Determination of Abnormal Fetal Growth or Amniotic Fluid with Third Trimester Ultrasounds in Uncomplicated Pregnancies: A Randomized Trial (UP Trial)

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Protocol

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PICO Question:

P: Women with uncomplicated pregnancies in the third trimester (30 weeks or more)

I: Ultrasound to assess fetal growth and amniotic fluid every 4 weeks, starting at 30 weeks.

C: Uncomplicated pregnancies who have clinically indicated obstetric ultrasound

O: Ultrasound diagnosis of abnormal growth or of abnormal amniotic fluid after 30 weeks.

1 Background

1.1 Abnormal Fetal Growth or Amniotic Fluid in 3rd Trimester

Abnormal fetal growth is defined as an estimate of less than 10% (fetal growth restriction; FGR) or greater than 90% (excessive growth) for gestational age. Amniotic fluid is considered to be low (oligohydramnios) if the single deepest vertical pocket is less than 2 cm or if amniotic fluid index is less than 5.0 cm, and it is regarded as being excessive (polyhydramnios) if the single deepest vertical pocket is greater than 8 cm or if the amniotic fluid index is $\geq$ 24 cm. The reason for accurately identifying these 4 conditions is that they are linked with adverse pregnancy outcomes, also known as peripartum complications. FGR, for example, is associated with stillbirth, cesarean for non-reassuring fetal heart rate tracing, neonatal seizure, sepsis, and neonatal death. Excessive fetal growth, also known as large for gestational age (LGA), or macrosomia, is associated with prolonged labor, cesarean delivery, traumatic birth, neurologic injury and death. Oligohydramnios is associated with stillbirth, emergency cesarean delivery, low Apgar score, and fetal anomalies. Lastly, polyhydramnios is associated with abruption, stillbirth, and postpartum hemorrhage (Table 1).

To minimize the complications with these four conditions, clinicians in the 3rd trimester have to identify these pregnancies, start antepartum surveillance, and time the delivery based on gestational age and the results of surveillance (Table 1).

Table 1. Abnormalities of fetal growth or of amniotic fluid

	Abnormalities of fetal growth		**Abnormalities of amniotic fluid**	
	FGR	**LGA**	**Oligohydramnios**	**Polyhydramnios**
Definition	Birth weight < 10% for GA	Birth weight > the 90% for GA	SDP $\leq$2.0 cm or AFI$\leq$ 5.0 cm	SDP $\geq$ 8 cm or AFI $\geq$ 24.0 cm
Rate in US	10%	10%	3%	7%
Increased risk of				

	Abnormalities of fetal growth		Abnormalities of amniotic fluid	
	FGR	**LGA**	**Oligohydramnios**	**Polyhydramnios**
Stillbirths	Yes	--	Yes	Yes
CD—NR FHRT	Yes	--	Yes	Yes
Traumatic birth	--	Yes	--	--
Neonatal seizure	Yes	--	--	--
Intubation	Yes	--	--	--
Neonatal death	Yes	Yes	Yes	Yes
Intervention to improve outcomes				
NST / AF assessment	Yes	--	Yes	Yes
Umbilical Doppler	Yes	--	--	--
Serial US for growth	Yes	Yes	Yes	Yes
Induction at 37-39 wks or earlier	Yes	Yes	Yes	Yes
Scheduled cesarean	Yes	Yes	--	--
Considered identified if	EFW < 10%	EFW > 90%	SDP <2.0 cm or AFI≤ 5.0 cm	SDP ≥8.0 cm or AFI> 24.0 cm
Identified in published reports	10-50% (11-17)	10% (18)	1% (20)	3% (20)

FGR, fetal growth restriction; LGA, large for gestational age; SDP, single deepest pocket; AFI, amniotic fluid index (summation of four SDP); CD-NR FHR, cesarean delivery for non-reassuring fetal heart rate tracing; EFW, estimated fetal weight

1.2 Current Methods of Detecting Abnormal Fetal Growth or Amniotic Fluid

The current guidelines by American College of Obstetricians and Gynecologists (ACOG) indicate that women without complications or co-morbidities should have their fundal height measured at prenatal visits. If the difference between fundal height and gestational age is 3 or more then ultrasound exam (USE) consisting of fetal growth and assessment of amniotic fluid should be undertaken (7).

