Title: **Early Anatomy Scan for Evaluation of Obese Pregnant Women (EASE-O): A Randomized Controlled Trial**

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Early Anatomy Scan for Evaluation of Obese Pregnant Women (EASE-O): A Randomized Controlled Trial

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TABLE OF CONTENTS

1. BACKGROUND AND RATIONALE 5

1.1. General Introduction 5
1.2. Rationale and justification for the Study 5
A. Rationale for the Study Purpose 5
B. Rationale for Study Population 6
C. Rationale for Study Design 6
D. Rationale for Dating Ranges and Images Required 7

2. HYPOTHESIS AND OBJECTIVES 9

2.1. Hypothesis 9
2.4. Definitions 9
2.5. Potential Risks and Benefits 10
A. End Points - Efficacy 10
B. End Points – Safety 10
3.1. List the number of subjects to be enrolled 11
3.2. Criteria for Recruitment 11
3.3. Inclusion Criteria 11
3.4. Exclusion Criteria 11
3.5. Withdrawal Criteria 11
3.6. Subject Replacement 11

4. TRIAL SCHEDULE 12

4.1. Randomization and Blinding 12
4.2. Study Flow Diagram 12
4.3. Study Visits and Procedures 14

5. TRIAL MATERIALS 15

5.1. Ultrasound Machines 15

6. IMAGING DETAILS 16

6.1. Rationale for Selection of Required Images in First Trimester Anatomy 16
6.2. Rationale for Selection of Required Images in Second Trimester Anatomy 16
6.3. Specific Restrictions / Requirements 16
6.4. Blinding 16
6.5. Concomitant therapy 16

7. SAFETY MEASUREMENTS 16

7.1. Collecting, Recording and Reporting of Adverse Events 16
7.2. Safety Monitoring Plan 17

8. DATA ANALYSIS 17

8.1. Data Quality Assurance 17
8.2. Data Entry and Storage 17

9. SAMPLE SIZE AND STATISTICAL METHODS 18

9.1. Determination of Sample Size 18
9.2. Statistical and Analytical Plans 18

10. ETHICAL CONSIDERATIONS 18

10.1. Informed Consent 18
10.2. IRB review 19
10.3. Confidentiality of Data and Patient Records 19

11. PUBLICATIONS 19

12. RETENTION OF TRIAL DOCUMENTS 19
13. REFERENCES 19
APPENDIX 1 22
APPENDIX 2 25
APPENDIX 3 30
APPENDIX 4 33

1. BACKGROUND AND RATIONALE

1.1. General Introduction

It is common practice in the United States and other countries worldwide to perform a detailed ultrasound to assess fetal anatomy, usually in the second trimester (18 weeks to 22 weeks gestational age). This time period makes ultrasound scans feasible to perform and interpret, because the fetus is large enough, and organ systems are well developed. Increasingly sophisticated ultrasound technology has prompted earlier scans, and first trimester anatomy ultrasound has become more feasible, even for complex organs such as the fetal heart. In some prospective cohort studies, first trimester ultrasound offers equivalent imaging to second trimester ultrasound in obese patients, who are difficult to scan abdominally in the second trimester due to the layer of adipose tissue between the ultrasound transducer and the fetus.

Obese women have lower rates of successful second trimester anatomy ultrasounds than do lean women. Difficult second trimester anatomy scans lead to suboptimal views and repeated scans, which has financial, emotional, and logistical costs. Fetal anatomy in these patients can be evaluated in the first trimester of pregnancy by ultrasound either transabdominally through the smaller layer of adipose at the pubic symphysis, or transvaginally, First trimester ultrasound has been studied in prospective cohort trials, it is safe and provides clear anatomic views, but randomized studies are necessary to determine whether this technique can decrease the number of scans required to completely evaluate the fetal anatomy in obese patients, without missing major anomalies.

This study aims to fill that gap by studying if first trimester anatomy ultrasound can significantly contribute in the fetal anatomic evaluation in obese patients, and to establish whether it is a complementary or an alternative technique to second trimester anatomy ultrasound for this population.

1.2. Rationale and justification for the Study

a. Rationale for the Study Purpose

Obesity is a prevalent disease in the US, affecting 600 million people and more women than men (1). Obesity makes ultrasound diagnosis difficult and simultaneously increases the rate of fetal anomalies (2). As BMI increases, anatomy visualization decreases in level I and level II ultrasounds (3-4). Timing of ultrasounds around 20 weeks seems to optimize completion in the 16 to 24 week range, and so for many years, a 20-week ultrasound has been the dominant practice in the United States and the world.

However, recent studies have investigated earlier ultrasound for these patients, given that it may offer better imaging and earlier diagnosis, especially of severe anomalies. Ultrasound before 14 weeks can detect major anomalies but misses others (8-9). This is related to technological limitations such as image resolution of soft tissues and small structures, but also to the development of complex organs, such as the heart. Solutions have begun to emerge as the field of fetal imaging advances in

understanding what imaging findings are significant for major conditions such as facial clefts and neural tube defects (10-11).

First trimester ultrasound has been recognized as a safe diagnostic technique for the embryo (8, 12-13). The field is moving towards standardizing and adopting the technique as an adjunct to second trimester ultrasound (15-16), and some studies have been done to compare its efficacy to second trimester ultrasound, and have found it equivalent (16) even in structures as complex as the heart (17).

Given that there is some literature to support first trimester evaluation of fetal anatomy, this study proposes to randomize women to first trimester or second trimester anatomy ultrasound. This study design will allow comparison of the first trimester technique to the gold standard (second trimester anatomy ultrasound). All women in the intervention arm who receive a first trimester ultrasound will also receive a backup second trimester scan (termed a “gold standard scan”) to ensure no missed diagnosis of anomalies.

b. Rationale for Study Population

A BMI(Kg/M^2) of ≥35 was chosen as the primary inclusion criteria given that the rate of completion of second trimester anatomy ultrasound does not significantly differ between women of BMI < 35, whether lean, overweight, or obese (7). The study population include women of child-bearing age and fetuses, even though these populations have some vulnerabilities, because it is designed to study an aspect of pregnancy.

c. Rationale for Study Design

Several cohort studies of first trimester ultrasound already exist (16, 17), but no randomized data is available. For these techniques (first and second trimester ultrasound) to be adequately compared, a randomized design is necessary. Other designs, such as before-and-after and prospective cohorts were considered, but given that this is a relatively simple intervention to directly compare, and randomization offers significant objectivity, a randomized controlled trial is proposed.

d. Rationale for Dating Ranges and Images Required

Required images in the first trimester anatomy ultrasound (the intervention) were selected based on peer-reviewed literature on the subject of early fetal anatomy assessment. A detailed list of images required in the intervention is appended. The following is a list of required planes and peer-reviewed literature to support their use as key in the evaluation of major and minor fetal anomalies. This list of planes is deemed sufficient by multiple experts in the field and the International Society for Ultrasound in Obstetrics and Gynecology, or ISUOG (14, 19).

1. Midsagittal fetus
2. Placental cord insertion
3. Profile
4. Lateral ventricles
5. BPD (transthalamic view)
6. Head circumference
7. Posterior fossa (cerebellum)
8. Orbits
9. Face (including retronasal triangle)
10. Heart rate
11. Situs
12. Four chamber heart
13. 3 vessel view
14. Bladder
15. Kidneys
16. Abdominal circumference
17. Fetal cord insertion
18. 3 vessel cord
19. Extremities
20. Spine

The first trimester required images largely correspond with second trimester required images, with very few differences which reflect that some structures (e.g. the lip) are hard to see in the first trimester, and are replaced by a feasible alternative (e.g. the retronasal triangle) based on peer-reviewed literature.

All ultrasounds performed in the second trimester, both the GSS for the intervention arm and the anatomy evaluation in the comparison arm, will be evaluated for completion based on UT's proprietary second trimester protocol, which abides by standards set out by the International Society of Ultrasound in Obstetrics & Gynecology (ISUOG) and the American Institute of Ultrasound in Medicine (AIUM) (20, 22-23). A list of images required for the comparison is given here in brief.

1. Fetal position
2. Placental cord insertion
3. Profile
4. Lateral ventricles
5. BPD (transthalamic view)
6. Head circumference
7. Posterior fossa (cerebellum)
8. Choroid plexus
9. Orbits
10. Face
11. Nose-lips
12. Heart rate
13. Heart rate
14. Situs
15. Four chamber heart
16. 3 vessel view
17. Interventricular septum
18. Bladder
19. Kidneys
20. Abdominal circumference
21. Fetal cord insertion
22. 3 vessel cord
23. Diaphragm

24. Extremities (including femur length, humerus length, hands, feet)

2. HYPOTHESIS AND OBJECTIVES

2.1. Hypothesis

1. An ultrasound evaluation in the late first trimester (12w0d to 13w6d) is more likely to provide a complete fetal anatomical evaluation than an ultrasound evaluation done in the second trimester (18w0d to 22w6d) of pregnancy in obese women.

2. Ultrasound evaluation of fetal anatomy in the first trimester (12w0d to 13w6d) *combined with* conventional ultrasound evaluation of fetal anatomy in the second trimester (18w0d to 22w6d) will provide with more information than either in isolation.

2.2. Primary Objectives

Assess the feasibility of ultrasound in the first trimester at our Center with our equipment and personnel. Assess the completion rate of ultrasounds for fetal anatomy in the first trimester (12w0d to 13w6d) compared to completion rates of ultrasounds for fetal anatomy in the second trimester (18w0d to 22w6d) in obese women.

2.3. Secondary Objectives

Assess the completion rate of the *combination* of one ultrasound in the first trimester and one in the second trimesters (12w0d to 13w6d *and* 18w0d to 22w6d), compared to the individual completion rates of both evaluations in obese women.

2.4. Primary Outcome

The primary outcome is the completion rate (number of scans that see all the views listed on pages 7 or 8 divided by total number of scans in that group) for first trimester ultrasounds, compared to the same metrics obtained in second trimester ultrasounds.

