

Study Title: Validation of a non-invasive cardiac monitor (NICOM) in pregnant women with structural heart disease

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Supplied Agent (s): Cardiac Monitor

Study Summary:

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|---|---|
| Special Population (s) | <input type="checkbox"/> Children <input type="checkbox"/> Children who are wards of the state <input type="checkbox"/> Adults Unable to Consent <input type="checkbox"/> Cognitively Impaired Adults <input type="checkbox"/> Neonates of Uncertain Viability <input checked="" type="checkbox"/> Pregnant Women <input type="checkbox"/> Prisoners (or other detained/paroled individuals) <input type="checkbox"/> Students/Employees |
| Sample Size | |
| Indicate the type of consent to be obtained | <input checked="" type="checkbox"/> Written <input type="checkbox"/> Verbal/Waiver of Documentation of Informed Consent <input type="checkbox"/> Waiver of HIPAA Authorization <input type="checkbox"/> Waiver/Alteration of Consent Process |
| Site | <input type="checkbox"/> Lead Site (for a multiple site research study) <input type="checkbox"/> Data Coordinating Center (DCC) |
| Research Related Radiation Exposure | <input type="checkbox"/> Yes <input type="checkbox"/> No |
| DSMB/DMC/IDMC | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |

Objective:

Aim 1: To compare the non-invasive hemodynamic measurements of cardiac output, stroke volume, and heart rate between a validated reference tool (i.e. echocardiogram) and the NICOM in pregnant women with structurally normal and abnormal hearts (in the first, second, and third trimesters, intrapartum and postpartum).

Aim 2: Assess the precision and accuracy of heart rate, stroke volume and cardiac output of the NICOM machine. The purpose of this study is to establish validity and clinical utility of the NICOM machine in women with structural cardiac disease in labor, which can further guide management while avoiding invasive (monitoring) procedures.

Our hypothesis is that there is acceptable correlation between NICOM and ECHO in cardiac output, stroke volume, blood pressure and heart rate with a mean percentage difference of < 30% throughout pregnancy (it has been proposed that a MPD of 30% between two methodologies is clinically acceptable for CO estimation). We expect the hemodynamic measurements of the NICOM machine will be within an acceptable mean percentage difference (clinically) to the measurements obtained by the echocardiogram. We will likely need to adjust for the increasing volume throughout gestation as a correction factor.

Analysis: An accepted "gold standard" for hemodynamic monitoring in women with both healthy and diseased hearts is not currently available. Pregnancy is associated with significant hemodynamic changes, both during and following delivery, which can be even more profound in the structurally-abnormal heart. Clinical

management of these women is based on surrogate markers of cardiac indices such as peripheral blood pressure, heart rate and oxygen saturation, rather than the use of invasive testing due to its associated complications. Echocardiography has largely replaced PAC in the obstetric population to measure cardiac output due to its non-invasive nature and good correlation with PAC¹⁸. However, its use is limited in the intrapartum period due to the need for clinical expertise in obtaining and interpreting the images. The proposed study has the potential to validate bio-reactance cardiac output monitoring using the NICOM against echocardiography for use in structurally abnormal pregnant hearts in order to better drive goal-directed (specifically delivery mode) therapy through continuous hemodynamic monitoring during the second and third stages of labor, and 24 hours postpartum.

Currently, some women with structural heart disease are undergoing cesarean delivery in an effort to avoid the dynamic physiologic changes purported to occur with labor. Furthermore, significant resources are expended when the delivery location requires a higher level of care (such as the CV ICU) as a result of these suspected changes and the risk associated with delivery. These recommendations are based on old data obtained in women with structurally normal hearts and extrapolated to women with congenital and acquired disease. Validation data of non-invasive technology in pregnancy against the current gold standard of PAC are practically and ethically unobtainable. If NICOM is correlative to echocardiogram parameters, there is the potential to enable further understanding about the hemodynamic changes during labor and use these data to develop recommendations for delivery mode in women with heart disease. This could potentially be beneficial to both the patient and the healthcare system by decreasing morbidity and its associated costs (ICU admissions, readmission, wound infections, etc.).