When performing USE based on indications the detection of abnormal growth is poor because majority are undetected. A summary of 7 publications from 6 countries indicates that only 1 out of 3 FGR infants were identified before birth (Table 2). Similarly, Heywood et al reported that at a teaching hospital, only 11% of newborns with excessive growth were identified before delivery. Alternatively if ultrasound exam is done within 4 weeks of delivery, then over 60% of abnormal growth is identified (19). A recent multi-center pilot randomized trial among uncomplicated pregnancies noted that with USE in the 3rd trimester, 67% of FGR were identified during pregnancy compared to 9% with routine care; 80% of LGA were identified with USE compared to 0% with routine care (20). Thus, a randomized trial is warranted to assess if serial

USE after 30 weeks, when compared to current routine care, increases the identification of abnormal conditions before birth.

Table 2. Antepartum detection of small for gestational age

	Published in	Country	Births	FGR Detected
Jahn A et al (12)	1998	Germany	2,339	32%
Lindqvist PG et al (13)	2005	Sweden	24,585	54%
McCowan LM et al (14)	2010	Aus, NZ, UK	5,606	27%
Mattioli KP et al (15)	2010	USA	1,502	10%
Verlijsdonk JW et al (16)	2012	Netherlands	4,247	37%
Chauhan SP et al (17)	2013	USA	11,487	25%
Monier I et al (18)	2015	France	14,100	22%
Total			**63,926**	**31%**

Aus, Australia; NZ, New Zeeland, UK, United Kingdom, USA, United States of America

2 Study Design

2.1 Primary Research Question

The primary research question is: In women at a gestational age of 30 weeks or more without comorbidities, does performance of serial 3rd trimester growth ultrasounds increase the frequency of identifying abnormalities in estimate of fetal growth (< 10% or > 90% for gestational age) or amniotic fluid (oligohydramnios or polyhydramnios), when compared with women who only receive indicated ultrasounds?

2.2 Secondary Research Questions

- Among women with abnormal growth identified on ultrasound, what is the rate of newborns with a birth weight < 10% or > 90% for gestational age?
- What is the composite neonatal morbidity among (CNM; defined below) among women with serial versus indicated USE? CNM is any of the following: 1) Apgar score < 5 at 5

min, 2) umbilical arterial pH < 7.00, 3) intraventricular hemorrhage grade III or IV, 4) periventricular leukomalacia, 5) intubation for over 24 hrs, 6) necrotizing enterocolitis grade 2 or 3, 7) stillbirth or 8) death within 28 days of birth.

(Intraventricular hemorrhage was classified by Papile's criteriawith grade III hemorrhage being associated with ventricular dilatation and grade IV with parenchymal extension. Necrotizing enterocolitis was diagnosed in the presence of more than one clinical sign, such as bilious gastric aspirate or emesis, abdominal distention, occult or gross fecal blood, and at least one radiographic finding of pneumatosis intestinalis, hepatobiliary gas, or pneumoperitoneum.) (24)

- What is the composite maternal morbidity (CMM) among those with serial vs indicated USE? CMM is defined as any of the following: 1) chorioamnionitis, 2) cesarean delivery in labor, 3) wound infection, 4) transfusion, 5) deep venous thrombus or pulmonary embolism, 6) admission to intensive care unit or 7) death.

(Chorioamnionitis defined as clinical findings of maternal fever, and maternal and fetal tachycardia in the absence of other localizing signs of infection. Wound infection defined as tenderness, erythema, or discharge associated with cesarean skin incision.) (26 &27)

2.3 Design Summary

This is a randomized clinical trial, comparing the frequency of identification of abnormal growth and / or amniotic fluid among low risk women who either have serial USE vs. those who have clinically indicated USE. Women will be randomized to one of two groups:

- Group 1: routine third trimester care with clinically-indicated ultrasound (control)
- Group 2: ultrasound evaluation for fetal growth and amniotic fluid every 4 weeks starting at 30 weeks (intervention group). Thus, if they continue to term, there will be 3 additional ultrasounds exams (30, 34 and 38 weeks).

Eligible subjects who meet inclusion/exclusion criteria will be randomized in a 1:1 ratio using permuted block randomization in order to prevent imbalances between groups.

2.4 Sample Size Calculation

The definition of the primary outcome is presence of SGA (EFW<10%), LGA (EFW>10%), oligohydramnios, or polyhydramnios and is not based on any outcomes after birth.