2.5. Secondary Outcome

Secondary outcomes include:
1. Completion rate of both first and second trimester scans (when considered as a single instrument to visualize the fetal anatomy, what is the rate of complete visualization divided by all women?)
2. Total length of scanning time in the first trimester ultrasound group
3. Number of anomalies identified (and missed) in each group
4. Neonatal outcomes (survival, gestational age at delivery, NICU admission, hospital LOS, neonatal morbidities including respiratory distress syndrome, transient tachypnea of the newborn, intraventricular haemorrhage, necrotizing enterocolitis)
5. Patient feedback to standardized surveys (see attached)

6. Cost of intervention compared to usual care (cost benefit analysis based on whether more ultrasounds were done in cases of early discovery of anomalies)

a. End Points - Efficacy

Anticipated benefits of first trimester detailed anatomy scan include a higher completion rate the initial ultrasound performed for anatomy. We anticipate that this will decrease the number of times future obstetric patients will have to return for additional ultrasounds. There will be no direct benefits to the participants in the prior trial apart from the intervention arm gaining an additional look at their baby, which may have potential social or psychological benefits.

b. End Points – Safety

Anticipated risks of ultrasound are low. While there is theoretical risk of the effects of high-output ultrasound techniques, such as color Doppler, causing increased core body temperature and possible teratogenic effects in the first trimester, there is not a well-accepted incidence of ultrasound-related fetal adverse outcomes, and ultrasound is generally deemed of low or no risk by professional organizations (21). Available guidelines suggest that judicious clinical use of ultrasound as appropriate to the patient risk profile should be employed (19-23).

Of note, expert opinion on this matter deems all patients included in this study as high risk for anatomic abnormalities (14), which justifies detailed investigation, including Doppler ultrasound.

3. STUDY POPULATION

Broadly speaking, the population is obese pregnant women with BMI ≥35 (Kg/M^2).

3.1. List the number of subjects to be enrolled.

A sample size of 118 women was calculated based on the primary outcome of initial scans which completely clear the fetal anatomy (see below for details of sample size calculation). It is necessary to include women in this study as this proposes a technique only possible in pregnancy. Minorities will be included to strengthen external validity of the study. Children will not be recruited.

3.2. Criteria for Recruitment

Once a potential subject expresses interest in participation, she will be asked to undergo a brief ultrasound to verify her gestational age. This ultrasound will be free of charge, will take approximately 5 minutes, and will not be entered in her medical record or saved as study images. This is to confirm viability gestational age, and number of fetuses.)

3.3. Inclusion Criteria

The subject must meet all of the following inclusion criteria to participate in this study:

- BMI ≥ 35
- Age 18-50 years

- Presented for ultrasound before 14 weeks at UT Professional Building, Memorial City, Bellaire, or Lyndon-Baines Johnson clinics
- Primary language is English or Spanish
- Consent to an extra transvaginal ultrasound if needed
- Singleton gestation
- No previous anomalies known before consent
- Missed abortion (nonviable pregnancy)

Missed abortion will be defined by ultrasound findings during recruitment according to Doubilet et al 2013 (18), which is the widely-accepted standard in the United States.

3.4. Exclusion Criteria

All subjects meeting any of the following criteria at baseline will be excluded from analysis, although will be reported as part of study flow:

- Elective abortion after recruitment
- Missed abortion after first trimester ultrasound
- Did not receive second trimester ultrasound

Missed abortion will be defined by ultrasound findings during recruitment according to Doubilet et al 2013 (18), which is the widely-accepted standard in the United States.

3.5. Withdrawal Criteria

An interim analysis is planned at recruitment of 50% of the patients (n=59) and if first trimester ultrasound is not completable in at least 50% of patients, the study will be stopped. An individual patient may withdraw from the study at any time.

3.6. Subject Replacement

Subjects who withdraw from the study will be replaced.

4. TRIAL SCHEDULE

September 2020 - June 2021	Recruitment
December 2020	Goal: 25% recruitment at end of month
February 2021	Goal: 50% recruitment at end of month
May 2021	Goal: 75% of recruitment mid-month
July 2021-August 2021	Follow up on delivery records, clean data
August 2021	Data analysis, review by entire team
September - November 2021	Manuscript preparation
December 2021	Manuscript submission

4.1. Randomization and Blinding

Randomization will be carried out in a 1:1 ratio with block size 4, stratified into three groups by pre-pregnancy BMI (see below) using RedCap.

Group 1 (First trimester ultrasound)

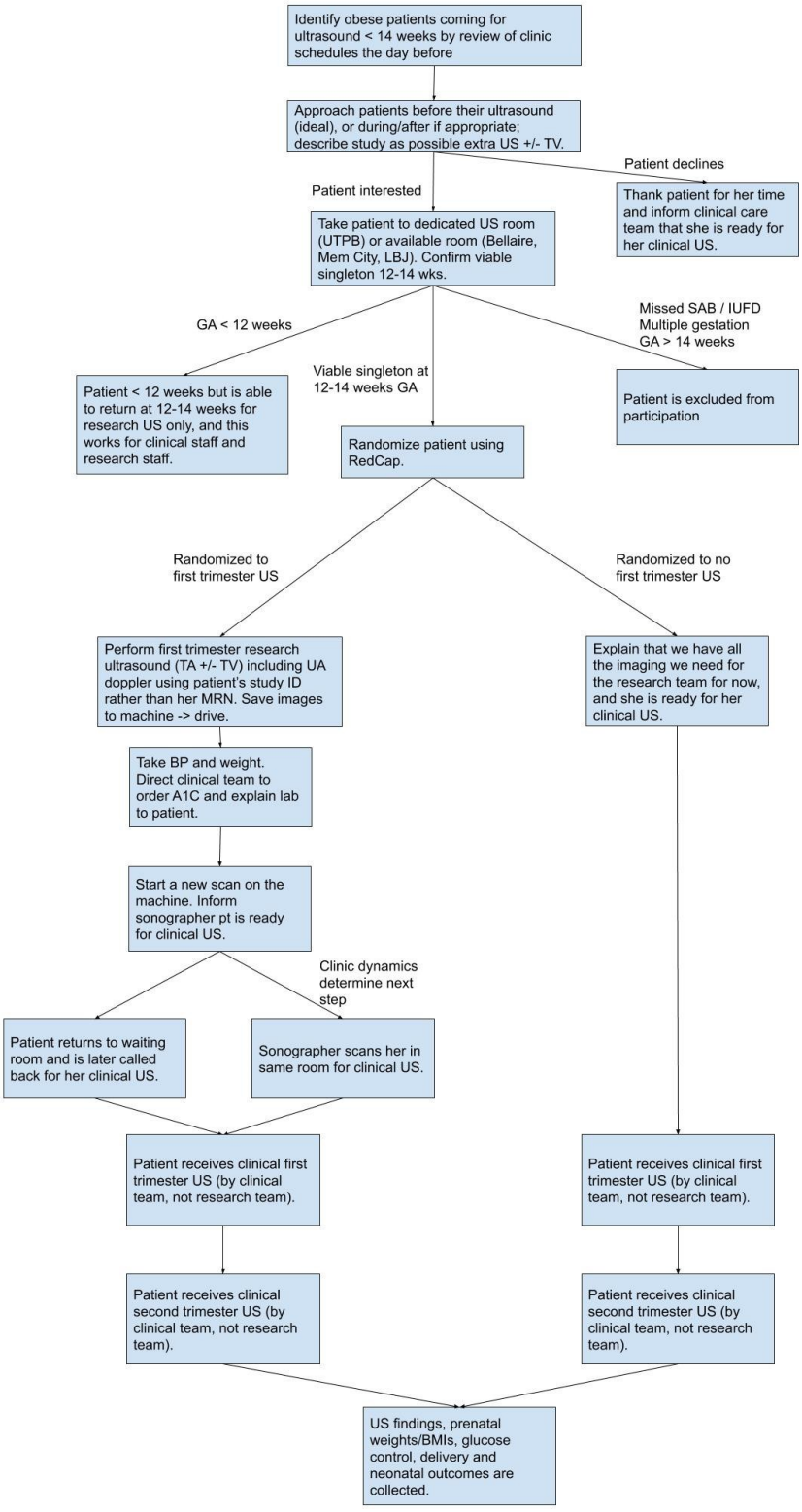
- BMI 35-39.9: 19 patients
- BMI 40-44.9: 20 patients
- BMI ≥45: 20 patients

Group 2 (Second trimester anatomy ultrasound)

- BMI 35-39.9: 19 patients
- BMI 40-44.9: 20 patients
- BMI ≥45: 20 patients

There is no plan for breaking of randomization codes, as randomization will be done through RedCap, nor are there plans for unmasking.

4.2. Study Flow Diagram


Identify obese patients coming for ultrasound < 14 weeks by review of clinic schedules the day before
Approach patients before their ultrasound (ideal), or during/after if appropriate; describe study as possible extra US +/- TV.
Patient declines
Thank patient for her time and inform clinical care team that she is ready for her clinical US.
Patient interested
Take patient to dedicated US room (UTPB) or available room (Bellaire, Mem City, LBJ). Confirm viable singleton 12-14 wks.
GA < 12 weeks
Missed SAB / IUFD
Multiple gestation
GA > 14 weeks
Viable singleton at 12-14 weeks GA
Patient < 12 weeks but is able to return at 12-14 weeks for research US only, and this works for clinical staff and research staff.
Patient is excluded from participation
Randomize patient using RedCap.
Randomized to first trimester US
Randomized to no first trimester US
Perform first trimester research ultrasound (TA +/- TV) including UA doppler using patient's study ID rather than her MRN. Save images to machine -> drive.
Explain that we have all the imaging we need for the research team for now, and she is ready for her clinical US.
Take BP and weight. Direct clinical team to order A1C and explain lab to patient.
Start a new scan on the machine. Inform sonographer pt is ready for clinical US.
Clinic dynamics determine next step
Patient returns to waiting room and is later called back for her clinical US.
Sonographer scans her in same room for clinical US.
Patient receives clinical first trimester US (by clinical team, not research team).
Patient receives clinical first trimester US (by clinical team, not research team).
Patient receives clinical second trimester US (by clinical team, not research team).
Patient receives clinical second trimester US (by clinical team, not research team).
US findings, prenatal weights/BMIs, glucose control, delivery and neonatal outcomes are collected.