Background:

Major hormonal and hemodynamic changes occur in the cardiovascular system in pregnancy that can unmask and impact underlying cardiac disease. Cardiac output can rise by up to 50% throughout gestation, with an additional 30% rise intrapartum. This increase is multifactorial, owing to an increase of 50% in maternal blood volume during pregnancy, a decrease in afterload due to a decline in systemic vascular resistance and a rise in the maternal heart rate of up to 20 beats per minute. Cardiac output has been the most extensively studied physiologic parameter of cardiac performance during pregnancy, and is dependent on both heart rate and stroke volume. Most of the changes in cardiac output on pregnancy are a result of stroke volume. However, during the mid-second trimester, stroke volume plateaus while heart rate continues to rise, becoming the major contributor to cardiac output in the latter half of pregnancy. During labor, cardiac output is further increased by the autotransfusion of blood from the uterus during a uterine contraction and maternal expulsive efforts. This can lead to an increase of up to 500cc of blood within seconds into the systemic circulation, which can significantly impact cardiac output and stroke volume.

Following delivery, many of these cardiovascular changes reverse in the first 2 weeks postpartum with further normalization toward preconception values 3-12 months later. Women without heart disease adapt well and adverse events are generally rare. However, the stress induced by these antenatal changes can cause a patient with underlying disease to decompensate during the latter half of pregnancy and more specifically, intrapartum when these changes peak. Studies on maternal morbidity attributable to cardiac disease in the

United States have shown the most likely time for an adverse cardiac event is intrapartum and immediately postpartum, owing to the drastic and acute changes in hemodynamic status during these time periods. Without an invasive monitor (PAC), hemodynamic monitoring during these time relies on surrogate markers such as blood pressure or heart rate.

There is relatively scarce data on continuous hemodynamic profiles in women with both congenital and acquired heart disease in pregnancy, specifically during labor. Previous literature on the use of invasive monitoring (PAC) during pregnancy have been performed only intermittently during the labor and postpartum process. However, the hemodynamic status during the second and third labor stages is not static and therefore the need for continuous evaluation cannot be underscored. Timing and mode of delivery are predicated on these prior studies, leading to an increase in cesarean delivery and general anesthesia is women with more severe disease, such as aortic stenosis. With the increased morbidity associated with cesarean delivery and the push from ACOG to avoid cesarean section (when clinically feasible), the recommendations for operative delivery in women with heart disease have been questioned. Cardiovascular complications are now the leading cause of maternal death and continue to climb in the United States at a rate unmatched by any other industrialized nation.

The increased morbidity associated with invasive monitoring limits the use of pulmonary artery catheters in the pregnant population and therefore a non-invasive way to obtain hemodynamic profiles in women with heart disease is desirable. Currently available minimally invasive monitors include LiDCOplus (LiDCO, Cambridge, United Kingdom), PiCCOplus (Pulision Medical Systems, Munich, Germany), Vigileo (Edwards Lifesciences, Irvine, CA), USCOM (Ultra Sound Cardiac Output Monitor, Sydney, AU) and NICOM (Cheetah Medical Inc., Portland, OR). The first three aforementioned monitors are not truly non-invasive, given they still require the use of an arterial line, which is a limiting factor on the obstetrics floor¹⁴. USCOM is an operator-dependent Doppler ultrasound device, potentially subject to inter- and intra-observer variation. Proficient use of this device is obtained through required training sessions and proof of 30 test cases. Although USCOM has clinical utility, it has low signal-to-noise ratio, limiting its accuracy in environments where there is ambient electrical noise (i.e. labor and delivery). It is also sensitive to placement of the electrodes on the skin, which can be altered by body temperature, BMI and humidity, impacting the conductivity.

The non-invasive cardiac output monitor (NICOM) is based on bio-reactance technology and is operator-independent, allowing negligible inter-observer variability in data collection and ease of use. Measurements of cardiac output and stroke volume are not dependent on the distance between the electrodes, which can significantly increase the accuracy of the results. It involves the application of four sensors on the thorax. Changes in aortic blood flow drive phase shifts of propagating waves which are detected by the sensors as the frequency changes. These changes correlate with instantaneous changes in blood volume and blood flow in the aorta. Bio-reactance has been validated against pulmonary artery catheters in non-pregnant populations which manifest various forms of hemodynamic instability and following cardiac surgery.

