

RESEARCH PROTOCOL

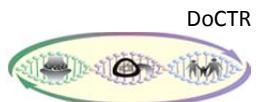
STUDY TITLE

Intraoperative Fetal Heart Rate (FHR) monitoring: a Feasibility Study

PI Name: Heather McKenzie, MD
PI Title: Assistant Professor of Anesthesiology
Washington University School of Medicine
Department of Anesthesiology
660 South Euclid Avenue
Campus Box 8054
St. Louis, MO, 63110
Voice: 314-362-2628
Fax: 314-362-9037
E-mail: mckenzieh@anest.wustl.edu

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1. SYNOPSIS

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|---|--|
| Study Title | Intraoperative fetal heart rate (FHR) monitoring: a Feasibility Study |
| Objective | The introduction of intraoperative fetal heart rate (FHR) monitoring; demonstrating that intraoperative FHR monitoring is technically feasible. |
| Study Period | Planned enrollment duration: 6 months Planned study duration: 6 months |
| Number of Patients | 55 patients |
| Study Treatment | |
| Study Design | Observational Study |
| Inclusion and Exclusion Criteria | <p>Inclusion Criteria:</p> <ol style="list-style-type: none"> 1. First 15 patients only— Elective induction of labor, not yet in active labor. 2. Subsequent 40 patient – Scheduled cesarean sections performed under spinal anesthesia 3. Patients ages 18-45 <p>Exclusion Criteria</p> <ol style="list-style-type: none"> 1. Urgent or emergent cesarean sections 2. Cesarean sections performed under general anesthesia |
| Statistical Methodology | Demographic, clinical characteristics will be summarized using descriptive statistics |

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2. STUDY PROTOCOL

2.1 Background and Significance

Fetal heart rate (FHR) monitoring has become the most widely used assessment of fetal well-being in the peripartum period and the only routinely used method that provides continuous fetal monitoring. Despite a false positive rate for the detection of intrapartum asphyxia leading to cerebral palsy of over 99% [1-3] FHR monitoring continues to be the mainstay of peripartum fetal surveillance. FHR monitoring is routinely available in the operating room, where it is typically reassessed in cases of urgent cesarean delivery for fetal distress since it may direct immediate anesthetic and peripartum management. However, despite the ubiquitous use of FHR monitoring in labor and the typical use of FHR monitoring on arrival to the OR, FHR monitoring is universally stopped once anesthesia has been performed in order to allow abdominal skin preparation and for surgery to proceed. From the moment of anesthesia induction until fetal delivery, no real-time data is available that allows assessment of fetal well-being. A few isolated studies and case reports in the 1970s-1980s examined intraoperative FHR monitoring using scalp-clip electrodes during Cesarean deliveries [4-7]. None of these studies assessed external FHR monitors or current anesthesia techniques. To our knowledge no studies since that time have examined FHR monitoring during Cesarean deliveries using external monitoring or spinal anesthesia.

2.1.1 Preliminary Data

None

2.2 Objective

The first objective of this study is the introduction of intraoperative fetal heart rate (FHR) monitoring as a novel fetal endpoint to be utilized in scheduled and urgent cesarean deliveries, in order to shed important light on the immediate fetal responses to maternal anesthetic and obstetric interventions. This research is intended to demonstrate that intraoperative FHR monitoring is technically feasible, and correlates with other traditional endpoints of immediate neonatal wellbeing (such as umbilical arterial blood gas analysis and Apgar score). Unlike these post-delivery neonatal outcomes, intraoperative FHR monitoring has the potential to serve as a real-time target for optimization of maternal and fetal condition in order to improve immediate neonatal outcome. We will first assess the fetal ECG monitors on a pilot of 15 patients for induction of labor who are not yet in active labor or in pain; the aim being to determine the best placement of the ECG leads. We will then assess the technical feasibility of intraoperative FHR monitoring using both the standard abdominal wall acoustic device used routinely in labor and a series of multiple ECG leads placed over the upper abdominal wall.

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2.3 Patient Selection

Patients enrolled in this study series will first be patients undergoing elective induction of labor (15 patients) and then patients undergoing elective cesarean delivery (40 patients.)