4.3. Study Visits and Procedures

a. Screening Visits and Procedures

Research staff will screen the schedules of the ultrasound clinics at Memorial City, Bellaire, UT Professional Building, LBJ, and Harris Health Aldine ultrasound clinics for patients undergoing clinically indicated ultrasounds before 14 weeks gestational age. (These existing clinic visits are usually for dating ultrasound or nuchal translucency, an early assessment of a marker of aneuploidy.) Research staff will approach patients at these visits and describe the study. If the patient is interested in participation, the sequence of events that should occur include confirmation of eligibility with a 5-minute ultrasound to determine a single viable fetus before 14 weeks. This is the only procedure necessary before recruitment. If the patient is eligible according to this screening ultrasound, she can be randomized at that time.

b. Study Visits and Procedures

After the screening ultrasound confirms eligibility and a patient is given informed consent, the patient can then be randomized. If the patient is randomized to the intervention (detailed first trimester anatomy ultrasound), this scan is performed at the randomization visit if the patient is between 12w0d and 13w6d. If she is less than 12w0d, a separate study visit is scheduled for a date at her convenience during the days she is between 12w0d and 13w6d. A dedicated room and time slots have been made available for these study visits at Memorial Hermann Southwest and at the Fetal Center at UTPB. This separate scan/visit is not billed as it is not part of the standard of care.

After this detailed research ultrasound, which will be limited to 15 minutes, she then receives her clinically indicated dating ultrasound or nuchal translucency measurement. The total estimated time of all these ultrasounds is expected to be approximately 30 minutes, with breaks in between to allow the patient some movement and the opportunity to use the rest room, and to allow the exchange of operators (research staff vs clinical staff) and the creation of distinct records (research ultrasound is not saved to electronic medical records, so a new scanning encounter must be opened for the clinical ultrasound that day). The patient will complete a survey about her satisfaction with this technique via email. In addition, as a safety measure, if an anomaly is suspected on the day of the detailed first trimester anatomy scan, the patient will be unblinded. The research team will inform the clinical team so that a more detailed evaluation can be done and so that this information can enter the clinical record and affect clinical management.

Patients randomized to the intervention arm are later scheduled for a second trimester ultrasound by the clinical team, as this is part of standard obstetrical care. Research staff will ensure patients have this scan scheduled and completed, as it is part of study procedure. Data about this scan will be recorded in the patient's research record. This scan can be repeated as indicated according to UT's protocol for assessing anatomy.

If the patient is randomized to the comparison arm, she does not undergo a detailed first trimester ultrasound that day, but she does receive her clinically indicated limited ultrasound for dating or for nuchal translucency. She then undergoes a second

trimester ultrasound by the clinical team as part of standard obstetrical care and completes a survey regarding her satisfaction with this technique via email. Research staff will ensure patients have this scan scheduled and completed, as it is part of study procedure. Data about this scan will be recorded in the patient's research record. This scan can be repeated as indicated according to UT's protocol for assessing anatomy.

c. Final Study Visit:

The final study visit is denoted by completion of the second trimester gold standard scan (GSS) for patients randomized to the intervention arm, and at the completion of the second trimester anatomy ultrasound for patients randomized to the comparison arm. Participants will continue to be followed through their pregnancy to document the number of ultrasounds required to complete the fetal anatomy evaluation.

d. Post Study Follow up and Procedures

Medical records will be reviewed after each study participant's due date to assess whether delivery has occurred and to record delivery outcomes from the medical records, when available. This is chiefly so that a post-natal evaluation can be recorded to confirm or exclude anatomical anomalies. Delivery outcomes are not a primary outcome and request of outside delivery records will not be required for a subject's record to be marked as completely collected.

Adverse outcomes, including discomfort during ultrasound as well as neonatal outcomes, will be recorded in the subject's research record.

e. Discontinuation Visit and Procedures

Subjects may withdraw voluntarily from participation in the study at any time. Subjects may also withdraw voluntarily from receiving the study intervention for any reason.

If a patient in the intervention arm withdraws from the study during to her first trimester anatomy ultrasound, she will be asked to complete the survey regarding her experience regardless of the duration of the first trimester ultrasound. She will then undergo her clinically indicated ultrasound (which are not transvaginal).

If a subject in the intervention arm withdraws from the study prior to her second trimester GSS ultrasound (done as "back up" for the intervention), a standard email will be sent to her confirming her withdrawal and encouraging her to seek a second trimester (standard of care) anatomy ultrasound as the anatomy evaluation she had in the first trimester is considered experimental.

If a subject in the comparison arm withdraws from the study prior to her second trimester anatomy ultrasound, she will not be required to complete the survey about her experience. A standard email will be sent to her confirming her withdrawal and encouraging her to seek a second trimester (standard of care) anatomy ultrasound outside the study.

If voluntary withdrawal occurs, the subject will be given standard care under medical supervision until the symptoms of any adverse event resolve or the subject's condition becomes stable.

5. TRIAL MATERIALS

5.1. Ultrasound Systems

All scans (screening ultrasound, first-trimester anatomy scan, GSS, and second trimester anatomy scans) will be performed using General Electric (GE) E8 or E10 machines, which are FDA approved for ultrasound in the first and second trimester (E8 510(k) number: K170445, E10 510(k) number: K173555). Approval for the E8 is available at https://www.accessdata.fda.gov/cdrh_docs/pdf17/K170445.pdf (last accessed 7/30/20) and approval for the E10 is available at https://www.accessdata.fda.gov/cdrh_docs/pdf17/K173555.pdf (last accessed 7/30/20).

6. BLINDING

Patients are not blinded to their group as they are aware of the timing of their detailed ultrasound. The clinical team will not be informed of the patient's randomization assignment, images from research ultrasounds will not be available to the clinical team, and the clinical team will not be made aware of whether the second trimester scan done by them is for comparison to the gold standard (the GSS in intervention arm patients) or for anatomy (in comparison arm patients).

Patients and the care team will be unblended from the results of the first trimester exam if there is an anomaly. There are no other plans for unblinding.

7. SAFETY MEASUREMENTS

7.1. Collecting, Recording and Reporting of Adverse Events

Adverse events are not likely during a study of ultrasound, given the very low risk of fetal effects during anatomy ultrasound (19-23). Fetuses of mothers in the intervention arm will be evaluated by the gold standard (GSS) in the second trimester, in order to rule out any missed anomalies. Fetuses in both arms are exposed to similar amounts of ultrasound time (all fetuses have at least two ultrasounds in the first trimester and one in the second trimester).

Intervention arm total number of scans:
1. Screening ultrasound (estimated time 2 minutes)
2. First trimester anatomy ultrasound (estimated time 25 minutes)
3. Scheduled limited first trimester ultrasound (estimated time 10 minutes)
4. GSS in second trimester to ensure standard of care is met (estimated time 45 minutes)

Comparison arm total number of scans:
1. Screening ultrasound (estimated time 2 minutes)
2. Scheduled limited first trimester ultrasound (estimated time 10 minutes)
3. Second trimester anatomy ultrasound (estimated time 30 minutes)

Multiple ultrasounds are common in this population.

Maternal adverse effects including discomfort will be noted in the study database but will not be reported to a study safety monitor.

7.2. Safety Monitoring Plan

The research ultrasound will be stored locally on an E8 machine or on a hard drive owned and protected by UT. It will not be available in the medical record. Data regarding ultrasound (length in minutes, date, gestational age, findings) will be stored in RedCap. Maternal and neonatal outcomes will be collected from Care4 or Epic (depending on the location of delivery) and stored in RedCap.

Adverse effects are not expected from an ultrasound intervention, although discomfort especially with transvaginal ultrasound is frequently reported by patients. In the case of patient discomfort with the ultrasound exam, the exam will be paused and the patient asked for permission to continue. If the patient declines the continuation of the exam, the exam will stop and completion will be assessed based on the images obtained before that point.

8. DATA ANALYSIS

8.1. Data Quality Assurance

Data will be checked by at least two members of the research team for integrity. The entire study team (CB, EH, BS) will have access to study documents in RedCap and to ultrasound images on the protected UT drive (encrypted and kept in a locked office in the Medical School Building at the medical center campus). A linking log will be used to limit spread of PHI into the RedCap record, so that inadvertent download of data does not compromise patient confidentiality and anonymity. This linking log will be kept in the same system as the data but will not be accessible with the dataset or ultrasound images, in order to protect patient identifying variables as much as possible.

8.2. Data Entry and Storage

Data will be entered directly by patients into RedCap with research staff supervision (for demographics) or independently (for survey replies), or by the research staff. A linking log will be used. The linking log and images will be destroyed at the close of the study (upon publication). De-identified records will be retained for 5 years and made available upon academic request to the corresponding author.

9. SAMPLE SIZE AND STATISTICAL METHODS

9.1. Determination of Sample Size

Approximately 85% of lean women only require a single anatomy ultrasound, as it completely images all parts of the fetal anatomy. A review of UT's data on anatomy ultrasound in the obese was performed to obtain data on our completion rates in order to calculate sample size. In obese women, only 70% of initial scans are complete and women are required to return for repeated ultrasounds, occasionally 3 or more times. Given that the primary hypothesis is that first trimester ultrasound will remove the difficulty associated with obesity, an increase from 70% completion to 85% completion is anticipated. A sample size of 118 is required to detect a 15%

increase in the number of complete initial scans with 80% power and alpha of 0.05. A sample size was also calculated for a Bayesian analysis, which would require fewer than 118 women with the same suppositions.