Additionally, it has been shown to produce hemodynamic profiles in the pregnant population consistent with other more invasive forms of monitoring. Although NICOM has been shown to overestimate measures of stroke volume and cardiac output as compared to echocardiogram in women in the second trimester, Doppler

echocardiography has been shown to underestimate these parameters as compared to invasive thermodilution. bio-reactance has been validated in pregnant and postpartum women with good correlation to echocardiography in the third trimester, but it has yet to be compared during labor. As well, previous studies showed a near-clinical acceptable agreement in the third trimester with a MPD of 32%, which may be attributable to the assumptions about thoracic shape and fluid volumes (which both change dramatically during pregnancy) in order to calculate hemodynamic parameters. NICOM can provide continuous data on heart rate, blood pressure, cardiac output, stroke volume, stroke volume variation, and total peripheral resistance. Fluctuation in these parameters throughout labor could potentially be useful information to drive clinical recommendations during the antepartum, intrapartum and postpartum process. However, NICOM has not been validated in the structurally abnormal heart and this therefore limits its use as a clinical tool in this pregnant population.

Although cardiac disease complicates a small number of all pregnancies, it has become a leading cause of maternal morbidity and mortality in the United States. Prior to the widespread institution of penicillin, rheumatic heart disease was the most common forms of heart disease encountered in pregnancy. Now with progress in both diagnostic techniques and surgical interventions for the treatment of congenital heart disease, more women with congenital cardiac malformations are reaching reproductive age and desiring fertility. Management guidelines and recommendations regarding timing and mode of delivery have been fully outlined in both the cardiac and obstetrical literature but there is a paucity of data on intrapartum management. This is a critical time for gravidas with cardiac disease. With an increase in cardiac output of up to 80% above baseline, women with a fixed cardiac output (as in mitral or aortic stenosis) are at increased risk for failure as a result of the hemodynamic changes during the second stage of labor. In an effort to avoid these cardiovascular shifts, many obstetricians and cardiologists recommend planned cesarean delivery, which is associated with significantly increased morbidity and recovery time compared to a vaginal birth. Optimally, assessment of cardiac output and stroke volume would be continuously monitored throughout the labor process in an effort to attain a vaginal delivery.

The gold standard for cardiac monitoring has been through invasive thermodilution (pulmonary artery catheterization [PAC]) however, recent literature does not suggest a benefit and may even increase the risk of morbidity in some patients. Transthoracic echocardiogram has been evaluated in pregnancy and shows excellent agreement with pulmonary artery catheterization, allowing for a non-invasive reference for validation of other cardiac output techniques. Continuous echocardiography is not feasible during the second stage of labor due to it's inherent limitations including user education and movement artifact. An optimal technique for evaluation of CO and SV during labor would be non-invasive, repeatable, reproducible, and not required specialized training for application.

Transthoracic bio-reactance, or the non-invasive cardiac output measurement [NICOM™, Cheetah Medical Inc., Portland, OR] system, is a new technique that is able to measure multiple hemodynamic parameters with four transdermal electrodes placed on the patients' thorax. It is based on frequency- and phase-modulation of the voltage signal measured in response to an applied transthoracic current. Its readings have been shown in multiple studies to correlate well with PAC in the non-pregnant population. It has shown acceptable accuracy, precision and responsiveness for cardiac output monitoring in patients experiencing a wide-range of

hemodynamic situations. However, it has not been validated in the pregnant, structurally abnormal heart i.e. congenital cardiac disease, as this was exclusion criteria in the aforementioned studies. Establishing normative values during the second stage of labor utilizing the NICOM in women with congenital cardiac disease has the potential to be clinically useful in developing goal-directed management therapy for these women.

Design:

We will be recruiting pregnant women with singleton pregnancies in their first trimester who present to either the heart disease in pregnancy clinic, two private obstetrical offices located at Saint Luke's or the medical education clinic for obstetrical care.

The control group will be approached during their first visit and asked to participate in the study; a detailed consent form will be reviewed with each patient and written consent to participate will be obtained at that time. The patients will be contacted by the research team as to when and where to present for each echocardiogram.

Four board-certified cardiologists (VR, AM, LS and AG) will read the echocardiograms for the study. They will be blinded to all of the results of the NICOM procedure. The first echocardiogram will be scheduled within the cardiovascular unit to be performed sometime prior to 14 weeks. Following that procedure, the patient will report to the Maternal-Fetal Medicine unit for the first NICOM procedure. The four leads will be attached and continuous monitoring will be obtained for 15 minutes. A similar protocol will be instituted for the second (between 14 and 28 weeks) and third trimester (after 28 weeks and prior to admission for labor) procedures. Once the patient is admitted for labor, the research team will be contacted. The patient will be monitored and managed per normal clinical protocol for cervical change. Once the cervical exam is 4 cm or greater, the echocardiogram will be performed bedside by a trained, certified echocardiography technician. Immediately following the echocardiogram, the NICOM leads will be placed and 15 continuous minutes of monitoring will be obtained. Following delivery of the neonate, the research team will once again be contacted and the final echocardiogram will be performed within the first 24 hours postpartum in the cardiovascular unit. Immediately following the echocardiogram, the NICOM leads will be placed and 15 minutes of continuous monitoring will be collected. For the study group, at each time point, a BNP will be collected by venipuncture and sent to the Saint Luke's lab for evaluation (per normal clinical protocol).

