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September 17, 2010

Evaluation of fetal arrhythmias with maternal transabdominal fetal electrocardiogram

A. Study Purpose and Rationale:

Fetal arrhythmias may occur in 1-2% of pregnancies and account for 10-20% of fetal echocardiogram (fECHO) referrals.^{1,2} They can lead to significant morbidity including hydrops fetalis and fetal demise. Current methods of diagnosis and monitoring are limited. The most accurate test for diagnosis of fetal arrhythmias may be magnetocardiography, but this modality has very limited availability and is prohibitively expensive for clinical use.³ Ultrasound (fECHO) is currently the gold standard in the clinical diagnosis of fetal arrhythmias. However, ultrasound also has limitations as electrical events are inferred rather than directly tested. Fetal echocardiogram can approximate rhythm via M-mode looking at the timing of atrial and ventricular contractions or via pulse-wave doppler looking at blood flow as a result of contractions.

After birth, an electrocardiogram can easily be placed on the patient's chest in order to obtain information about the rhythm, but in a fetus there are significant obstacles to a rhythm tracing. These include interference from maternal electrical signals, inability to directly place leads on the fetus' chest, movement of the fetus, etc. Fetal electrocardiograms have been recorded in the past, but were never of sufficient quality due to these limitations.^{4,5} The scalp electrode fECG and STAN fECG, although better quality, rely on scalp electrode placement.^{6,7} This type of monitoring is only possible after membrane rupture and is not routinely used even in this situation.

The Monica AN24 is a new, non-invasive transabdominal monitor that records both maternal and fetal electrocardiograms (fECGS). A small wireless device collects electrical information in a manner similar to a holter monitor using 5 electrodes on the maternal abdomen. Four channels of signal are obtained using this technique. Maternal signal is then filtered out via a software program to yield a fetal tracing. Separate ongoing studies in our group have suggested that a clear fetal signal can be obtained in >85% of recordings. The Monica AN24 is approved for use as a fetal heart monitor in the European Union and has been used in the context of assessing fetal heart rate and variability for obstetricians. No previous studies have utilized this device to look at fetal rhythm.

The proposed study is a pilot study that will compare the accuracy of fECG with fECHO in the diagnosis of fetal arrhythmias. If the fECG shows promise as a diagnostic modality for fetal arrhythmias in this small study, it would provide incentive to conduct a large multicenter study of the Monica AN24 in this context. Ultimately, if it proves effective, this monitor could replace traditional fECHO in certain contexts for the diagnosis and monitoring of fetal arrhythmias.

B. Study Design and Statistical Analysis:

This is a prospective pilot study of a diagnostic test..

Fetal echocardiograms and fetal electrocardiograms will be performed on the same day. fECGs will be recorded for at least 20 minutes. Rhythms identified on fECG and fECHO will each be defined as regular rhythm or a specific arrhythmia. The diagnoses will be considered concordant if they are the same in both fECG and fECHO. fECHO rhythm will be taken from the documented rhythm on the echocardiogram report. The single investigator interpreting the fECGs will be blinded to the results of the fECHOs and the cardiologists performing and interpreting the fECHOs will be blinded to the results of the fECGs.

The result of concordance will be a simple percentage of corresponding fECGs and fECHOs in which the same diagnosis is achieved. The recordings without clear fetal tracings will be excluded from this portion of the analysis.

Our hypothesis is that of the fECGS recorded by the Monica AN24 in which a clear fetal tracing can be identified, 80% of them will be diagnostically concordant with fECHO performed on the same fetus on the same day.

It is expected that 15% of recordings will not reveal a clear fetal tracing. Of the remainder, it is expected that there will be a 90% concordance rate between diagnoses obtained by fECG and fECHO. Using a chi square test, the sample size to achieve 80% power with an alpha-error rate of 0.05 is obtained as follows:

$$\begin{aligned} N_1 &= 8 * (p_1q_1 + p_2q_2)/\text{effect}^2 + 2/\text{effect} + 2 \\ &= 8 * (0.9*0.1 + 0.8*0.2)/(0.1)^2 + 2/0.1 + 2 \\ &= 222 \end{aligned}$$

Because 80% is a fixed number and there is only one variable, the actual sample size of subjects with clear fetal tracings needed is

$$\begin{aligned} N_2 &= N_1/2 \\ &= 111 \end{aligned}$$

However, because we expect 15% of patients to be excluded for lack of clear fetal tracings, the actual sample size required is:

$$\begin{aligned} N &= N_2/0.85 \\ &= 131 \end{aligned}$$

We will assume that the final number of subjects may be closer to **150**, as we may obtain a smaller percentage of recordings without a clear fetal tracing.

C. Study Procedure

The study procedure will involve performing a fetal electrocardiogram on a pregnant woman before or after her fetal echocardiogram. The device to be used and its application are partially described above. Five specific areas of the maternal abdomen will be cleaned with alcohol and rubbed with a mild sand-paper like substance to remove dead skin that may interfere with signal. Electrode stickers will be placed on top of these areas, which will then be connected to the Monica AN24 for data collection. The recording itself will take from 20-40 minutes or more depending on patient time restrictions. The entire process typically will take from 1 hour to 1 hour and 15 minutes.