2.3.1 Inclusion Criteria

1. First 15 patients only– Elective induction of labor, not yet in active labor.
2. Subsequent 40 patient – Scheduled cesarean sections performed under spinal anesthesia
3. Patients ages 18-45

2.3.2 Exclusion Criteria

1. Urgent or emergent cesarean sections.
2. Cesarean sections performed under general anesthesia

2.4. Study Design

This will be an observational study to determine the feasibility of intraoperative FHR monitoring

2.4.1 Study Procedures

Patients enrolled in this study will be enrolled on the labor and delivery ward prior to their elective cesarean section. This will be done with the help of research assistants/nurses. Patients will be provided with written information about the study that they are enrolled in (see below) and consented for participation in the study as well as use of collected non-identifiable information; information on FHR (fetal heart rate) monitoring.

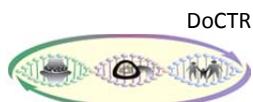
2.4.2 Minimization of Bias

The demographic sought in this study are female patients ages 18-45. No other particular demographic will be sought.

2.4.3 Pre-Study Period

The pre-study period will involve education of research assistants/nurses and anesthesiology providers, evaluation of availability of resources (includes BioSemi ECG, Fetal heart rate Doppler).

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2.4.4 Study Period

The study period is anticipated to be 6 months. This will start October 1st, 2016

Methods:

2.4.6 Observations and Measurements

This will be an observational study. We will first assess the fetal ECG monitors on a pilot group of patients for induction of labor who are not yet in active labor or in pain. We will then assess the technical feasibility of intraoperative FHR monitoring. Fetal heart rate will be assessed by:

a) External abdominal wall fetal ECG sensors placed at the top of the belly, outside the sterile field, or on the participant's back. This data is captured via BioSemi FLAT Active electrodes that interface with an ECG system that employs the algorithm ActiView to analyze the data. [See Appendix A].

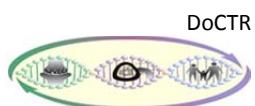
b) An acoustic fetal heart sensor, as used routinely in labor will be used as a comparator in this feasibility study. When this device is used intraoperatively, sterility and acoustic contact are both maintained by placing the acoustic probe inside a sterile nylon sleeve containing electrode gel, and by using sterile electrode gel between the sterile sleeve and the abdominal wall. This technique may require the presence of an investigator "scrubbed into" the case to hold the abdominal wall probe (ie surgical scrub, sterile gown and gloves). This will be decided on a case-by-case basis. If needed, this investigator will need acoustic input to ensure adequate contact. So as not to distract the surgeon, this will be transmitted to the investigator by earphone input. These are scheduled cesarean deliveries and no fetal heart rate anomalies are expected; if there is an unexpected fetal bradycardia, this will be communicated to the surgeon.

c) Routine maternal vital signs (heart rate, blood pressure and oxygen saturation).

Group 1 – Patients for elective induction – not in active labor

- a) We will use the routine acoustic fetal heart rate sensor and try to determine the best placement of external abdominal wall fetal ECG sensors (either at the top of the belly outside the sterile field, or on the participant's back)
- b) We aim to capture 10 minutes of FHR with the ECG sensors comparing it to the acoustic monitor
- c) We will start with 5 patients. If we are able to capture FHR for the allotted period of time with the fetal ECG, then we will proceed to the intraoperative group. If not, we will assess another 5 elective induction patients.
- d) We will plan for an upper limit of 15 patients in this group

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Group 2 – Patients for scheduled cesarean section

- a) We will use the acoustic FHR sensor and the fetal ECG sensors.
- b) We will start with 5 patients and determine if we can capture fetal ECG. If this information correlates with the acoustic FHR, we then use only the fetal ECG sensors for the remaining 35 patients. We will adjust placement of leads for each group of 5 patient if there proves to be difficulty with capturing FHR intraoperatively, though all leads will be placed on the belly outside the sterile field or on the participant's back
- c) We will plan for an upper limit of 40 patients in this group

2.4.6.3 Primary Outcome Measures

The primary endpoint of the feasibility study is the use of external abdominal wall fetal ECG sensors to assess FHR; its use-friendliness, the signal-noise ratio and the correlation with acoustic data.