The estimate for the primary outcome is based on the following assumptions:

- In uncomplicated pregnancies, the likelihood of identifying abnormal growth or amniotic fluid is 10% in the control group.
- In the intervention group, we hypothesize the likelihood of detecting abnormal condition to be 25%.
- To detect an increase in the primary outcome from 10% in control to 25% in the intervention group with 80% power and alpha of 0.05, a total of 194 (97 in each arm) women need to be randomized.
- We estimate that 5% of patients will be lost to follow up based on a previous pilot study (21). The total sample size will be 206 women (103 /group) to allow for loss to follow-up.

2.5 Eligibility Criteria

2.5.1 Inclusion Criteria

1. Maternal age of 18 at the time of consent
2. Singleton gestation

2.5.2 Exclusion Criteria

1. First sonographic examination after 20 weeks
2. Women with any of the following co-morbidities:
   a. Autoimmune disorders (antiphospholipid antibody, lupus, rheumatoid arthritis, scleroderma)
   b. Cerclage in the index pregnancy
   c. Diabetes mellitus—gestational or pre-gestational
   d. Hematologic disorders (coagulation defects, sickle cell disease, thrombocytopenia, thrombophilia)
   e. Hypertension (chronic or pregnancy induced) before enrollment
   f. HIV (human immunodeficiency virus)
   g. Institutionalized individuals (prisoners)
   h. Prior obstetric history of: 1) intrauterine growth restriction, 2) preterm birth before 34 weeks, 3) severe preeclampsia, eclampsia, HELLP syndrome, and 4) stillbirth after 24 weeks or neonatal death
   i. Preterm labor or ruptured membranes before enrollment
   j. Psychiatric disorder (bipolar, depression) on medication
   k. Placenta previa / 3rd trimester bleeding
   l. Renal insufficiency (serum creatinine > 1.5 mg/dL)
   m. Restrictive lung disease
   n. Fetal red blood cell isoimmunization
   o. Seizure disorder on medication
   p. Thyroid disease on medication
   q. Body Mass Index (BMI) above 40 kg/m^2
3. Major fetal Anomaly including: anencephaly, spina bifida, bilateral renal agenesis, cystic hygroma with hydrops, diaphragmatic hernia, or congenital heart defects

4. Unable to understand consent in English or Spanish

2.5 Informed Consent Criteria

Written informed consent must be obtained before entry into the study. Full disclosure of the nature and potential risks of participating in the trial is to be made. A copy of the signed consent form for the study will be provided to the patient.

Women randomized to the intervention group will not be charged for ultrasound exams which are part of the study design. The departmental funds will pay for these exams. If ultrasound abnormalities are noted (e.g. abnormality of the fluid or growth) subsequent ultrasound exams are needed, according to American College of Obstetricians and Gynecology (ACOG) guidelines (Table 3). For these indicated ultrasound exams the insurance company will be billed and these exams are not covered by the departmental funds.

Among women in the control arm, the ultrasound exams will be done only when indicated according to the ACOG guidelines. Some of the common indications for USE include: 1) difference in GA and fundal height > 3 cm; 2) new onset hypertension; 3) decreased fetal movement; 4) spotting/ bleeding; 5) preterm premature rupture of membranes, 6) preterm labor; 7) maternal trauma. Since these exams are indicated, the charges will be submitted to the appropriate insurance company.

2.6 Projected study sites

1. UT Physicians Women's Center-Texas Medical Center
2. UT Physicians Women's Center-Bellaire

3 Study Procedures

3.1 Methods

After gestational diabetes is ruled out, usually by 28-30 weeks, and the woman is confirmed to meet the eligibility criteria, she will be approached for participation. Patients will be randomized using the random permuted block randomization method using allocation tables created by a statistician. The sonographic examination will be done by a registered diagnostic medical sonographer (RDMS).

The examinations will be done after the prenatal visits and there will be no charges for the ultrasound. No economic burden will be imposed on participants. Consistent with the ACOG recommendations that the sonographic exams be repeated every 4 weeks, we will repeat the exams every 4 weeks. Thus, if a women is recruited at 30 weeks, she will have sonographic examination at 30, 34 and at 38 weeks. If a woman develops obstetric complications, such as preterm labor or hypertensive disease of pregnancy, which requires sonographic examination

she will have exams by RDMS but based on intent-to-treat principle continue to be in the group she is randomized to. Clinicians managing the women will be informed of the findings of the USE.

