PROTOCOL

Pre-pregnant body mass index and complications in pregnancy and childbirth

-a study combining data from birth cohorts in Norway and Denmark

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Introduction

Worldwide, the prevalence of overweight and obesity has doubled over the last twenty years (1, 2). Body mass index (BMI) is a widely used measure of overweight and is calculated from weight in kilograms (kg) divided by the square of height (m²) (3). According to WHO, overweight is defined as BMI ≥ 25 kg/m² and obesity as BMI ≥ 30 kg/m² (3). In Norway more than 12% of women of reproductive age are obese (4), and in a regional population cohort from Norway, half of women in the age 30-39 years had a BMI ≥ 25 (5).

The increase of overweight and obesity in the reproductive part of the population has serious consequences for pregnancy, childbirth, postnatal care and for the child in the short and long term as it increases the risk of numerous complications (6-10). Obese pregnant women are at increased risk of developing diabetes, hypertension, preeclampsia, fetal congenital anomalies, stillbirth (11-15), infant death (10, 16) and low Apgar score in the newborn (17-19). Results from our first paper revealed a two to three-fold increased risk of perinatal mortality in women with a pre-pregnant BMI ≥30 (20). Pre-pregnant obesity is associated with increased risk of post term pregnancy, induction of birth, failed induction, increased incidence of instrumental delivery and caesarean section (7, 21). Pre-pregnant BMI and gestational weight gain both seem to be factors influencing the outcome (22-24).

Moderate gestational weight gain is associated with a reduced risk of adverse pregnancy outcomes (24, 25), while excessive weight may be an independent factor increasing the risk of complications during delivery (24). However, the effects of gestational weight gain on pregnancy outcome seem to depend on pre-pregnant BMI (23, 25). A low weight gain during pregnancy seems to be protective in obese women (23).

The importance of physical activity in promoting health and well-being in public health is crucial (26). Physical activity is likely to lower blood pressure, increase lipid metabolism, reduce oxidative stress, increase insulin sensitivity and therefore has the potential to reverse negative effects of obesity (26). There is evidence that moderate physical activity early in pregnancy improves placental growth and function and may have beneficial effects on
pregnancy (27, 28). Physical activity may reduce the risk of gestational diabetes mellitus and preeclampsia (26, 29, 30).

Overweight is a consequence of high energy intake combined with low physical activity level (3). However, the underlying causes of obesity seem to be a complex interplay between genes, behavior and environment (31). Overweight increases with increasing age and parity, and research shows that there is an inverse relationship between BMI and socioeconomic status, contributing to social inequalities in health. Several mechanisms have been proposed, though yet, no biological pathway has been established for the increased risk associated with overweight in pregnancy (17, 32). Compared with normal weight, studies of overweight pregnant women reveal an altered metabolism with dyslipidemia characterized by higher levels of triglycerides, lower HDL concentrations, hyperinsulinemia, elevated leptin concentration and low-grade inflammation, known as the metabolic syndrome (33). This is likely to affect the blood- and nutrient flow in placenta and to the developing fetus (33), predispose to hypertension, preeclampsia and gestational diabetes mellitus in pregnancy and may cause dysfunctional uterine activity in labour (17).

The health of women of reproductive age is a crucial factor for future public health (3). It is therefore important to examine obesity as a health determinant and risk factor in order to find effective health promoting measures.

**Objective**

The aim of this study is to:

1) Estimate the risk of low 5 minute Apgar score and admission to neonatal intensive care unit, according to maternal pre-pregnant body mass index.
2) Estimate the risk of uterine atony according to pre-pregnant body mass index.
3) Assess the moderating effect of gestational weight gain and recreational physical activity in pregnancy upon the above associations.

**Hypotheses**

We hypothesize that:

1) There is an association between pre-pregnant body mass index and the risk of low 5 minute Apgar score in the newborn, admission to the neonatal intensive care unit and uterine atony.
2) Gestational weight gain and physical activity during pregnancy may moderate these associations.
Methods and materials

Design
Our study is a prospective observational cohort study using data from: 1) The Norwegian Mother and Child Cohort Study (MoBa) linked with data from the Medical Birth Registry of Norway (MBRN) and 2) The Danish National Birth Cohort (DNBC) linked with data from the Medical Birth Registry in Denmark (MBRD).

Data
*The Danish National Birth Cohort (DNBC)*
DNBC is a nationwide study including a total of 100,418 pregnancies and women were enrolled between 1996 and 2002 (34, 35). The number of pregnancies resulting in the birth of a single live-born child was 92,670. Exposure variables are obtained from the first (week 12) and second (week 30) computerized telephone interviews and from the postnatal telephone interview when the child was 6 months old (34).

*The Norwegian Mother and Child Cohort Study (MoBa)*
MoBa is a nationwide study including 109,000 children, 91,000 women and 71,700 men and women were enrolled between 1999 and 2008 (36, 37). Exposure variables are obtained from self-reported (self-administered) questionnaire Q1 completed in pregnancy week 13-17, Q3 completed in pregnancy week 30 and Q4 answered when the child was 6 months old (37).

*Medical Birth Registry in Norway and Denmark*
Information on pregnancy outcome and maternal comorbidities is based on data from the Medical Birth Registry in Norway and Denmark, which have been linked to MoBa and DNBC by the personal identification numbers (35, 36, 38).