2.4.6.4 Secondary Outcome Measures

Secondary endpoints are the incidence of any non-reassuring FHR patterns during the "silent" period which is the period when the FHR monitor is removed, the patient's abdomen is scrubbed, sterile prep and drape until delivery of the fetus. If there are any non-reassuring FHR patterns (tachycardia, bradycardia, decelerations), maternal vital signs at the time will be noted.

2.4.6.5 Statistical Methods

Demographic and clinical characteristics will be summarized using descriptive statistics; FHR data will be compared for the two tests using Receiver Operating Characteristic or ROC curve.

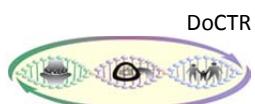
2.4.6.6 Sample Size

55 patients

2.5 Management of Intercurrent Events

Should something interfere with the collection of data that is other than disconnection of the FHR devices or loss of power, these will be noted and the attempt to rectify the situation will also be documented. We will not however delay surgery in order fix the problem.

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Monitoring of maternal blood pressure and treatment of hypotension will follow standard routine protocol. Maternal blood pressure data and vasopressor therapy will be recorded in metavision as routine.

2.5.1 Adverse Experiences

The likelihood of adverse events is very low as the devices that will be used in the study are ones that have been used in the obstetric population for years. The participants, will however be monitored for adverse experiences. These events will be reported and the patients followed. The possible adverse events with this study are allergic reaction/skin sensitivity to the adhesive used for the fetal ECG, impression left on the subjects body from the Doppler.

2.5.2 Premature Discontinuation

Patients will be withdrawn from the study upon request. Patients will also be withdrawn from the study if it is believed to be in the best interest of the fetus or the patient. If a patient withdraws from any study in the series they will be replaced to maintain the estimated required number of patients for that particular study in the series.

2.5.3 Potential Risks

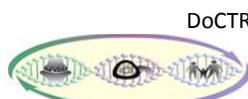
The potential risks in this study series involve the potential side effects/reactions to the electrocardiogram adhesive, Doppler and the psychological effects of being involved in a study. We do not anticipate risks related to privacy invasion or socio-economic status.

2.5.4 Procedures to Minimize Potential Risks

Studies are conducted under the supervision of the PI and the co-investigators. The investigators are trained and experienced in performing research in human volunteer subjects. The investigators are anesthesiologists with extensive experience in the obstetric population. As this is an observational study, patients will be treated and monitored as per usual standards of care. All investigation will occur in an operating room on labor and delivery.

Inclusion and exclusion criteria, fasting requirements, monitoring, and the clinical protocol are designed to ensure that risks are absolutely minimal. Subjects are informed that participation is voluntary and they may refuse to participate and may withdraw from the study at any time without penalty.

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2.5.5 Data and Safety Monitoring Plan

Studies conducted in the Department of Anesthesiology follow the Washington University Institutional Review Board Policies and Procedures (last revision April 20, 2015). All individuals working on the study are required to read and be familiar with and compliant with the IRB Policies and Procedures. The specific monitoring plan for this investigation is commensurate with the risks and the size and complexity of the investigations planned. The potential risks are attributable to the potential side effects/reactions to the electrocardiogram adhesive, Doppler and the psychological effects of being involved in a study. Based on the small size and relatively low risk nature of the protocol, the investigating physicians are involved in the monitoring plan. These individuals will review the annual summary of adverse events. All reports of a Serious Adverse Event, or an Unexpected Adverse Event will be reviewed immediately and reported as outlined in Section X of the IRB Policies and Procedures.

3. HUMAN SUBJECTS RESEARCH

3.1 Protection of Human Subjects

The study will be directed under the supervision of the primary investigator, a board certified, GCP certified anesthesiologist and a mentor with many years' experience with human volunteer studies. The study team also involves additional anesthesiologists with experience in human volunteer studies.

3.2 Sources of Materials

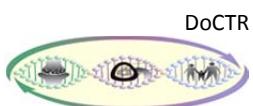
The source of data for the study will come from the patient's electronic record. This information includes fetal heart rate, patient blood pressure, dose of vasopressor, patient cardiac output, fetal blood gases.