The third trimester ultrasounds will follow the American Institute of Ultrasound in Medicine (2007) guidelines. In particular, biparietal diameter (BPD) will be measured at the level of thalami and insula, and measurement taken from outer edge of the proximal skull to the inner edge of the distal skull. The head circumference (HC) will be measured at the same level as the biparietal diameter, around the outer perimeter of the calvaria. Since HC is not affected by head shape, it will be used if the head is flattened (dolichocephaly) or rounded (brachycephaly). Abdominal circumference (AC) measurement will be determined at the skin line on a true transverse view at the level of the junction of the umbilical vein, portal sinus and the fetal stomach. Femoral length (FL) will be measured with the beam of insonation being perpendicular to the shaft, excluding the distal femoral epiphysis (Chervenak 1998, ACOG 2009). Estimated fetal weight will be derived using the regression equation proposed by Hadlock (1985): Log_{10} (EFW) = 1.5662 – 0.0108(HC) + 0.0034$(HC)^2$ + 0.0468(AC)+0.171(FL)-0.003685(AC)(FL) with EFW being estimated fetal weight; HC, head circumference; AC, abdominal circumference, and; FL, femur length. If a fetal anomaly which was not noted in early survey is discovered during the 3rd trimester USE, clinicians and women be informed.

Abnormalities of fetal growth are fetal growth restriction (FGR) and large for gestational age (LGA). A fetus will be considered to have FGR if the estimated fetal weight is < 10% for gestational age and LGA if the estimate is > 90% for gestational age. Amniotic fluid will be estimated using single sonographic deepest pocket (SDP), which involves finding and vertically measuring the largest cord-free pocket of amniotic fluid or will be calculated by the sum of the maximum vertical pockets in all 4 quadrants. Oligohydramnios, or decreased amniotic volume, is a SDP less than 2 cm or amniotic fluid index < 5.0 cm; hydramnios, or excessive amniotic fluid, is a SDP >8 cm or amniotic fluid > 24.0 cm(ACOG 2009).

3.2 Baseline Procedures

In addition to information for eligibility, project gestational age, the following variables will be collected from the patient's chart.

- Demographics (maternal age, race, ethnicity)
- Medical history (obstetrical history, body mass index pre-pregnancy and at delivery, maternal comorbidities)
- Ultrasound information (fetal growth and amniotic fluid measurements)
- Delivery characteristics
- Timing of delivery
- Neonatal outcomes while hospitalized

3.3 Patient Management

Clinicians managing these women will be informed of the sonographic findings if any of the following is noted: 1) FGR or estimated fetal weight < 10% for gestational age, 2) LGA or estimated fetal weight > 90% for gestational age, 3) oligohydramnios, 4) hydramnios, or 5) sonographic findings which influences clinical management e.g. spontaneous bradycardia or previously undetected fetal anomaly. Women with abnormal findings will be notified. They will also be informed that their clinicians are aware and management will be according to guidelines and departmental practices (Table 3).

Table 3. Abnormal findings and recommendation to clinicians

Abnormalities seen on Ultrasound	**Recommendation to Clinicians**
FGR (estimated fetal weight < 10% for GA)—from ACOG Practice Bulletin # 134 (reference 7)	• Unless previously done, perform a detailed fetal anatomic survey • Serial ultrasound evaluations of the following: (1) Fetal growth with Doppler velocimetry (every 3- 4 weeks) (2) Biophysical profile with or without non-stress test (weekly) along with umbilical artery Dopplers • One course of antenatal corticosteroids between 24 and 34 weeks of gestation in the week before delivery is expected • Delivery at 38-39 weeks or sooner if abnormal results of antepartum testing or co-
LGA (estimated fetal weight)—from ACOG Practice Bulletin # 22 (reference 22)	• If EFW is ≥ 5,000 in non-diabetic, recommend primary cesarean delivery
1. Oligohydramnios—from ACOG Practice Bulletin # 145 (reference 2)	• Consider a repeat fetal structural survey to rule out possible missed a fetal malformation • Non-stress test (NST) and AFI (or biophysical profile) once or twice weekly until delivery • For women with idiopathic oligohydramnios, we suggest delivery at 36 to 37 completed weeks of gestation rather than expectant management
Polyhdyramnios—(reference 23)	• A repeat comprehensive sonographic evaluation is recommended to determine whether fetal anomalies or fetal hydrops is present. • Suggested laboratory evaluations depend upon

