Associations between maternal first trimester SIMPLE nutritional score, early placental markers and pregnancy outcome: a prospective multicenter Italian study (SIMPLE study) protocol

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Abstract

Currently, the adherence to nutritional guidelines is critically low, with alarming rates of obesity worldwide and micronutrient deficiencies documented even in industrialized countries. As a consequence, nutritional screening and counselling represent a critical subject in early pregnancy, aiming to improve pregnancy outcome and population health. In this setting, the development of a simple and reproducible nutritional checklist is of utmost importance. The Simple Study is a longitudinal prospective multicenter study aiming to identify the associations between nutritional habits in the first trimester, early markers of placental function, and pregnancy outcome on a large population of singleton pregnancies in Italy. Ongoing healthy singleton pregnancies will be enrolled at the ultrasound scan of the first trimester combined screening test (11+0-13+6 gestational weeks). A nutritional score measuring the adherence to a healthy diet and nutritional deficiencies will be collected at recruitment. Fetal (crown-rump length, nuchal translucency, biparietal diameter, femur length) and utero-placental (placental volume, uterine arteries Doppler velocimetry) ultrasound data and biochemical placental markers (Pregnancy Associated Plasma Protein A (PAPP-A), free ß-Human Chorionic Gonadotropin (HCG)) will be collected. Second and third trimester ultrasound records and birth outcomes will be recorded from medical registers. The present study will set the stage for introducing a reproducible, time-saving and low-cost nutritional screening in pregnancy. The nutritional score will allow the implementation of specific corrective measures with potential large impact on placentation and pregnancy outcome.

INTRODUCTION

Starting with the Barker's hypothesis in the early 90', maternal nutrition during pregnancy has been recognized as a crucial determinant of placental function and intrauterine growth, with long-lasting and intergenerational effects on future disease risk profile of the offspring (1-4). This long-term "programming" of future health status has been related to maternal nutritional exposures mainly through epigenetic modifications, that could realize both before conception -by affecting the process of gametogenesis- and during pregnancy (5,6).

Currently, the adherence to nutritional guidelines is dangerously low, with alarming rates of obesity worldwide and micronutrient deficiencies that have been documented even in industrialized countries (7-10). Therefore, a universal nutritional counselling and screening represent a pivotal issue in early pregnancy, requiring proper evaluations in order to improve both individual and population health. In this setting, the development of a simple and reproducible nutritional checklist is of utmost importance.

In this context, a pilot study on 112 healthy women with singleton pregnancies and non-malformed outcome demonstrated that a first trimester nutritional score measuring the adherence to a healthy diet and lifestyle

in early pregnancy was significantly associated with first trimester biochemical and ultrasound markers of placental function (11). In particular, higher maternal nutritional scores were associated with increased serum pregnancy-associated plasma protein-A (PAPP-A) concentrations, lower uterine artery mean pulsatility index, and decreased placental volume at the first trimester screening ultrasound, whereas no associations were detected with free β-human chorionic gonadotropin (free β-HCG). The analysis on birth outcomes additionally showed a significant positive association between first trimester maternal nutritional score and gestational age at birth. These results provided the evidence of a strong association between maternal nutritional habits and pregnancy outcomes, possibly mediated by early impacts on placental function and development. Furthermore, this study possibly provided a simple clinical tool for an early nutritional screening deeply impacting on pregnancy outcome and clinical practice.

The Simple Study is a longitudinal prospective multicenter study designed to identify possible associations between first trimester maternal nutritional score, early markers of placental function, and pregnancy outcome on a large population of singleton pregnancies in Italy. In particular, the aims of the study are:

- to assess first trimester nutritional score and nutritional adequacy in a large population of singleton pregnancies;

- to investigate associations between first trimester maternal nutritional score and early markers of placental function and fetal growth;

- to evaluate associations between first trimester nutritional score and maternal, fetal and neonatal outcomes, including: birthweight, gestational age at birth, blood loss at delivery, gestational weight gain, adverse maternal (hypertensive disorders, gestational diabetes and cesarean section) and feto-neonatal outcomes (intrauterine growth restriction, preterm delivery).