Study population
The study population consists of pregnant women with singleton pregnancies, giving birth ≥ 37 week gestational week, with no serious congenital anomalies in the fetus, with information on pre-pregnant BMI and with pregnancies resulting in a live born child.

Participation in MoBa and DNBC was voluntary and informed consent was obtained from each participant upon recruitment (35, 36). Only already collected data from MoBa, DNBC and linked data from the medical birth registries will be used.

Exposures
Main exposure will be pre-pregnant BMI calculated by:
- Pre-pregnant height
- Pre-pregnant weight
BMI will be categorized according to WHO (3) in underweight (<18.5), normal weight (18.5-24.9), overweight (25-24.9), obese I (30-34.9), obese II (35-39.9) and obese III (≥40).
Parity
Marital status
Maternal age
Maternal comorbidities (hypertension, diabetes mellitus, preeclampsia)
Birth weight
Gender
Gestational age (according to ultrasound or in case of missing according to last menstrual period)
Fetal congenital anomalies

Maternal and fetal diagnoses will be identified and classified according to the diagnoses of The International Classification of Diseases (ICD)-10 codes.

Life style
Smoking
Weight gain in pregnancy (reported when the child was 6 months old)
Physical activity during pregnancy
Maternal occupation

Outcome
Apgar score at 5 minute (continuous in nature) and admission to neonatal intensive care unit (dichotome) will be the main outcomes in our first paper. The variables are registered in the Medical Birth registry of Norway and Denmark.

The outcome in the second paper will be uterine atony defined as vaginal bleeding ≥ 500 ml registered in the Medical Birth registry of Norway and Denmark.

Modifying variables
Maternal gestational weight gain
Physical activity in pregnancy

Statistics
Data will be analyzed by using standard statistical methods appropriate for the type of outcome variables. Categorical data will be analyzed by stratification and logistic regression that enables adjustment for confounders. Continuous data will be analyzed by linear regression and adjusted for confounders. Also correlation coefficients may be calculated as well as partial correlation coefficients that enables adjustment for confounders. The group holds extensive knowledge in methodology and statistical analyses as well as extensive experience in use of various analytical methods and statistical packages such as SPSS, STATA and R. Plotting of results and creation of figures will be performed in Sigma-Plot.
Collaborators

Linn Marie Sørbye, midwife and Master in health promotion and health psychology, is a PhD candidate in this project. She is a member of the research group “Registry based studies of familial risks” at the Department of Global Public Health and Primary Care at the University of Bergen, Norway. Professor Rolv Skjerven is the leader of the research group and will be assisting supervisor in the project. Associate professor Nils-Halvdan Morken (Department of Clinical Sciences, University of Bergen, Norway) is a specialist in obstetrics and will be the main supervisor. Professor Kari Klungsøyr (The Institute of Global Public Health and Primary Care, University of Bergen, Norway) will be assisting supervisor. Associate professor Nils-Halvdan Morken (Department of Clinical Sciences, University of Bergen, Norway) is a specialist in obstetrics and will be the main supervisor. Professor Ellen Aagaard Nøhr (Institute of Clinical Research, University of Southern Denmark) is together with Sørbye the formal applicant for the DNBC data. The other collaborators are Katrine Mari Owe (The Norwegian Advisory Unit on Women’s Health, Oslo University Hospital, Rikshospitalet, Norway) and Mette Juhl (Department of Public Health, Copenhagen University, Denmark).

Data management

After having received data from Denmark by safe transfer, data from the two cohorts will be pooled by Linn Marie Sørbye at The Department of Global Public Health and Primary Care, University of Bergen. The Danish data will have been through an additional encryption, and only professor Ellen Aagard Nøhr will have the key file, making it possible to link the Danish cohort data. For defining variables, we will make use of the programmes prepared by MOBAND (39). Data will be stored in a safe server according to ethical principles for sensitive data. After the end of the project, the pooled dataset will be deleted.

There has been sent an application for this project to The Danish Data Protection Agency. The approval will be forwarded as soon as we receive this confirmation.

Time schedule

The PhD project is fully financed from 14 September 2015 to 13 September 2018 by The Norwegian Advisory Unit on Women’s Health, Oslo University Hospital, Rikshospitalet, Norway.

The project has been approved by the MoBa Steering Committee (PDB591) and by the Regional Ethical Review Board in the Western Region of Norway (Refno 2015/1703/REK vest). The Norwegian data has already been handed over to the research group.

Analytic work and draft preparation will begin as soon as data from the Danish National Birth Cohort (DNBC) and linked data from the Medical Birth Registry in Denmark (MBRD) has arrived.
The following two articles are planned as part of the Phd project of Linn Marie Sørbye:

1) Pre-pregnant BMI and the risk of low Apgar score and admission to the neonatal intensive care unit. Can weight gain and physical activity in pregnancy modify the risk?

2) Pre-pregnant BMI and uterine atony. Can weight gain and physical activity in pregnancy have a modifying effect?

We expect all analyses to be published by September 2018.

References

18. Cedergren M. Maternal morbid obesity and the risk of adverse pregnancy outcome. Obstet &