Bayesian sample size per group to obtain 80% power under different scenarios			
Usual Care Outcome Rate	Usual Care Outcome Rate	Usual Care Outcome Rate	Usual Care Outcome Rate
70%	70%	70%	70%
70%	70%	70%	70%
65%	65%	65%	65%
65%	65%	65%	65%

It is planned to recruit 118 women to lend the maximum power to the analysis. Bayesian analysis will be performed only if recruitment proves challenging.

To obtain a sample size of 118 given a recruitment rate of 50%, 236 women will need to be approached over an expected recruitment time of 2 years.

9.2. Statistical and Analytical Plans

Analysis will be carried out according to the intention-to-treat principle. All randomized subjects will be included in analyses for which they have data. Frequentist statistics will be reported, including mean number of scans in each group (compared with t tests, with ANOVA between classes of obesity), the proportion of complete scans in each group (compared with chi square test), and the mean total scan time (t tests). Secondary outcomes will also be analysed with a frequentist approach. Descriptive statistics will also be provided about anomalies found and missed (anticipated to be low, so likely few significant findings to report). In addition, patient perspectives will be described.

10. ETHICAL CONSIDERATIONS

10.1. Informed Consent

Informed consent will be obtained in either English or Spanish and will preferably be performed by e-consenting (no paper copy of the consent). Patients will consent via a tablet or mobile device directly into RedCap and will be provided with an emailed copy of their consent form.

10.2. IRB review

A copy of the protocol will be submitted to the Institutional Review Board (IRB) for written approval. The Principal Investigator will obtain approval from the IRB for all subsequent protocol amendments.

10.3. Confidentiality of Data and Patient Records

Subject confidentiality will be maintained and all records will be securely stored.

11. PUBLICATIONS

We anticipate three primary publications coming out of this study. Completion rates and multiple second outcomes can be published in journals of maternal-fetal medicine or ultrasound.

12. RETENTION OF TRIAL DOCUMENTS

All records, including all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, etc) as well as IRB records and regulatory documents will be retained by the PI in a secure storage facility. The records will be accessible for inspection and copying by authorized authorities.

13. REFERENCES

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List of Attachments

Appendix 1 **Questionnaires used in the Trial**

Appendix 2 **Consent Form**

Appendix 3 Standardized Patient Emails

APPENDIX 1
Patient survey after detailed anatomy ultrasound for EASE-O

Version 1.0, last revised 8/2/20

This survey is 12 questions long and should take about 15 minutes.

Recently, you had a "[first/second] trimester detailed anatomy ultrasound," or an ultrasound that looked at the body parts of your baby in detail at [12-14/18-22] weeks. These questions will ask you about your experience with your ultrasound and your opinions about finding birth defects early in pregnancy.

1. Overall, how satisfied were you with today's ultrasound?
    a. Very satisfied
    b. Somewhat satisfied
    c. Neither satisfied nor dissatisfied
    d. Somewhat dissatisfied
    e. Very dissatisfied

2. How would you rate the level of discomfort required by this ultrasound?
    a. Very comfortable
    b. Somewhat comfortable
    c. Neither comfortable nor uncomfortable
    d. Somewhat uncomfortable
    e. Very uncomfortable

3. How would you rate the length of time it took to complete this ultrasound? Don't count the time it took to do other things, like park or wait in the waiting room.
    a. Much longer than I expected
    b. A little longer than I expected
    c. About the time I expected
    d. A little shorter than I expected
    e. Much shorter than I expected

4. How satisfied are you with the length of time it took to complete this ultrasound? Don't count the time it took to do other things, like park or wait in the waiting room.
    a. Very satisfied
    b. Somewhat satisfied
    c. Neither satisfied nor dissatisfied
    d. Somewhat dissatisfied
    e. Very dissatisfied

5. How likely are you to recommend [first/second] trimester anatomy screening to other pregnant women?
    a. Very likely
    b. Somewhat unlikely
    c. Neither likely nor unlikely
    d. Somewhat unlikely

e. Very unlikely

The next questions ask for your opinions on finding out about birth defects early. Most birth defects are discovered at 18-22 weeks, but EASE-O is studying ultrasounds which can discover many of the same birth defects at 12-14 weeks. For this section, remember that:

- Finding out about a birth defect early can lead to more ultrasounds and testing
- Finding out about a birth defect early means a longer time knowing about the problem, when there may be no therapy for the fetus until birth
- Abortion (ending a pregnancy before birth) is safer for the woman when done earlier in pregnancy

6. For you, how important is finding out about any birth defects early in your pregnancy?
    a. Very important
    b. Important
    c. Fairly important
    d. Slightly important
    e. Not important

7. How much testing would you seek if an abnormal ultrasound finding was discovered during your detailed scan?
    a. All available testing, even invasive options
    b. Some available testing, only invasive options if highly recommended
    c. Some available testing, but not invasive options
    d. Very little testing, definitely no invasive options
    e. No testing at all, even if recommended

8. If there was a therapy or surgery that you could undergo during pregnancy for a birth defect discovered in your fetus, how likely would you be to agree to it?
    a. Very likely
    b. Somewhat unlikely
    c. Neither likely nor unlikely
    d. Somewhat unlikely
    e. Very unlikely

9. Some women in this study got an ultrasound at [18 to 22/12 to 14] weeks instead of when you got your ultrasound. Please tell us whether you agree or disagree with the following statement: “I wish I could have been in the other group, and gotten my detailed anatomy ultrasound at [18 to 22/12 to 14] weeks.”
    a. Strongly agree
    b. Agree
    c. Neither agree nor disagree
    d. Disagree
    e. Strongly disagree

10. You got your detailed anatomy ultrasound at at [12-14/18-22] weeks. If given the choice in another pregnancy (even if another baby is not your plan), how likely are you to choose the same timing again?
    a. Very likely
    b. Somewhat likely
    c. Neither likely nor unlikely
    d. Somewhat unlikely
    e. Very unlikely

The last two questions involve questions about abortion. These questions may be sensitive and you may skip them. If you can answer them, you help us understand how women feel about issues that affect early diagnosis of birth defects.

[SKIP ENTIRE SECTION]

11. Some birth defects are very serious and limit the fetus' length of life and/or future quality of life. In certain cases, abortion is offered as an option. What are your feelings on abortion (ending a pregnancy before birth) in general?
    a. Very supportive of abortion
    b. Somewhat supportive of abortion
    c. Neither supportive nor opposed to abortion
    d. Somewhat opposed to abortion
    e. Very opposed to abortion
    f. [SKIP THIS QUESTION]

12. Imagine that you were pregnant with a fetus with a very serious birth defect, that limited the fetus' length of life and/or future quality of life. If your doctor offered abortion as an option, how likely would you be to seek an abortion for yourself?
    a. Very likely
    b. Somewhat likely
    c. Neither likely nor unlikely
    d. Somewhat unlikely
    e. Very unlikely
    f. [SKIP THIS QUESTION]

Thank you for your participation! This survey helps us understand how you feel about when you get your ultrasound and what you want to do with the information.

Autopopulated fields:

[Study ID]

[Survey completion date]

[EDD]

[Gestational age at survey completion]

[Group: intervention/comparison]

[Primary outcome (initial anatomy scan complete?): Y/N]

APPENDIX 2

CONSENT TO TAKE PART IN RESEARCH

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

APPENDIX 3
Standardized Emails for EASE-O
Version 1.0, last revised 8/2/20

Standardized Welcome Email
Dear [Name],

Thank you for participating in EASE-O, a randomized clinical trial to find out when is the best time for a detailed anatomy ultrasound in women with a BMI of 35 or greater. We're so glad you're part of the study. If you haven't already filled out your demographics with the research staff, please click this link to do so.

You are in the group that gets a detailed anatomy ultrasound in the [first/second] trimester. Based on this, a survey [has been/will be] made available to you about your experience after your detailed anatomy ultrasound. Filling out this survey helps us understand what women like you prefer regarding their ultrasounds. We want to hear from you!

Because you are in the group that gets a detailed anatomy ultrasound in the [first/second] trimester, your next step in the study is to get [an ultrasound to check on the baby/your detailed anatomy ultrasound] between 18 and 22 weeks, which will be scheduled by your doctor. You don't have to do anything—we'll take care of everything, and all your information will be kept confidential.

If you have any concerns about the study or want to withdraw, please email cara.m.buskmiller@uth.tmc.edu. Have a great day!

Sincerely,

Cara Buskmiller, MD
Principle Investigator, EASE-O

Standardized second trimester detailed anatomy survey email (comparison arm after detailed second trimester anatomy scan)
Dear [Name],

I hope you haven't forgotten about EASE-O, a randomized clinical trial to find out when is the best time for a detailed anatomy ultrasound in women with a BMI of 35 or greater. You're almost done with your participation! [If you haven't already filled out your demographics with the research staff, please click this link to do so.]

You are in the group that gets a detailed anatomy ultrasound in the second trimester. Based on this, you may have already had your detailed anatomy ultrasound, or it might be coming up soon! After your ultrasound, please fill out this survey. Filling out this survey helps us understand what women like you prefer regarding their ultrasounds. We want to hear from you!

This is the last step for you in the study. After this survey, you don't have to do anything—we'll take care of everything, and all your information will be kept confidential.

If you have any concerns about the study or want to withdraw, please email cara.m.buskmiller@uth.tmc.edu. Have a great day!

Sincerely,

Cara Buskmiller, MD
Principle Investigator, EASE-O

Standardized second trimester safety ultrasound reminder (intervention arm)
Dear [Name],

I hope you haven't forgotten about EASE-O, a randomized clinical trial to find out when is the best time for a detailed anatomy ultrasound in women with a BMI of 35 or greater. You're almost done with your participation! [If you haven't already filled out your demographics with the research staff, please click this link to do so.]

You are in the group that got a detailed anatomy ultrasound in the first trimester. Even though that was neat, that ultrasounds is still considered experimental (that's why we are researching them)! You deserve to have a complete re-evaluation of your baby's body parts between 18-22 weeks, which is coming up soon.