The echocardiograms in the first trimester will all be a full assessment of outflow tracts, function, etc. in both the control and the study group. However, the second trimester, third trimester, intrapartum and postpartum echocardiograms for the control group will only assess cardiac output and left ventricular outflow tract (in order to calculate the stroke volume). All of the echocardiograms for the study group – as per routine clinical practice and normal standard of care – will be full echocardiograms.

Blinding: We will have two physicians (VR, AM) reading the echocardiograms and the information obtained by the NICOM will not be available to them during the study. However, the results of both the NICOM and the echocardiogram will be available to the obstetrician who will be managing the patient during her labor course. The results of the echocardiogram will be used to guide management throughout the pregnancy.

We will set the limit of bias (for cardiac output) at 0.5 L. In order to reach >90% power to show non-inferiority⁷ (an absolute mean difference in CO <1.0L between the NICOM and echocardiogram), we would need to enroll at least 38 patients in each arm. We will plan on enrolling 50 in each arm to account for drop-out, the development of exclusion factors (i.e. the development of pre-eclampsia or preterm delivery prior to third trimester) or loss to follow up.

Procedures:

Laboratory tests: As per routine clinical care, the study group will undergo a baseline EKG (which is performed at their first Heart Disease and Pregnancy visit) and a BNP each trimester. The EKG and BNP will both be obtained in the Maternal-Fetal Medicine unit. Approximately 3 cc of blood/serum will be needed for the BNP measurement. The fate of any body component (blood, CSF, bone marrow, etc.) used in the study, emphasizing confidentiality of labeling of the sample and the sample's destruction or storage. All BNPs will be sent to the lab and disposed as per hospital protocol.

Study Procedures: It is not standard clinical practice to obtain echocardiograms in pregnant women with structurally normal hearts, therefore each echocardiogram obtained in the control group will be performed solely for research purposes and the funds will be provided from the aforementioned grants. If clinical indications arise in this group of women that would warrant an echocardiogram, the patient will have this performed in the cardiovascular institute and insurance will be billed. It is standard clinical practice to obtain serial (each trimester) BNPs and echocardiograms in women with known structural heart disease in pregnancy. Therefore, these procedures will be billed to insurance and performed in the cardiovascular institute.

This information will also be used for research purposes. Part of a first-visit to the heart disease in pregnancy program includes an EKG and this will be billed through insurance. We have purchased the NICOM machine with grant funding and all NICOM data obtained is not part of routine clinical care. The expenses for the machine (the machine itself, electrode pads, cord) will be supplied by the aforementioned grants and donations.

All echocardiograms will be performed by trained, certified echocardiographers from the cardiovascular institute. For both the control and study group, the following will be obtained: an echocardiogram (performed in the cardiovascular institute) in the first trimester (< 14 weeks gestation), in the second trimester (> 14 weeks to 28 weeks) and the third trimester (> 28 weeks). An echocardiogram will also be obtained once the patient is deemed to be in labor (contractions causing cervical change, generally at > 4 cm dilated). This echocardiogram will be done at the patient's bedside while on labor and delivery. One additional echocardiogram will be obtained within 24 hours after delivery. On average, an echocardiogram requires 30 minutes to obtain the proper images. For both the control and study group, the following will be obtained: 15 continuous minutes of the NICOM data in the first trimester (< 14 weeks gestation), in the second trimester (> 14 weeks to 28 weeks) and the third trimester (> 28 weeks). NICOM data will also be obtained once the patient is deemed to be in labor (contractions causing cervical change, generally at > 4 cm dilated). This echocardiogram will be done at the patient's bedside while on labor and delivery. Fifteen additional minutes of NICOM data will be obtained within 24 hours after delivery. The NICOM contains four electrode pads that are applied by adhesive on the patient's thorax.

The echocardiograms in the first, second and third trimester will be performed in the cardiovascular institute. The intrapartum echocardiogram will be performed bedside in the labor and delivery unit.