METHODS

Study design

Multicenter prospective observational cohort study coordinated by" V. Buzzi" Children Hospital, Milan (Coordination Unit), and involving the following 20 Italian maternity units: "L. Sacco" University Hospital, Asst-Fbf-Sacco, Milan; "M.Melloni" University Hospital Asst-Fbf-Sacco, Milan; S.Pio X, Humanitas University Hospital, Milan; "Careggi" University Hospital, Florence; "Santa Maria della Misericordia" University Hospital, Perugia; "Sant'Anna" University Hospital, Torino; Modena Polyclinic University Hospital, Modena; "G. Martino" University Hospital, Messina; "San Matteo" Hospital, Pavia; "Arcispedale Sant'Anna" University Hospital, Ferrara; "V. Emanuele" University Hospital, Catania; "Cisanello" University Hospital, Pisa; "Gemelli" University Hospital, Rome; "Ospedali Riuniti" University Hospital, Foggia; Verona Polyclinic University Hospital, Verona; Bari Polyclinic University Hospital, Bari; "Vanvitelli" University Hospital, Naples; "Federico II" University Hospital, Naples; San Salvatore University Hospital, L'Aquila.

Each participating center has access to a database and all patients are prospectively registered by trained operators.

After the study protocol presentation in January 2021, a monthly newsletter with regular update on the research status and recruitment is sent to all centers. The Coordination Unit will monitor the case reporting and completeness of data collection for all the participating centers on a monthly basis. The final statistical analyses will be performed by the Coordination Unit.

Study population and sample recruitment

Eligible patients will be enrolled during the ultrasound scan of the first trimester combined screening test for aneuploidies (11-13^{+6} weeks), according to the following inclusion criteria: singleton viable pregnancy undergoing prenatal screening, gestational age between 11 and 13^{+6} weeks of pregnancy, further confirmed by a crown-rump length (CRL) measurement of 45-84 mm, and signed written informed consent. Language barrier, any known maternal disease or required chronic therapy, oocyte donation pregnancy, as well as fetal congenital anomalies and aneuploidies confirmed at birth, represent the exclusion criteria.

Figure 1 summarizes the study step points with maternal, fetal and neonatal data collection.

At enrollment, all women will fill a general questionnaire covering details on age, pregestational body mass index (BMI), ethnicity, mode of conception, lifestyle habits, family and personal history. A modified version of the nutritional checklist developed by the International Federation of Gynecology and Obstetrics (FIGO) in 2015 will be used to provide a 0 to 10 nutritional score measuring the adherence to a healthy diet and lifestyle, as presented in Figure 2. Additional adaptations of the checklist are based on the Italian guidelines on maternal nutrition during pregnancy, including one additional question on the consumption of iodized salt and the modified recommended intake of fruit and vegetables to five portions per day. In detail, the FIGO Nutrition Checklist consists of four sections covering 1. specific dietary requirements (e.g. diet or allergy), 2. BMI calculation, 3. diet quality, and 4. specific micronutrients deficiency queries (e.g. folic acid), thus giving the healthcare providers the possibility to collect baseline information on maternal nutritional status and to promote conversations about nutrition during pregnancy. A one-point score is calculated in case of affirmative answer for: consumption of meat 2–3 times per week, fruit and vegetables at least 5 times per day, fish 1–2 times per week, dairy products daily, whole cereals at least once per day, sweet and snacks less than 5 times per weeks, first trimester hemoglobin concentrations higher than 11 g/L, folic acid supplementation, use of iodized salt, and sun exposure at least 10–15 min per day. The questionnaire provides a final calculation of a 0 to 10 score, as the sum of single question scores.

As required by the first trimester combined screening test, biochemical parameters and fetal ultrasound parameters will be collected. Biochemical parameters, including serum pregnancy-associated plasma protein-A (PAPP-A) and free β-human chorionic gonadotropin (free β-HCG), will be obtained from one venous blood sample collected at 10 weeks of gestation, by using a solid-phase two-site sequential chemiluminescent immunometric assay (BRAHMS Kryptor, Hennigsdorf, Germany). All ultrasound measurements will be performed by a Fetal Medicine Foundation certified sonographer according to the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guidelines. In addition to parameters required for the combined screening test and including crown-rump length (CRL), nuchal translucency (NT), and biparietal diameter (BPD), transabdominal measurements of Doppler velocimetry of uterine arteries (UA) and two-dimensional placental volume will be performed. Transabdominal UA Doppler velocimetry is achieved identifying the artery along the uterine body from a midsagittal section and moving laterally to the paracervical vascular plexus (12). The two-dimensional estimated placental volume (EPV) measurement will be performed according to the formula proposed by Sonek J. et al, by acquiring assessment of placental width (measuring the distance among placental edges, perpendicular to surface of placenta), height (as distance from uteroplacental interface to line used to measure width) and thickness (as distance from uteroplacental interface to fetal surface of placenta) (13).