3.2.1 List of Protected Health Information Collected for Study

We do not anticipate using any of the 18 HIPPA privacy rule identifiers.

3.2.2 Data Management

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Fetal heart rate recorded by external abdominal wall fetal ECG sensors is captured via BioSemi FLAT Active electrodes that interface with an ECG system that employs the algorithm ActiView to analyze the data.[See Appendix A]. .

With regard to confidentiality; 1) all subjects will be assigned a study ID number, 2) The link to identifiers will be destroyed at the end of the study 3) Paper data will be stored under lock and key (office, file cabinet) and only the investigators and research team will have access. Electronic data will be stored on a secure drive with limited individual password access. If data are published, there will be no link to identifiers. Study data will not be revealed to any organization, individuals other than the subjects, or the subjects themselves. 4) Maternal vital signs will be extracted from MetaVision and entered into a spreadsheet using only the study-specific ID. None of the 18 HIPAA identifiers will be recorded for research purposes.

3.3 Recruitment and Informed Consent

Patients will be recruited for this study on the Labor and Delivery ward at Barnes Jewish Hospital. The recruiters in this study will be the current obstetric research nurses/assistants. The recruiter will enroll patients that are scheduled for an elective/non-urgent cesarean section. Research nurses will conduct phone screening recruitment by reviewing the Labor and Delivery schedule and contacting those patients having elective Caesarian deliveries the day before the surgery to inquire about their interest. If interested, they will invite them to arrive a 30 minutes early for admission and obtain written informed consent prior to their procedure. Potential participants will also be approached on the day of their procedure in the Labor and Delivery unit.

3.4 Potential Benefits of the Proposed Research to the Subjects and Others

There is not expected to be an immediately appreciable benefit to either the fetus or the patient in every study in the series. Future patients/fetuses may benefit from a change in anesthetic management if any study in this series shows an improvement in fetal (improved Apgar scores, blood gases) or patient (improved blood pressure, cardiac output) outcome from any proposed regimen in this series.

3.5 Inclusion of Women

The patients/volunteers in this study series will exclusively be women.

3.6 Inclusion of Minorities

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This study series will make a large effort to include patients of all demographics as they are typically represented on the labor and delivery ward at Barnes-Jewish Hospital.

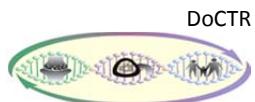
3.7 Inclusion of Children

Pregnant female patients ages 18-45 will be included in this study.

4. REFERENCES

1. Low JA, et al. *Obstet Gynecol*. 1999; 93: 285-91.
2. Nelson KB, et al. *N Engl J Med*. 1996; 334: 613-8.
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4. Petrikovsky BM, et al. *Int J Gynaecol Obstet*. 1989; 29: 215-8.
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7. Timor-Tritsch I, et al.. *Obstet Gynecol*. 1976; 48: 292-6.

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Appendix A. BioSemi ECG System

Per the BioSemi FLAT Active ECG System Standard Terms and Conditions of Sale:

2. Intended Use

2.1 Our products are designed and intended to be used for research applications only.

2.2 Our products are not designed or intended to be used for diagnosis or treatment of disease. Our products are not sold as a Medical Device as defined in EU directive 93/42/EEC, Article 1, Sec 2 (a) (European Union), or as defined in the Federal Food Drug & Cosmetic (FD&C) Act, Chapter II, Sec 201 (h) (USA).

2.3 Our equipment is only authorized to be used on humans, if this application is explicitly stated in the respective manual.

2.4 Our products are not authorized for use as critical components in life support systems. As used herein:

a) Life support systems are systems which (1) are intended for surgical implant into the body, or (2) support or sustain life, and whose failure to perform when properly used in accordance with the instructions for use provided in the labeling can reasonably be expected to result in significant injury to the user

b) A critical component is any component in a life support system whose failure can reasonably be expected to cause failure of the life support device or system, or to affect its safety or effectiveness

21 USC 321[h] [revised Chapter 9, Subchapter II] cited in support of section 2.2 above states:

(h) The term "device" (except when used in paragraph (n) of this section and in sections 331(i), 343(f), 352(c), and 362(c) of this title) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is-

(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,

(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

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