The postpartum echocardiogram will be performed in the cardiovascular institute. The NICOM hemodynamic assessments will be performed in the MFM unit for the first, second and third trimester evaluations. The intrapartum NICOM assessment will be done at the bedside on the labor and delivery unit. The postpartum evaluation with NICOM will be done on the mother-baby unit in the patient's postpartum room. Each patient will be in the lateral recumbent position at 35 degree tilt (left) to avoid aortocaval compression. The EKGs for the study group will be performed per normal clinical protocol in the MFM unit at the first heart disease in pregnancy clinic visit.

Venipunctures for BNP will be obtained at the bedside at each NICOM assessment by a trained nurse in the MFM unit. All records will be recorded in Redcap data collection system which can only be accessed by username and password of each of the participating researchers.

Inclusion and Exclusion Criteria

- **Inclusion criteria:** We will enroll two groups of pregnant women: women with and without structural heart disease. The healthy pregnant women (arm A) group will be selected by the following criteria: pregnant in the first trimester (14 weeks or less) planning delivery at Saint Luke's on the Plaza, singleton gestation without history of heart disease. The structural cardiac patients (arm B) will be selected by the following criteria: pregnant women with a history of any congenital (corrected or non-corrected) or acquired cardiac disease in the first trimester (14 weeks or less) who present to the Heart Disease in Pregnancy program for consultation or complete care, singleton gestation.
- **Exclusion criteria:** Both groups will exclude women with chronic hypertension, pre-gestational diabetes, multiple gestation, preeclampsia, autoimmune disease, and anyone with a history of cardiomyopathy but currently with an EF >45%. In the healthy pregnant group, we will also exclude women on any cardiac or antihypertensive medications (beta blockers, calcium channel blockers, hydralazine). Women who are unable to give informed consent will not be included. Poor quality imaging in the control group will also be excluded (in order to avoid echo contrast).
- **Withdrawal/Termination criteria:** In the event any woman who was already enrolled decides to leave the study, the data obtained to that point in the study will be used (for example, if a woman withdraws during labor but a complete set of comparative data was obtained prior to that point, her 1st, 2nd and 3rd trimester data will be used for analysis).
- **Participation in other studies:** Any woman who decides she would like to participate in additional research studies while enrolled in this study may do so as long as they continue to meet our exclusion criteria.

Vulnerable Populations

Our study population will exclusively include pregnant women. They will be approached in the Heart Disease in Pregnancy program located within the Maternal-Fetal Medicine unit or (for the control group) during their routine office visits. We have one research coordinator who discusses management plans with patients at each prenatal visit. She will approach each individual patient in an exam room prior to their visits informing them of a potential research project and evaluate their interest in participating. Women interested will be approached by a MFM or cardiology provider following the prenatal visit/consultation to go over the requirements and involvement of the study protocol. Each woman in our program receives at least one echocardiogram during the course of the pregnancy and many times, one per trimester. Therefore, the majority of the study involving echocardiographic imaging does not differ from standard of care.

Recruitment Methods

Women will be recruited from the Maternal-Fetal Medicine unit, the Saint Luke's affiliated OB GYN groups, and the Medical Education Clinic at Saint Luke's Hospital of Kansas City. We will limit recruitment to these units as to ensure completeness of the dataset through the postpartum period (women who will be delivering at Saint Luke's Hospital of Kansas City).

Recruitment will be conducted by the primary investigator, the co-investigators, the OB/GYN residents at Saint Luke's Hospital. Patients will be approached to participate during their first OB visit. Any interested patient will then be screened by the study staff and consented.

Each patient will receive this questionnaire during the first prenatal visit. We will use this to assess whether 1) they qualify as a control subject or 2) whether their cardiac disease can be qualified as "structural." This will be provided by any of the co-investigators, nurses or OB/GYN residents in the office at the first visit after assessing the patient's willingness or interest to participate. Once the patient has been assessed, the PI or co-investigators will come in to review the consent.

Following initial contact with a prospective subject and assessing their willingness to participate, this letter will be given to the patient to review prior to reviewing the consent form.

Compensation for participation in research activities

We will be covering the cost of the control group's echocardiograms and not be submitting any procedures through insurance (for the control group). If an abnormality is found in one of the control patients, they will become part of the study group (if desired) and all procedures will be billed through insurance at that point. If insurance refuses the costs of the echocardiograms for the study group, we will perform a peer-to-peer review as we normally do in these situations. We will not be paying for any of the echocardiograms out of the research funds for the study group as they would normally require the scheduled imaging (echocardiograms per trimester).

