference, body composition by bioelectrical impedance analysis (BIA), ultrasound and blood pressure. Standing height will be measured using a portable stadiometer with a movable headboard and vertical backboard (Seca 217, SECA, Hamburg, Germany). The body weight and total body fat percentage will be assessed by using a BIA (Tanita MC-780U). BMI will be calculated from measured weight and height and expressed as SDS according to the Flemish growth charts. Pubertal development will be assessed according to Tanner stages. Skinfold measurements will be performed at biceps, triceps, subscapular and supriliac site with a Harpenden skinfold caliper (Baty international, RH15 9LB England). A portable ultrasound device with a linear probe 7.5 MHz (Mindray, Diagnostic Ultrasound System, model M 7) will be used to measure the abdominal subcutaneous fat thickness at the four sites of the skinfold measurements. The girths of neck, abdomen and hip will be measured with a flexible Lufkin steel anthropometric tape (Lufkin W606PM). Blood pressure will be measured using a Mindray VS-900. After performing the measurements with the EndoPAT device, Harpenden caliper and ultrasound, the children will be asked to fill out a Faces Pain Scale, validated for children aged 4–16 years old and obtained for use from the International Association for the Study of Pain.²⁶ The International Standards for Anthropometric Assessment set by the International Society for the Advancement of Kinanthropometry and standard operation procedures will be taken into account to ensure data quality.²⁷

Biochemical data

A blood sample will be taken by a venipuncture after an overnight of fastening. The serum samples will be stored in appropriate manner during transportation to be processed in a centralised laboratory. All laboratory analyses will be performed by using the laboratory techniques available in the University Hospital of Brussels. Following biochemical parameters will be determined: glucose, insulin, total cholesterol, Low Density Lipoprotein cholesterol (LDL), High Density Lipoprotein cholesterol (HDL), triglycerides, uric acid, IGF-1, adiponectin,



Figure 1 This figure provides a graphical overview of the data collection process as it was designed for the EFFECTOR study. BIA, bioelectrical impedance analysis; BMI, body mass index; hs-CRP, high-sensitivity C reactive protein; TNF, tumour necrosis factor alpha.

Table 2 Overview of used questionnaires in the data collection process with the purpose

Questionnaire	Who?	Purpose
Socodemographic (designed for the study)	All	Obtain family composition, education level and employment status of the parents, medical history and school level of the child.
Dutch Eating Behaviour ³⁰	All	Measurement of restrained, emotional and external eating.
Food Frequency ^{31–33}	All	Evaluation of food intake based on the frequency and portion size of 47 food items.
Developmental milestones (designed for the study—short 8-item)	All	Obtain child's age at achieving the most obvious developmental milestones.
Strengths and Difficulties Questionnaire ^{34–36}	All	Screening tool for mental health problems and common forms of psychopathology.
Developmental Coordination Disorder Questionnaire ³⁷	≥5 years	Detect Developmental Coordination Disorder (DCD) in children aged 5–15 years.
Ages and Stages Questionnaire ³⁸	≤5 years	Screening tool for neurodevelopmental disorders.
Paediatric Quality of Life Inventory ³⁹	≥6 years	Measure the health-related quality of life according to the core dimensions of health.
Children's Behaviour Questionnaire (very short form) ⁴⁰	≤6 years	Investigate temperament in preschool children.
Child Behaviour Checklist	≥6 years	Additional differentiating (eventual) psychopathology.

leptin, high-sensitivity CRP, IL-6, tumour necrosis factor alpha and ICAM-1.

A urine sample will be taken to evaluate the albumin to creatinine ratio. This urine sample will be a morning urine portion and we will ask the participants not to engage in physical activity in the preceding 48 hours. This method has been validated by Bartz *et al* and is considered an early marker of endothelial dysfunction.²⁸

Questionnaires data

Prior to the home visit, the parents will receive a web-based link to fill in the questionnaires. If they do not have a computer or internet available at their home, the investigator will offer them the chance to fill in the questionnaires on a laptop or tablet during the home visit. In order to avoid bias, the investigator will not provide them with any additional information. An overview of the used questionnaires is provided in [table 2](#).

ETHICS AND DISSEMINATION

Consent

The study will be conducted only after obtaining a prior informed consent of the legal representatives of the children and obtaining an assent of the children according to their age and maturity. The legal representatives of the children will sign an informed consent form and the assent of the children will be noted in the corresponding file. The informed consent form and the assent are reviewed and approved by the Ethics Committee prior to the start of recruitment.

The collection, processing and disclosure of personal data, such as patient health and medical information, is subject to compliance with applicable personal data protection and the processing of personal data (Directive

95/46/EC and Belgian law of 8 December 1992 on the Protection of the Privacy in relation to the Processing of Personal Data). The data will be coded. The research team will protect the data from disclosure outside the research according to the terms of the research protocol and the informed consent document. The subject's name or other identifiers will be stored separately from their research data and replaced with a unique code to create a new identity for the subject.

Safety

The venipuncture for the blood sample can cause transient pain, a syncope, a haematoma or a local skin infection. The peripheral arterial tonometry can cause a tingling feeling in the occluded arm that will disappear after deflation of the cuff. All of these aforementioned adverse events are not considered as serious adverse events. If they occur, however, they will be reported according to the rules of Good Clinical Practice in the case report form.

Publication policy

All publication rights of unprocessed and processed data belong to the investigators. The data are coded and treated confidential. Participant anonymity is guaranteed during the publication of the study results.

Contributors KVDM, IG and RD contributed to the design of the study. KVDM wrote the manuscript. IG and RD did a critical revision of the manuscript. The funding organisations performed a peer-review of the protocol.

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Competing interests None declared.

Patient consent Not required.

Ethics approval The study obtained approval from the central Ethics Committee UZ Brussels, which provides final ethical approval (22 February 2017), and the local Ethics Committee UZ Leuven/KU Leuven. The Faces Pain Scale was added as an amendment, which was approved by the Ethics Committee (15 January 2018). Changes to the study protocol will be submitted to the Ethics Committee and will not be performed before obtaining an approval.

Provenance and peer review Not commissioned; externally peer reviewed.

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