This safety measure is the last step for you in the study. Afterwards, you don't have to do anything—we'll take care of everything, and all your information will be kept confidential. If you have any concerns about the study or want to withdraw, please email cara.m.buskmiller@uth.tmc.edu. Have a great day!

Sincerely,

Cara Buskmiller, MD
Principle Investigator, EASE-O

Withdrawal Email 1 (for intervention arm, withdrawing during her detailed first trimester ultrasound)
Dear [Name],

We are sorry to see you go! Thank you for considering EASE-O, a randomized clinical trial to find out when is the best time for a detailed anatomy ultrasound in women with a BMI of 35 or greater. This email confirms that you have withdrawn from the study. Your data will not be analyzed and no further data will be collected.

You do not have to do anything further, but we ask that you tell us about your experience during your ultrasound, at this link. Filling out this survey helps us understand what women like you prefer regarding their ultrasounds. We want to hear from you!

Sincerely,

Cara Buskmiller, MD
Principle Investigator, EASE-O

Withdrawal Email 2 (for intervention arm, withdrawing after her detailed first trimester ultrasound, before her safety second trimester ultrasound)
Dear [Name],

We are sorry to see you go! Thank you for participating in EASE-O, a randomized clinical trial to find out when is the best time for a detailed anatomy ultrasound in women

with a BMI of 35 or greater. This email confirms that you have withdrawn from the study. Your data will not be analyzed and no further data will be collected.

You do not have to do anything further, but we encourage you to seek out an ultrasound between 18 and 22 weeks gestational age, if you haven't already gotten one. You did have an ultrasound in the first trimester looking at all the baby's parts, but these ultrasounds are still considered experimental (that's why we are researching them)! You deserve a later ultrasound, it is still recommended and will be covered by your insurance as part of your routine prenatal care.

Sincerely,

Cara Buskmiller, MD
Principle Investigator, EASE-O

Withdrawal Email 3 (for comparison arm, withdrawing from study before detailed second trimester ultrasound)
Dear [Name],

We are sorry to see you go! Thank you for participating in EASE-O, a randomized clinical trial to find out when is the best time for a detailed anatomy ultrasound in women with a BMI of 35 or greater. This email confirms that you have withdrawn from the study. Your
data will not be analyzed and no further data will be collected.

You do not have to do anything further, but we encourage you to seek out an ultrasound between 18 and 22 weeks gestational age, if you haven't already gotten one. The ultrasound you got in the first trimester was only to establish the dating of your pregnancy or check on the back of the baby's neck, and didn't look at all the baby's body parts. A detailed ultrasound between 18 and 22 weeks recommended and will be covered by your insurance as part of your routine prenatal care.

Sincerely,

Cara Buskmiller, MD
Principle Investigator, EASE-O

APPENDIX 4

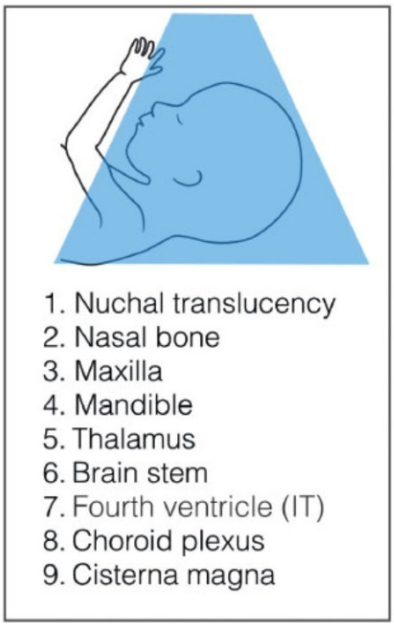
First Trimester Anatomy Ultrasound Protocol

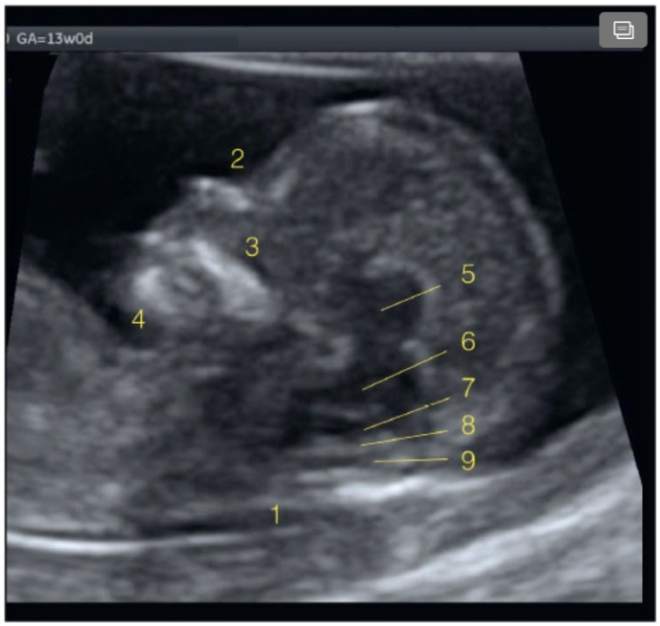
Initial survey:

1. Document location of an intrauterine gestational sac (confirm not in prior hysterotomy or uterine isthmus)
2. Document cardiac activity using M-mode
3. Document fetal number and chorionicity if applicable
4. Document placental position in relation to the cervical os (most previas are of no clinical significance)
5. Document any subchorionic hemorrhage
6. Biometry:
    a. Document CRL *or*
    b. Document HC, AC, BPD, and FL if greater than 11 weeks

Planes:

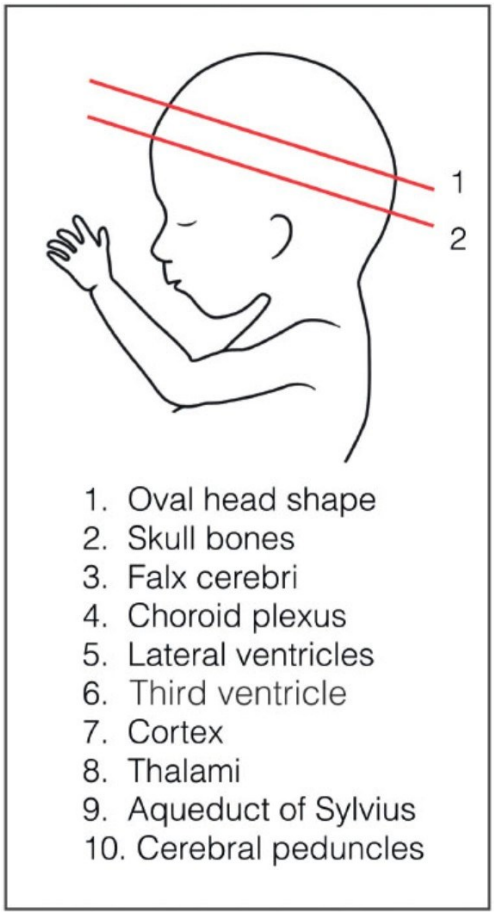
1. **Midsagittal fetus.** Landmarks required for optimal image: NT, nose, cord insertion, bladder
2. **Profile.** Landmarks required for optimal image: NT, nasal bone, maxilla

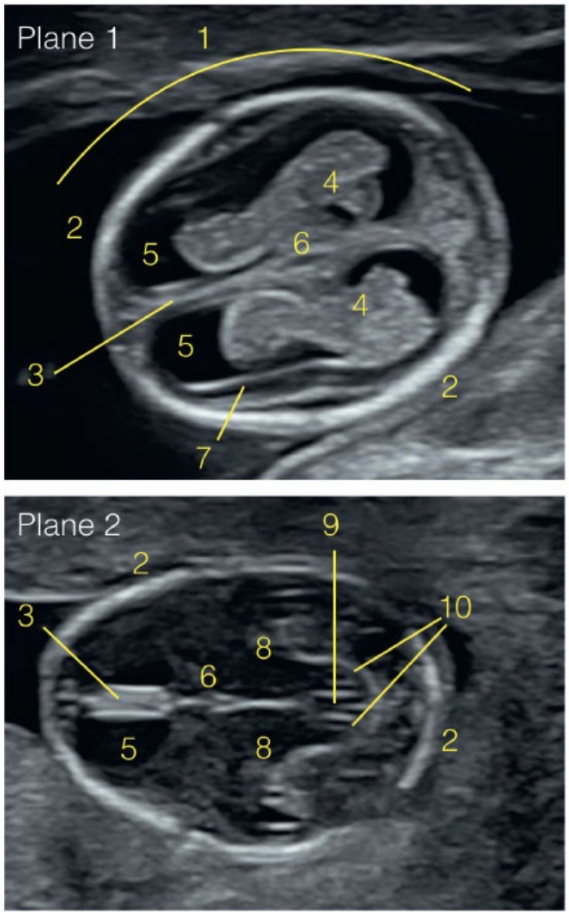




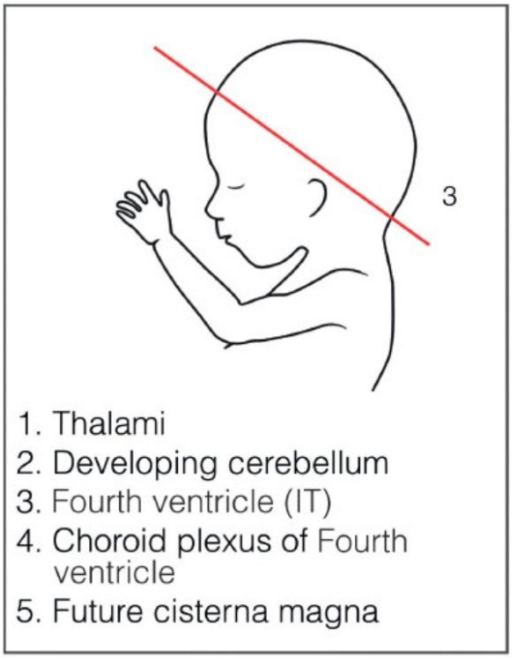
3. **Transventricular plane.** Landmarks required: bilateral symmetrical choroid plexus.