There will be no stipend or payment for participants in this study. However, following delivery, we will be providing patients with a \$10 gas gift card.

Compensation for research-related injury

If you have a bodily injury as a result of participating in this study, treatment will be provided for you at the usual charge. Treatment may include first aid, emergency care and follow-up care, as needed. Claims will be submitted to your health insurance policy, your government program, or other third party, but you will be billed for the costs that are not covered by the insurance. In no way does signing this consent form waive your legal rights nor does it relieve the Study personnel, Sponsor or involved institutions from their legal and professional responsibilities.

To help avoid injury, it is very important for you to follow all study directions.

Risks to Participants

- **Physical risk:** The physical risks to both groups include discomfort during the echocardiogram (i.e. probe pressure), allergic reactions to conductance gel, allergic reactive to adhesive (on the NICOM electrodes). We will assess each patients' allergies prior to study enrollment and utilize alternative conductance medium if necessary. Given obtaining a venipuncture for the BNP is part of routine clinical care, we will counsel the study group regarding the risks of pain and bleeding during the procedure.
- **Psychological risk:** There is minimal risk of psychologic harm in this study given it involves non-invasive monitoring and the results are blinded to the patient except when clinically relevant.
- **Social risk:** There is no social risk in this study.
- **Economic risk:** The only economic risks incurred are those that would otherwise be clinically present in the study group (i.e. co-pays for appointments, co-pays for echocardiograms)
- **Potential benefit of participating in the study:**
 - The potential benefit to the control group includes diagnosis of an unknown cardiac disorder that otherwise would not have been evaluated (due to lack of symptoms). The benefit to the study group may be in detecting postpartum complications that may arise that otherwise may not warrant an echocardiogram (i.e. early signs of heart failure).
 - The benefit to the population drawn is that potential use of a non-invasive method for evaluating cardiac disease.

Benefits to Participants

- The potential benefit to the control group includes diagnosis of an unknown cardiac disorder that otherwise would not have been evaluated (due to lack of symptoms). The benefit to the study group may be in detecting postpartum complications that may arise that otherwise may not warrant an echocardiogram (i.e. early signs of heart failure).
- The benefit to the population drawn is that potential use of a non-invasive method for evaluating cardiac disease.

Alternative to Participation

The alternative to participation is to continue routine care in the Heart Disease in Pregnancy Program; the care will not be altered for the study group (i.e. each patient will receive imaging and treatment according to the standards of care). The control group will not receive any echocardiograms unless clinically indicated if participation in the study is declined.

Statistical Analysis

Statistical analysis will be carried out using R statistical package. We will perform Shapiro-Wilks to assess normality of the data. Correlation between the two methods will be assessed using either Pearson's (for normally distributed data) or Spearman (for non-normally distributed data) correlation coefficients. We will assess accuracy and precision by evaluating bias (mean difference between methodologies), the standard deviation of the differences, 95% limits of agreement (LOA=bias \pm 1.96 SD) and mean percentage differences (=LOA/mean of two methodologies). Bland-Altman plots will be constructed to compare the two measurement techniques. We will evaluate the inter-and intra-observer reproducibility by intraclass correlation coefficients (ICC).

There will be no interim analysis since this is a non-inferiority trial comparing two diagnostic techniques, one of which is the is clinically-known to be equivalent to pulmonary artery catheterization (gold standard). Women will be recruited in the Maternal-Fetal Medicine office at their routine obstetrical visits. There will be no randomization as this will be an open-label, prospective study with each patient undergoing evaluation utilizing both diagnostic techniques. Statistical analysis will be carried out using R statistical package. We will perform Shapiro-Wilks to assess normality of the data. Correlation between the two methods will be assessed using either Pearson's (for normally distributed data) or Spearman (for non-normally distributed data) correlation coefficients. We will assess accuracy and precision by evaluating bias (mean difference between methodologies), the standard deviation of the differences, 95% limits of agreement (LOA=bias \pm 1.96 SD) and mean percentage differences (=LOA/mean of two methodologies). Bland-Altman plots will be constructed to compare the two measurement techniques. We will evaluate the inter-and intra-observer reproducibility by intraclass correlation coefficients (ICC).