As required by national guidelines of low risk pregnancy care, second (20-22 weeks) and third (30-32 weeks) trimester ultrasound data of fetal biometry (BPD, HC, AC, FL) and Doppler velocimetry (uterine arteries doppler, fetal umbilical artery Doppler, fetal middle cerebral artery Doppler) will be obtained from medical records. Data on delivery outcomes, including gestational age, delivery mode, blood loss, neonatal data and placental weight will be recorded from medical registry or phone interview.

The recruitment process and follow up will last 30 months.

Data collection tool

Data will be collected online by using an IT platform named 'Datareg' and developed in collaboration with the University of Milan.

Sample size calculation

In a cohort of 2300 patients and for a normally distributed continuous outcome (i.e. ultrasound and biochemical parameters, birth weight), it is possible to detect with a type I error of 5% and a type II error of 20% (power 80%) a difference of 0.24 SD and 0.16 SD if 10% and 50% of all subjects has the relevant exposure respectively (i.e. nutritional score > 6).

Statistical analyses

All study variables will be described as median and range or mean and standard deviation for quantitative variables, and absolute and relative frequencies for categorical variables. A first trimester nutritional score representing the adherence to a healthy diet and lifestyle will be calculated as the sum of 10 questions. Bivariate correlations will be performed to investigate the associations between maternal baseline characteristics and the first trimester nutritional score. A multivariate analysis adjusted for confounding factors including pregestational BMI, age, gestational weight gain, smoking habit, ethnicity, and fetal sex, will be conducted to assess the associations between maternal nutritional status and study outcomes. The relative risk of adverse outcomes (e.g. low birth weight, gestational diabetes, hypertensive disorders and preterm birth) will be calculated in case of low nutritional scores in the nutritional questionnaire, considering a threshold of 6. P -values < 0.05 will be considered statistically significant. Statistical analyses will be performed using SPSS Statistics for Windows, Version 21.0 (IBM Corp. Armonk, New York, NY, USA) and R version 3.2.1 (The R Foundation for Statistical Computing).

ETHICS AND DISSEMINATION

Ethical considerations

Developed as a consequence of the Declaration of Helsinki, Ethical Principles regarding the conduct of clinical research involving humans (World Medical Association-WMA, 1964) and of the Oviedo Convention (EU, 1997) are required by the Italian NHS Research Ethics Committee.

Participants involved will be completely informed about the aim of the study and will be asked to sign an individual paper consent form. Women will be free to decline participation or to retire any moment. Data will be stored securely on hospital storage and IT platform protected by password (Data Protection Code, 2003; GDPR, 2018).

Ethical approval for this study was obtained from the Milano Area 1 Ethics Committee (N°46091, November 7^{th}, 2018) prior to the commencement of the research. All respondents will be provided the name, telephone number, and email of the Principal Investigator and the Iocal Review Board's contact details, in case of any question about the study.

Dissemination plan

The target audience for this study includes different stakeholders: clinicians, in particular Obstetricians and Midwives, policymakers, healthcare managers, researchers, and the public, especially women in their reproductive age.

The findings from this study would make a significant contribution to both obstetrics recommendations and knowledge, also as regards public health.

The dissemination plan includes the presentation of abstracts and findings at national and international scientific meetings.

Patient and public involvement

Women were not involved in the design of the study.

Women and their partners will be involved as participants after a detailed explanation of the study by a team researcher and will be fully informed about findings of the study.

Limitations of the study

The nutritional score is calculated in the late first trimester, when modifications of nutritional behaviors could not be excluded due to nausea or vomit. Subsequent changes in nutritional habits, exposures, and supplementation could impact on the observed pregnancy outcomes. In addition, energy intake, as a crucial component of nutritional habits and risk, might be relevant to know.

Implication for practice

The present study will provide findings about the utility of a very easy tool of nutritional screening to evaluate the most relevant nutritional deficiencies in pregnancy, with impacts on the first stages of placentation and pregnancy outcome, in a large Italian population of singleton pregnancies. A multicenter prospective observational study involving 22 Maternity Units would therefore make a significant contribution to this topic and public health, with a possible impact on future clinical routine care.

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