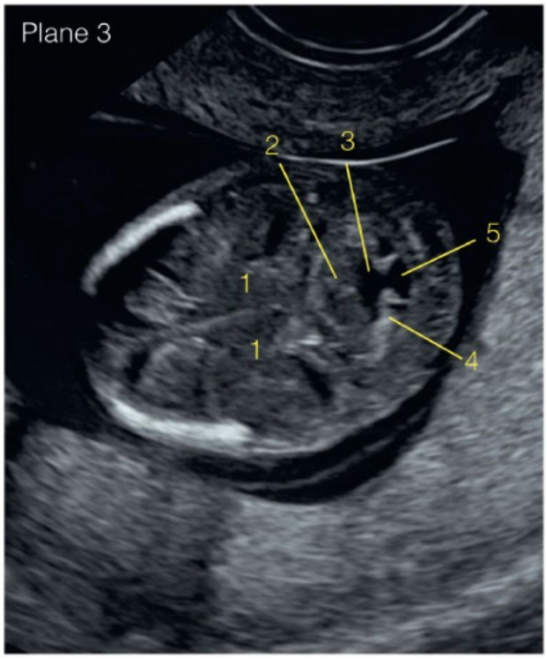
4. **Transthalamic plane.** Landmarks required: bilateral thalami, falx cerebri between anterior horns of the lateral ventricle.



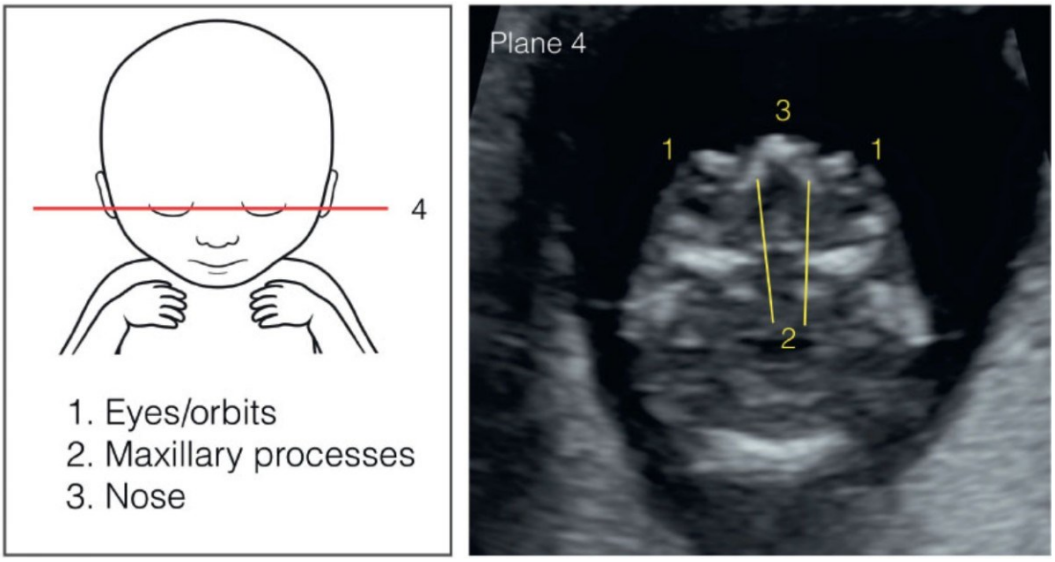


5. **Transcerebellar plane.** Required landmarks: bilateral thalami, fourth ventricle.

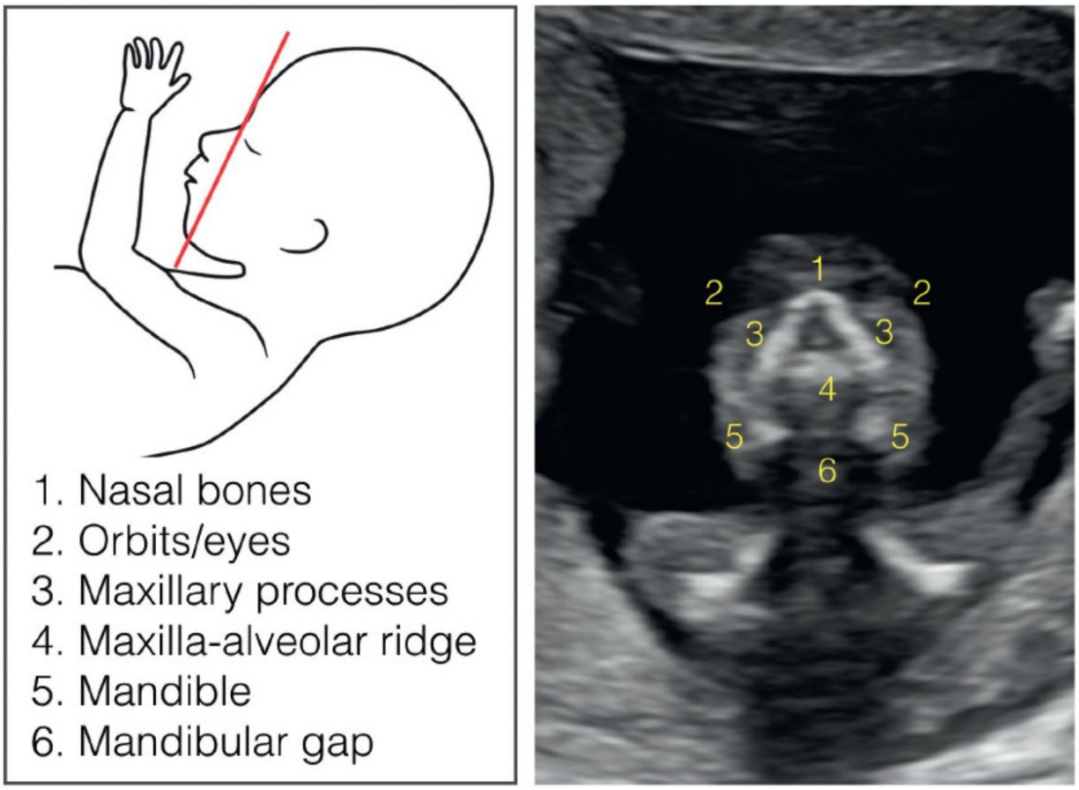




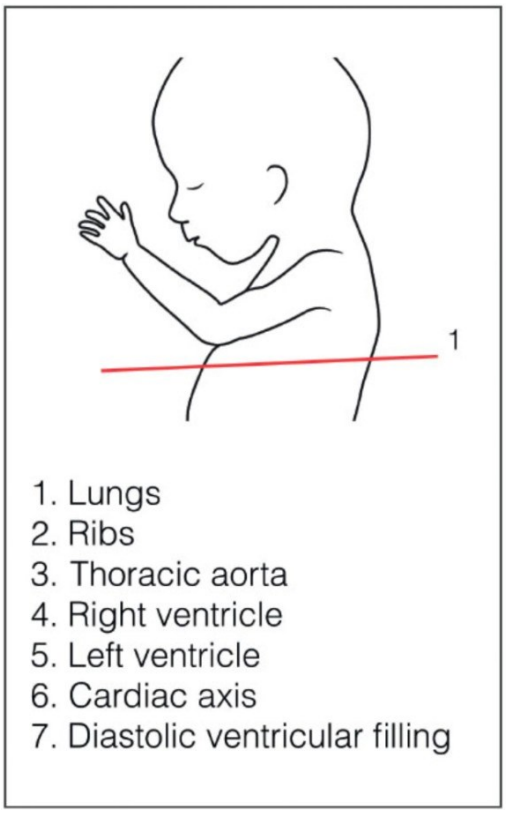
6. **Orbital plane.** Required landmarks: bilateral orbits.

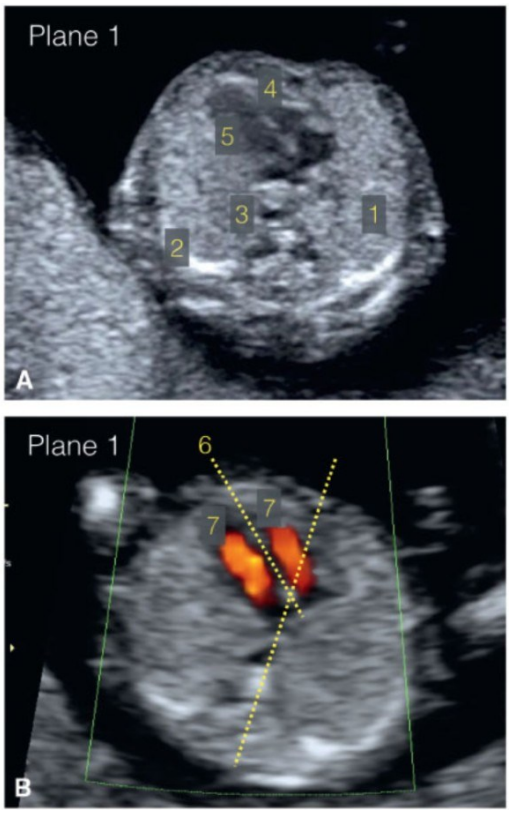


7. **Facial plane.** Required landmarks: bilateral orbits, bilateral maxillary processes.