Data Management, Security, Confidentiality, and Safety

The primary investigator and the co-investigators will have access to the study data. The controls will only be accessed by this aforementioned group of researchers. As the study group's care will not be altered from a clinical standpoint, any provider that usually has access to the patient record will be able to view the imaging/documentation as clinically indicated in EPIC.

The data will be collected and stored in Red Cap, which is a pass-coded data collection system located on the hospital network, accessible only to the investigators. All paper documentation (consents, questionnaires) will be locked in the PI's office within the MFM office in a locked filing cabinet.

All personal health identifiers will be removed and coded in order to protect confidentiality. The information will be stored in RedCap, which is pass-coded on the hospital network. The co-investigators and the PI will have access to the key code for all collected data.

Each subject will have an identifying code (i.e. S1, S2, etc.) and the code will be maintained by the PI. All personal health information linking patients will be de-identified in this way. This will be stored in a locked filing cabinet in the PI's office within the MFM division, accessible only to the PI.

The data will be coded and the master code list will be kept in the PI's office, under lock and key, within the MFM division. The de-identified data will be collected within the pass-coded Red Cap data collection system on the hospital network, accessible only to the co-investigators and the PI.

There will be no mobile devices used for data collection or storage. Red Cap is reachable only by accessing the hospital network (via password). Only the investigators will be granted access to Red Cap by individual passwords.

If a security issue has been identified, we will alert the IRB immediately and discuss alternatives to data storage and alert the patients as necessary to the breach.

The only samples that will be collected are those that would normally be performed for routine clinical care (i.e. BNP's for the study group). These will be handled via normal hospital protocol for clinical care.

We will store all patient information in a data collection system that is pass-coded and accessible only by first accessing the hospital network with a passcode. All the investigators will be granted access to the de-identified data stored in Red Cap, again through a passcode. We will protect patient confidentiality by approaching patients in the privacy of an exam room. We will maintain all HIPPA laws outlined in the hospital by-laws and protocols. There is no particular part of the study that places patients at greater risk for confidentiality breach than what is normal for routine clinical care.

We will limit the data collection to physicians and nurses trained in data collection (the aforementioned PI and co-investigators). The cardiac imaging will be read by board-certified cardiologists. The maternal-fetal medicine physicians will be trained by the NICOM company in proper placement of the NICOM leads and will be the only personelle applying the NICOM pads. The data from the NICOM will be collected only by the PI who is trained in the NICOM system.

Each echocardiogram will be reviewed by a board-certified cardiologist after each study has been completed. In the event there are any abnormalities, they will be discussed with the patient in detail and a management plan will be devised. There will be no interim analysis during this study. The data will be analyzed under the analytics and statistical section.

As this is a non-inferiority trial comparing two diagnostic techniques, we do not foresee any triggers that would cause the study to stop or be altered. In the event one of the control subjects is found to have a structural cardiac anomaly, we will treat her according to the standard of care for that particular disease state.

The risk of harm during this study is minimal and therefore we do not anticipate any adverse events. We will perform a thorough history and physical exam at the initial OB visit to assess the patient's eligibility and willingness to participate. If at that time she is found to have allergies to adhesive or conductance gel, we can use alternative measures (i.e. non-adhesive pads, latex-free conductance pad, lotion instead of conductance gel) to perform the procedure. If at any point we deem the risk is greater than minimal, we will not ask that

patient to participate in the study. Any unanticipated problem will be reported to the PI. At that point, we will have the study co-investigators discuss the issue with the PI and come up with a solution as a team. If the risk or event is deemed serious, it will be reported to the IRB within 2-3 days (depending on if it is a weekend).

If a patient does experience (what is deemed to be) an adverse event, she will be asked to leave the study. The results of the study will be shared via a peer-reviewed journal.

Consent Process

Once it has been established that the patient is willing to participate and has met inclusion criteria, any one of the co-investigators or the PI will approach the patient and review the consent in detail.

The consent will be typed and legible. It will be reviewed with each patient prior to written consent. We will explain that regardless of participation, each patient will receive the same high-quality care regardless of enrollment in the study. Coercion can be avoided because there is no monetary incentives to participate. At the end of the study, each subject will be presented with a \$10 gas gift card. The same confidentiality and HIPPA regulations will be applied to study patients and those that chose not to participate. All health information will be on the PI's computer which is pass-coded and on the hospital network. It is maintained behind a locked door in the MFM office.