Abnormalities seen on Ultrasound	Recommendation to Clinicians
	sonographic findings and may include testing for karyotype analysis, fetomaternal hemorrhage if fetal anemia is suspected, maternal serology to determine exposure to infectious agents (eg, syphilis, parvovirus, cytomegalovirus, toxoplasmosis, rubella), and appropriate tests for hereditary anemias (eg, alpha thalassemia) or metabolic abnormalities. • We suggest treatment for polyhydramnios in singleton pregnancy only if there is preterm labor or significant maternal discomfort with amnioreduction.
Undetected fetal anomaly	• A repeat detailed sonographic evaluation • Recommend offering karyotype analysis in if knowledge of the karyotype will affect management
Spontaneous Bradycardia	• Prolonged fetal monitoring on labor and delivery triage unit

3.4 Study Outcome Measures and Ascertainments

3.4.1 Primary outcome:

The primary outcome is presence of SGA (EFW<10%), LGA (EFW>10%), oligohydramnios, or polyhydramnios among uncomplicated pregnancies that have indicated versus serial USE starting at 30 weeks or more. These parameters are not based on any outcomes after birth.

3.4.2 Secondary outcomes:

- Composite Neonatal Morbidity (CNM) among the two groups
- Composite Maternal Morbidity (CMM) among the two groups.

3.4.3 Statistical Analysis

Intention to treat analyses will be performed. The rate of the primary outcome, abnormal fetal condition (estimated fetal weight < 10% or > 90% for GA, oligohydramnios or polyhydramnios) , will be compared between the intervention and control group using a log binomial (or Poisson in case of nonconvergence) model with treatment group as a covariate to estimate relative risk and 95% confidence interval (CI). The definition of the primary outcome is presence of FGR (EFW<10%), LGA (EFW>90%), oligohydramnios, or polyhydramnios and is not based on any outcomes after birth. Therefore there is no issue about false-positives or false-negatives.

Each secondary outcome will be analyzed similarly. Based on the MFMU Network data that stated CNM occurs in 1.9% of women with uncomplicated pregnancies, we estimate that over 29,000 women need to be randomized to show one-third improvement in CNM (power 90%) among uncomplicated women that have routine ultrasound exams vs. those that have indicated ultrasound examinations. Hence our purpose for these outcomes is to calculate unbiased estimates to provide information for the large multicenter trial in MFMU Network.

We will also conduct a Bayesian analysis of the primary outcome to calculate probability of treatment benefit or harm. We will use a neutral prior distribution for the intervention effect that excludes implausible large treatment effects: Normal (0, SD=0.70) in the log RR scale (prior 95% interval for the RR of 0.23-4.35) (28) Point estimates of treatment effect and 95% credible intervals will be reported with posterior probabilities of benefit and/or harm.

4 Ethics

4.1 IRB approval

IRB approval will be obtained through the Committee for Protection of Human Subjects (CPHS) prior to initiation of the study.

4.2 Consent process

We will have patients sign an informed written consent at the beginning of the study.

4.3 PHI

The MRN of the mother and the newborn will be kept on a separate list paired with a study ID number. The MRN will be maintained to track neonatal outcomes, which will not be readily available at the time of delivery. This database will be password protected and located on a folder within the UT server which will only be accessed by the principal investigator.

4.4 Data Handling and Record Keeping

The data for this study will be recorded on a spreadsheet that will be stored on computers in the medical school which are password protected and located in a locked office. A master list containing study ID linked with MRN will be maintained on these same computers. The MRN will be stored solely to track neonatal outcomes. The list will be discarded at the end of the study.

5 Quality Assurances

5.1 Data collection

Data will be collected on premade data sheets (see attachment) by either the principal investigators or Maternal-Fetal Medicine fellows.

5.2 Publication Plans

The study will be listed in the public database on clinical studies www.clinicaltrials.gov. A summary report of the study will be made available after the conclusion of the study. It is the intention to publish the results of this study in a peer-reviewed journal.

6 Financial Disclosure

6.1

All rules and regulations on the documentation and disclosure of any potential financial conflicts will be adhered to.

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