D. Study Drugs

There are no study drugs.

E. Medical Devices

The device to be used is the Monica AN24 transabdominal monitor. It has been described in the study rationale and procedure. It is a non-validated medical device. However, this study may provide pilot data to inform future studies. There is no risk associated with this device apart from minor skin irritation to the mother, and thus no ethical issues regarding its use.

F. Study Questionnaires

Study questionnaires will be administered at the time of the echocardiogram to record relevant background information on the mother and fetus. This will include simple questions addressing whether the fetus has congenital heart disease, maternal caffeine ingestion, cocoa butter lotion use (thought to interfere with fECG signal), etc.

G. Study Subjects

Inclusion criteria:

Pregnant woman of at least 18 weeks gestation

Having fetal echocardiogram performed on the same day at CPMC

Exclusion criteria:

Multiple gestation

The fetuses will not be representative of normal babies as they will all have been referred for fECHO, and in most cases will be returning for a follow-up visit for fECHO. This will lead to a sample of patients that can be grouped into 3 categories. The majority will be fetuses with congenital heart disease and a normal heart rhythm. A smaller portion

will be fetuses with normal heart structure and rhythm who are being evaluated for external reasons such as maternal conditions including diabetes mellitus or family history of congenital heart disease. The third group will be fetuses with arrhythmias, which is also expected to consist of the minority of patients.

There are only vulnerable populations involved, which are pregnant women and fetuses. This is necessary because these are the subjects that we are studying. Women are expected to be of all races, but a disproportionate number of Black and Hispanic women will be enrolled due to the local community that uses the hospital for medical care. There will be no difference in the attempts at recruitment of women of different races out of those who obtain fetal echocardiograms.

H. Recruitment of Subjects

Fetal cardiologists will ask their patients if they would be amenable to an investigator speaking to them about the study at the time of their fetal echocardiogram. If they consent to participate, fECG will be performed after their fECHO on the day they consent, and before or after their fECHO on subsequent visits if they elect to participate again.

There are multiple barriers to enrollment. One of the potential difficulties in enrollment will be the time constraints of the women. The amount of time may be difficult as some women travel from far to come to this referral center and schedule multiple appointments in the same day. Additionally, there is expected reluctance by some women of using an experimental device on them during pregnancy, even after it is explained that there is no risk to the fetus.

I. Confidentiality of Study Data

Confidentiality will be maintained with IDs created for all women, and protected health information contained within the fECG files. A list will be securely maintained with patient's protected health information such that it can be referenced for the purposes of looking up records of fetal echocardiograms.

J. Potential Conflicts of Interest:

Monica Healthcare has provided their devices at reduced cost and is aware of the ongoing study. They have asked that any publications be sent to them before submission or concurrently, but have no authority to request any changes. Monica Healthcare has no role in funding. There are no other conflicts of interest.

K. Location of Study

Patients will be recruited from the echocardiography suite on 2 Babies North and will have their fECGs performed either in 2 Babies North, in the VC3 GCRC outpatient center, or PH10.

L. Risks of Study:

There are no significant risks to participation. Some women report minor skin irritation or redness after the fECG.

M. Potential Benefits

There are no benefits to participation for the subject. Any benefits from the study would be to future patients.

N. Alternative Therapies

There is no therapy being offered and thus no alternative

O. Compensation to Subjects

Subjects will not be compensated for participation in the study

P. Cost to Subjects

There will be no costs to the subject, apart from time.

Q. Minors as Research Subjects

The fetuses involved are considered minors for the purposes of this study. Their mothers will provide informed consent on their behalf, and as there is no risk to participation there are no ethical issues surrounding their participation.

R. Radiation or Radioactive Substances

Not applicable

S. References:

References and some of the background information obtained from Ismee Williams, the principle investigator.

¹ Southall DP, Richards J, Hardwick RA, Shinebourne EA, Gibbens GL, Thelwall-Jones H, de Swiet M, Johnston PG. Prospective study of fetal heart rate and rhythm patterns. *Arch Dis Child*. 1980 Jul;55(7):506-11.

² Srinivasan S, Strasburger J. Overview of fetal arrhythmias. [Curr Opin Pediatr](#). 2008 Oct;20(5):522-31.

³ Strasburger JF, Cheulkar B, Wakai RT. Magnetocardiography for fetal arrhythmias. *Heart Rhythm*. 2008 Jul;5(7):1073-6. Epub 2008 Mar 4.

⁴ *Munch Med Wochenschr* 1906;53:811

⁵ HON EH. The electronic evaluation of the fetal heart rate; preliminary report. *Am J Obstet Gynecol* 1958;75:1215-30

⁶ HON EH. Instrumentation of fetal heart rate and fetal electrocardiography. II. A vaginal electrode. *Am J Obstet Gynecol* 1963;5;86:772-84

⁷ Doria V, Papageorghiou AT, Gustafsson A, Ugwumadu A, Farrer K, Arulkumaran S. Review of the first 1502 cases of ECG-ST waveform analysis during labour in a teaching hospital. *BJOG*. 2007 Oct;114(10):1202-7.