We do not plan to enroll patients who require a legal guardian in order to give informed consent. We will assess each patient's ability to give informed consent at the initial visit and if an individual is deemed incapable, she will be excluded.

Sharing New Information

Our program and study coordinator will handle any initial communication regarding results to patients. Any new information will then be conveyed in person or over the phone with the patient from either a maternal-fetal medicine physician or a cardiologist. If the information is clinically relevant, it will be documented appropriately in the patient chart/record.

We plan to publish our findings in a peer-reviewed obstetrics (American Journal of Obstetrics and Gynecology) or cardiology (JACC) journal.

References

- 1 Canobbio MM et al. Management of pregnancy in patients with complex congenital heart disease. AHA Scientific Statement. *Circulation*. 2017; 135:e50-e87.
- 2 Velissaris D et al. The use of pulmonary artery catheter in sepsis: A literature review. *J Clin Med Res*. 2016; 8(11): 769-776.
- 3 Cornette J et al. Validation of maternal cardiac output assessed by transthoracic echocardiography against pulmonary artery catheterization in severely ill pregnant women: prospective study and systematic review. *Ultrasound Obstet Gynecol*. 2017; 49: 25-32.
- 4 Ohashi Y et al. Non-invasive hemodynamic assessment of non-pregnant, healthy pregnant and preeclamptic women using bio-reactance. *Rev Bras Anesthesiol*. 2010; 60: 603-13

- 5 Keren H et al. Evaluation of a non-invasive continuous cardiac output monitoring system based on thoracic bio-reactance. *Am J Physiol Heart Circ Physiol*, 2007;293:H583-589
- 6 Squara P et al. Non-invasive cardiac output monitoring (NICOM): a clinical validation. *Intensive Care Med*, 2007;33:1191-1194.
- 7 Vinayagam D et al. Non-invasive cardiac output monitoring in pregnancy: comparison to echocardiographic assessment. *Ultras Obstet Gynecol*. 2016; 11: Epub ahead of print
- 8 McLaughlin K et al. Clinical validation of non-invasive cardiac output monitoring in healthy pregnant women. *JOGC*. 2017; 1008-1014.
- 9 Roberts LA et al. Maternal hemodynamics, fetal biometry and Dopplers in pregnancies followed up for suspected fetal growth restriction. *Ultrasound Obstet Gynecol*. 2018 [Epub ahead of print].
- 10 Sandham JD, Hull RD, Brant RF et al. – A randomized, controlled trial of the use of pulmonary artery catheters in high-risk surgical patients. *N Engl J Med*, 2003;348:5-14.
- 11 Mabie WC, DiSessa TG et al. A longitudinal study of cardiac output in normal human pregnancy. *AJOG*. 1994; 170: 849-56.
- 12 Hunter S et al. Adaptation of the maternal heart in pregnancy. *Br Heart J* 1992; 68: 540-3.
- 13 Waksmonski CA et al. Acquired heart disease and pregnancy. 2015.
<http://uptodate.com/contents/acquired-heart-disease-and-pregnancy?topicKey=Cardiology>
- 14 Dyer RA, James MF – Maternal hemodynamic monitoring in obstetric anesthesia. *Anesthesiology*, 2008;109:765-767
- 15 Engoren M, Barbee D – Comparison of cardiac output determined by bioimpedance, thermodilution, and the Fick method. *Am J Crit Care*, 2005;14:40-45.
- 16 Lee W et al. Noninvasive maternal stroke volume and cardiac output determinations by pulsed Doppler echocardiography. *Am J Obstet Gynecol*. 1988; 158: 505-510.
- 17 Easterling TR et al. Measurement of cardiac output during pregnancy: validation of Doppler technique and clinical observations in preeclampsia. *Obstet Gynecol* 1987; 69: 845-850.
- 18 Vinayagam D et al. Cardiac output assessment in pregnancy: comparison of two automated monitors with echocardiography. *Ultrasound Obstet Gynecol*. 2017; 49: 32-38.
- 19 Critchley LH et al. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. *J Clin Monit Comput*. 1999; 15: 85-91.
- 20 Doherty A et al. Comparison of bioreactance and echocardiographic non-invasive cardiac output monitoring and myocardial function assessment in primigravida women. *Brit J Anaesth*. 2017; 118: 527-532.
- 21 Vinayagam D et al. Non-invasive haemodynamic monitoring in pregnancy: a comparative study using ultrasound and bioreactance. *Fetal Diag Ther*. 2017; 41: 273-282.