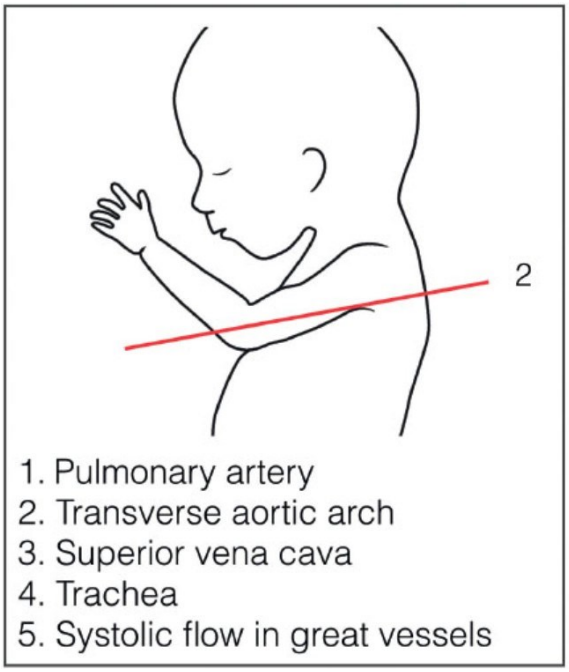


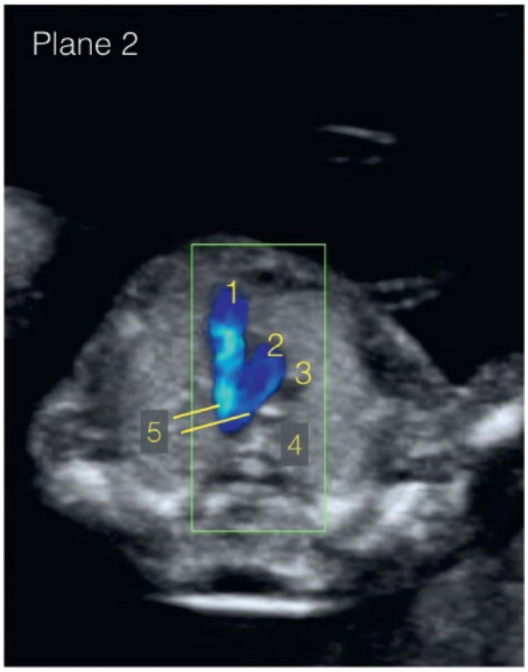
8. **Four chamber view.** Required landmarks: two ventricles, two atria in diastole.



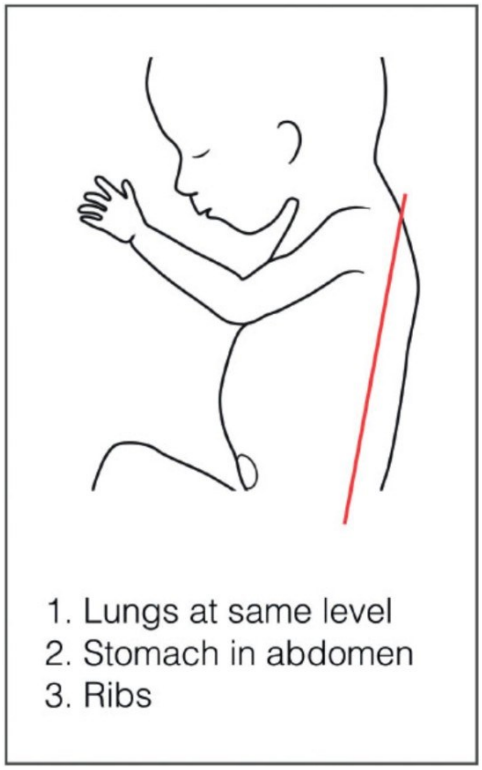


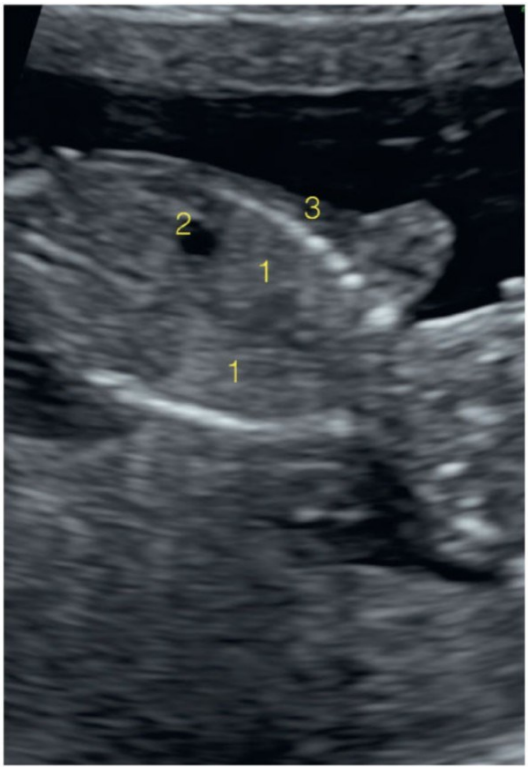
9. **Three-vessel-trachea view.** Required landmarks: V-shaped aorta/PA with same directional flow, trachea.

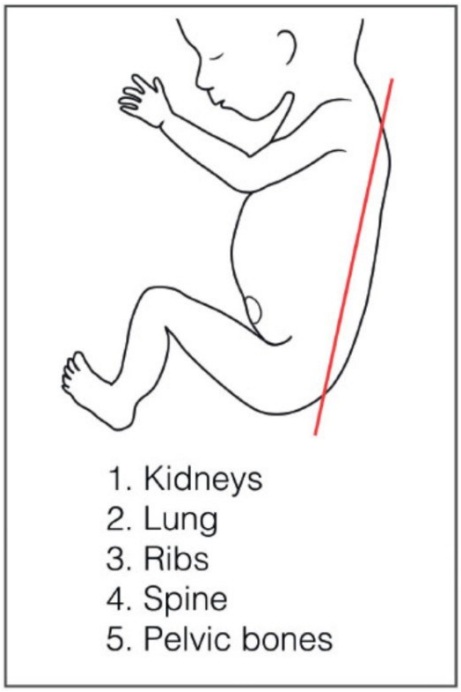


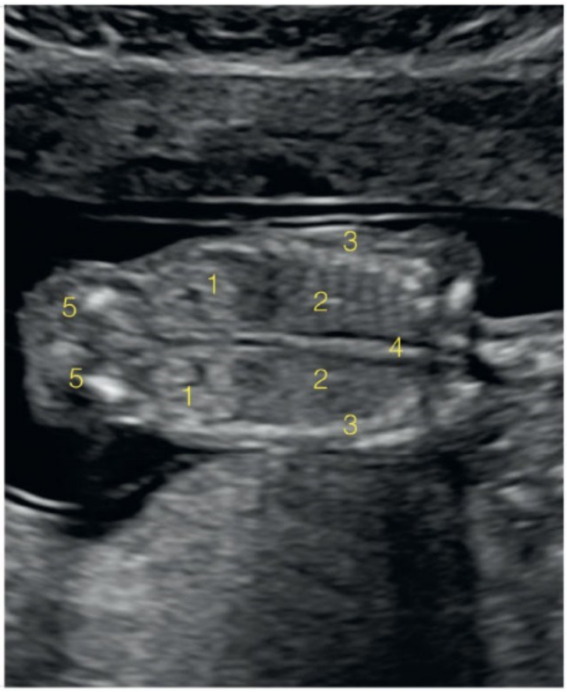


10. **Coronal trunk.** Required landmarks: stomach/diaphragm.
11. **Retroperitoneum.** Required landmarks: bilateral kidneys

