Title of Study:
Reproducibility of sonographic measurements of placental growth in the 2nd trimester.

Investigators
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Rationale
Three tests of placental function are now used in clinical practice in our high-risk clinic to define the risk of pregnancy complications, based upon our published research in 212 women\(^1\). These 3 tests are: a) re-interpretation of the first and second trimester maternal blood tests for Down's syndrome and spina bifida (PAPP-A, AFP, DIA, hCG), b) uterine artery Doppler, and c) placental morphology. In two recent publications from our group, the placental shape (small and thick = abnormal vs. long and thin = normal) was found to be a key risk factor for stillbirth and extreme preterm delivery (<32 weeks gestation)\(^2\)\(^-\)\(^3\). However these studies were conducted in high-risk women and the cut-off of a maximum placental length of 10cm to define abnormal was arbitrarily made by retrospective review of the ultrasound images. We need to conduct a standard reproducibility assessment of placental growth at the key time points of 16 weeks and 22 weeks in low-risk normal women, in order to define the cut-off values that assign under-development of the placenta. Several investigators are computing the 3-dimensional shape and volume of the placenta and assert that 3D measurements are superior to standard 2D assessment in real-time ultrasound\(^4\). We wish to add the 3D assessment of the placenta, as well as the "panoramic" modification of 2D ultrasound in order to produce a publishable reference range for these parameters, with the aim of a) deciding the optimal 2D assessment, and b) to determine if 3D confers any advantage over simpler 2D assessment. All of these measurements can be obtained in a short period of time (10 minutes) as the senior investigators (RW, Y-ML and JK) are all experienced in placental ultrasound. The imaging is low-intensity "gray-scale" and does not involve any high-intensity color Doppler of the fetus, nor does it apply any significant pressure to the maternal abdomen.

REFERENCES
Purpose

The purpose of this prospective cohort study is to evaluate the reproducibility of 2nd trimester ultrasound and Doppler assessment of placental function in women with normal pregnancies.

Population

The study population will include patients with normal First Trimester Screen (FTS) results and no medical or obstetric risk factors for placental insufficiency, identified by Dr Kingdom and his Nurse Practitioner (Anne Jordan) in the Perinatal Associates low-risk clinic at Mount Sinai Hospital.

Inclusion Criteria:

- Singleton pregnancy
- Normal FTS results (Nuchal translucency < 2 mm and PAPP-A > 1.0 MoM)
- < 16 weeks’ gestation

Exclusion criteria:

- Multiple pregnancy
- Major fetal anomaly
- Medical risk factor for placenta insufficiency syndrome, including: chronic hypertension, thrombophilia disorder (heterozygote factor V Leiden gene mutation, prothrombin gene mutation, elevated anti-cardiolipin antibodies [> 15 GPL], or presence of lupus anticoagulant), autoimmune disease (systemic lupus erythematosus, mixed connective tissue disorder, or type 1 diabetes) or advanced maternal age (≥40 years).
- Obstetric risk factor/s for placenta insufficiency, including: previous stillbirth at >20 weeks of gestation, extreme preterm delivery (<32 weeks of gestation), placental abruption, molar pregnancy, pre-eclampsia, birth weight <10th centile, or ≥3 miscarriages.
- Abnormal Quad MSS defined as:
  - AFP > 2.0 MoM
  - DIA > 2.0 MoM
  - Total hCG > 2.0 MoM
- Placenta previa
- Accessory lobe of the placenta
- Previous Cesarean delivery or any uterine scar
- Current or recent smoker (within 12 months of conception).
- Fibroids

Recruitment for this study will take place for one year from the date of approval, with the goal of consenting 100 eligible patients.
Procedures

Dr Kingdom or co-investigators will approach eligible subjects about the study at their 12-13 week first visit to Perinatal Associates. Patients will take the information home and decide on participation before their follow-up appointment at 15 weeks. Written informed consent will be obtained by Anne Jordan, RN or a co-investigator, but not by Dr Kingdom or any other Staff Physician providing clinical care.

At 15 weeks’ gestation, patients will undergo a Quad Maternal Serum Screening (MSS) blood test. If the Quad MSS is in the normal range, a trans-abdominal placental ultrasound scan and uterine artery Doppler assessment will be performed at 16 weeks’ gestation. This will include 2D measurements of placenta length, thickness, cord insertion and texture, a 3D assessment of placental volume, and measurements of the left and right uterine artery pulsatility index. Trans-abdominal ultrasound and uterine artery Doppler measurements, as above, will be re-assessed at a second time point between 20+0 and 22+6 weeks’ gestation.

Ultrasound and Doppler measurements will be carried out in triplicate by a Maternal-Fetal Medicine fellow (Renee Wong or Shay Porat), an ultrasound technician (Yee Man Lee), and a staff perinatologist (John Kingdom or Rory Windrim). These measurements will be used to derive intra- and inter-observer variation data.

The placenta will be sent to pathology for analysis after delivery.

Each patient’s chart will be reviewed, as well as the chart of their infants. We will collect relevant data, which includes:

- Patient demographic data (age, past medical history, ethnicity, previous obstetric history, drug history, and relevant family history)
- Pregnancy data (placental ultrasound and uterine artery Doppler measurements, nuchal translucency, First Trimester Screen results, Quad Maternal Serum Screening results, karyotyping)
- Details of the delivery and pregnancy outcome
- Pathology and autopsy result if applicable

Intervention

This is an observational study with no intervention, apart from additional sonographic measurements and blood tests.

Tests and Measurements

Patients will be offered the regular antenatal care and obstetrics ultrasound, according to the guidelines of the Society of Obstetricians and Gynecologists of Canada. In addition, patients will give a blood sample for the 16-week Quad MSS. This blood test is normally offered to women as part of routine clinical practice. Patients will also have
two additional standard placental ultrasound examinations (placental shape and uterine artery Doppler) at 16 weeks’ gestation and 20-22*6 weeks’ gestation. These are the same components of placental ultrasound currently in use in the Placenta Clinic at Mount Sinai Hospital for the evaluation of placental function in clinically high-risk women (REB#02-0079-E). There are no significant side effects or risks with these additional tests.

In the unlikely event that a patient (with a normal PAPP-A blood test result) is found to have the dual combination of bilateral (left/right) abnormal uterine artery Doppler and a small and/or thick placenta (<10cm long) they will be told that these findings place them at risk of complications of pregnancy due to "placental insufficiency" and be referred for a consultation to the Placenta Clinic as they would become eligible for the HEPRIN Trial (REB#06-0246-A).

**Risks and Benefits**

There are no risks attached to this study. The results of the study will add to our knowledge base on placental function and help identify those patients at low and high risk of placental disease and offer them an appropriate management plan.

**Proposed Data Analysis**

One hundred patients will be recruited for this study. Statistical analysis of intra- and inter-observer variations of placental size and volume will be performed using SAS and STATA software.

**Implications of Research**

This prospective cohort study will evaluate the reproducibility of sonographic measurements of placental size and assessment of uterine artery Doppler in the 2nd trimester. The standardization of placental function testing between sonographers will facilitate estimations of adverse pregnancy outcome risks due to placental dysfunction in the present pregnancy, and to offer an appropriate management plan.

**Ethical Issues or Concerns**

Confidentiality will be safeguarded by storing all patient data in a database on the hospital T: drive, protected by password access. Data will be accessible to Dr Kingdom and the co-investigators only.