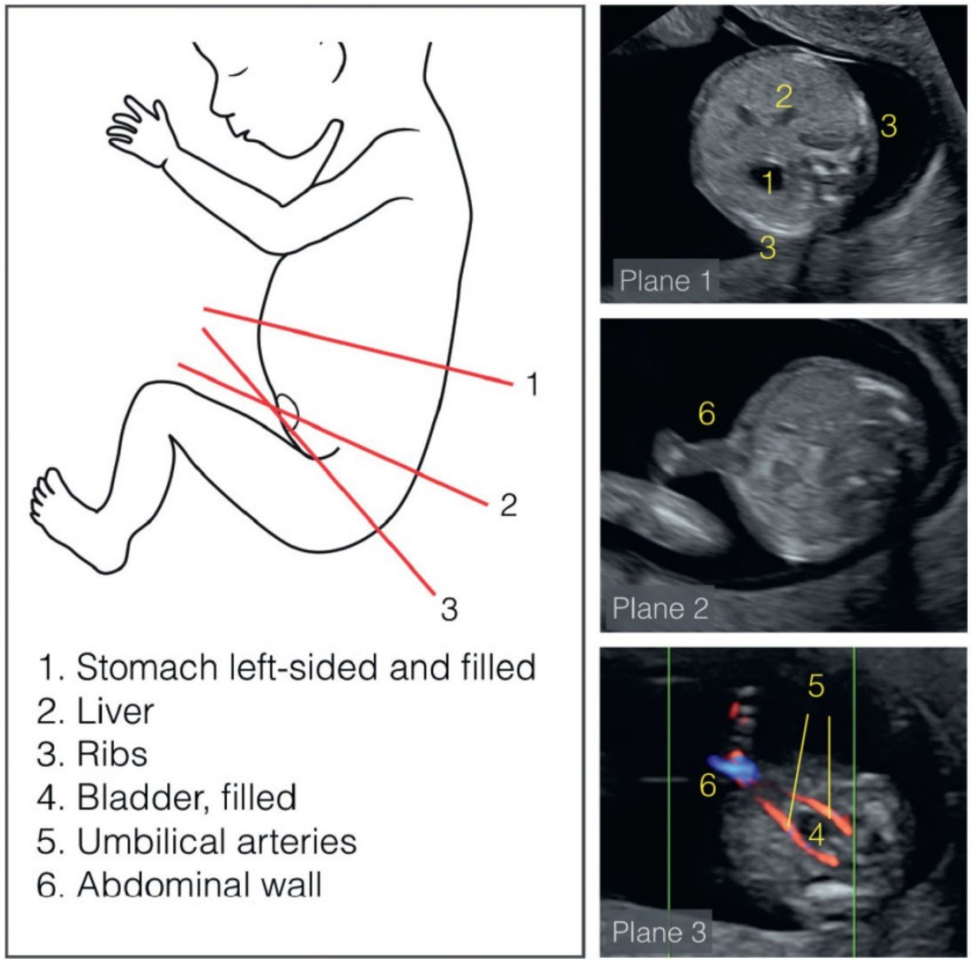




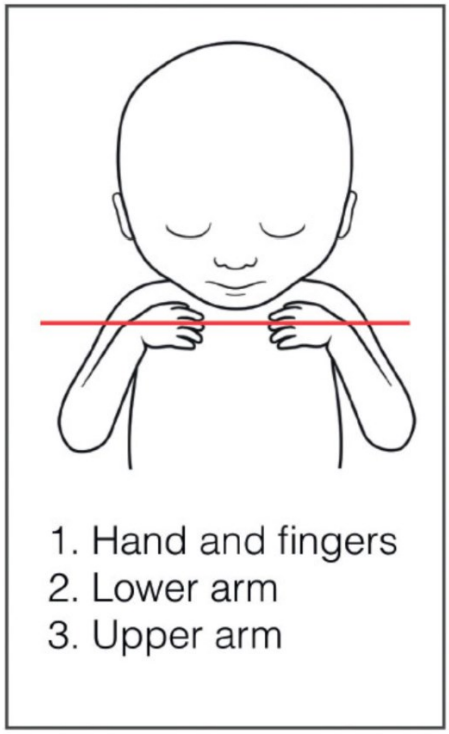




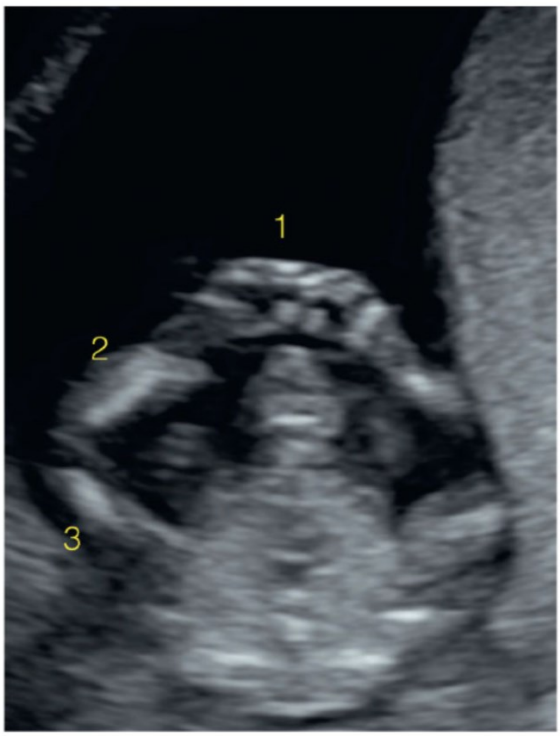
12. **AC.** Required landmarks: stomach, umbilical vein.
13. **Cord insert**. Required landmarks: cord insertion with abdominal skin away from adjacent tissue
14. **3VC**. Required landmarks: bladder, bilateral umbilical arteries using Doppler.

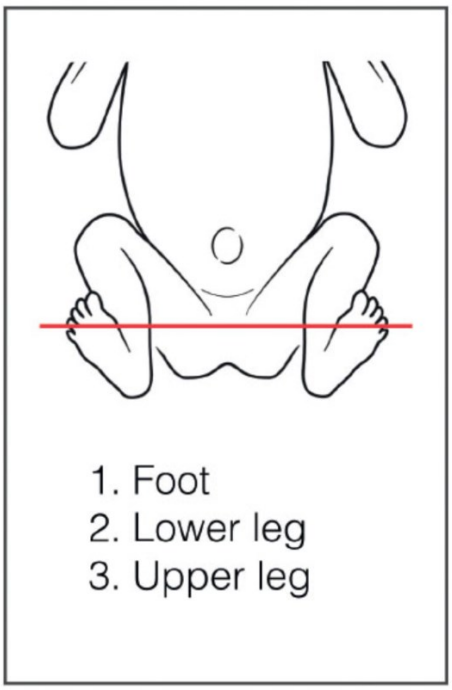


15. **Extremities**. Can be captured by imaging bilateral arms/hands, then bilateral legs/feet, or by imaging the right extremities together and the left extremities together. Required landmarks: four upper and four lower limbs. Can also be captured in 3D. (Fingers and toes not required.)

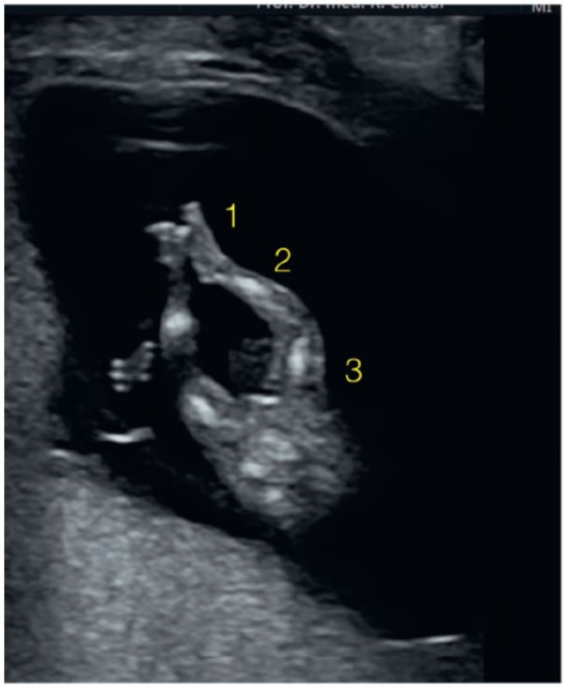


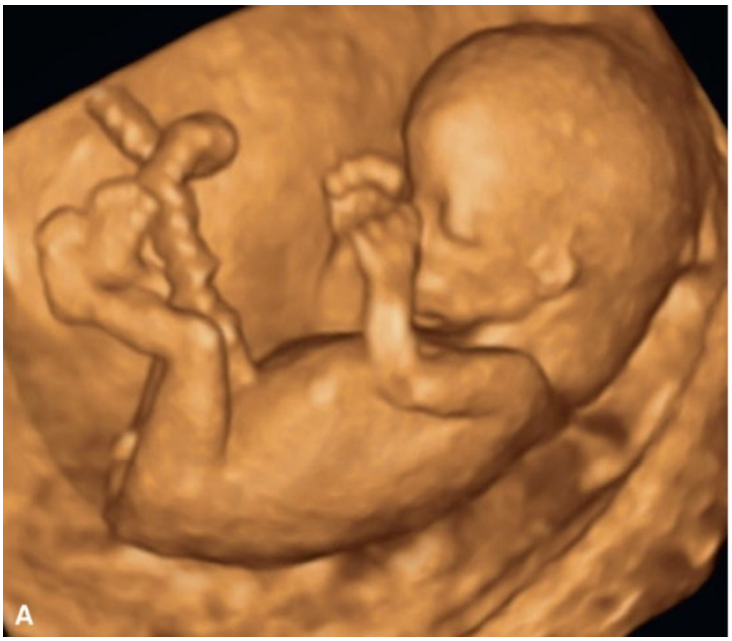
1. Hand and fingers
2. Lower arm
3. Upper arm



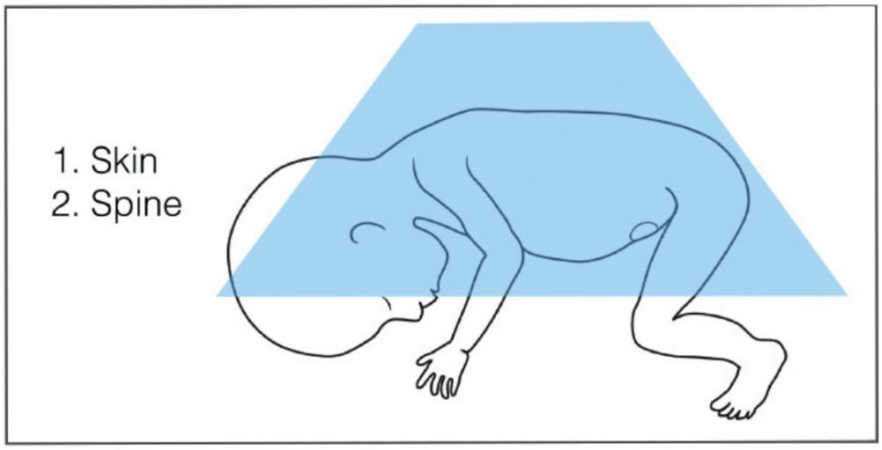


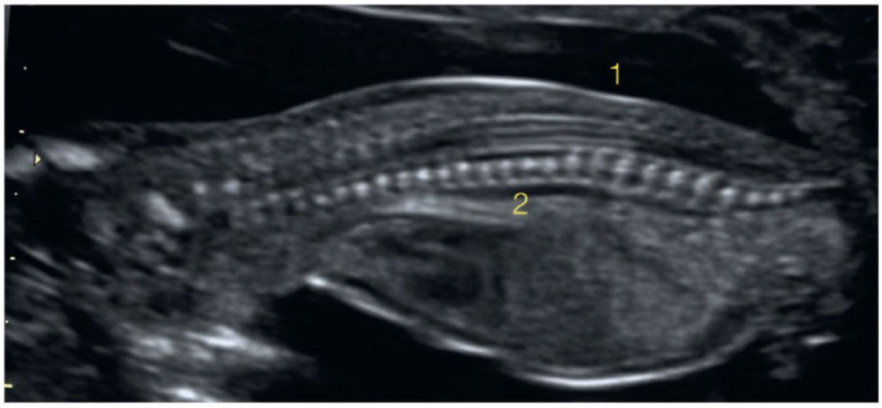
1. Foot
2. Lower leg
3. Upper leg





16. **Spine.** Required landmarks: entire spine with overlying skin not adjacent to any other structures.





Additional planes:

1. Assess maternal anatomy

2. Assess prior hysterotomy if applicable
3. Obtain uterine artery doppler measurements
4. Obtains subtraction imaging of amniotic fluid volume