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IRB Proposal

A. Study Proposal and Rationale-

Congenital heart disease (CHD) is the most common group of congenital abnormalities and affects about 1% of live newborns (1). Despite significant therapeutic advances, the morbidity and mortality of CHD remains substantial. One such handicap includes neurodevelopmental delay, which has been found at an increased incidence in patients with CHD. For example, 70% of infants with hypoplastic left heart syndrome (HLHS) were found to have attention deficit hyperactivity disorder (ADHD) and 18% with mental retardation with an IQ less than 70 (2). In addition, a study of 18-month old patients with transposition of the great arteries (TGA) also demonstrated significant deficits in motor (30%) and mental (22%) development (3). Further studies are needed to understand the mechanism of neurodevelopmental delay in CHD patients and to identify those CHD fetuses at greatest risk.

Autonomic regulation is a mechanism of physiologic response to changes in external stimuli. Changes in autonomic regulation can be measured by markers, such as fluctuations in fetal heart rate (4), which have been associated with neurodevelopmental outcomes in infants (5). Using these markers, DiPietro et al. recently found that maternal pregnancy-specific psychological stress was associated with changes in fetal neurological maturation (6). Fifer et al. noted alterations in fetal autonomic functioning in response to fetal exposure to alcohol, smoking, and maternal depression. The proposed mechanism of these autonomic abnormalities includes brainstem changes in cardiac and respiratory regulation, but details of these changes have not yet been elucidated (7). Changes in fetal blood flow secondary to structural heart disease can be considered as a type of stressor that may impact ANS development.

While few studies on fetal autonomic regulation have emerged, there is scarce literature on fetal autonomic regulation in CHD survivors. Infants with CHD have been found to have abnormal heart rate variability and decreased heart rate response likely resulting from a combination of pre-operative, fetal, and surgical factors (8). Preliminary studies in CHD fetuses by Williams et al. demonstrate abnormalities in fetal blood flow to the brain with a suggested association with 18-month neurobehavioral outcomes in these patients (9). Recent studies by Siddiqui et al. (manuscript under review) found that autonomic regulation in CHD fetuses differs from controls with HLHS fetuses most markedly affected. These autonomic regulation parameters were measured using the Monica AN24 fetal heart rate monitor. However, coupling fetal ECG with fetal movement signals has yet to be attempted. This study proposes to further investigate effects of CHD on the fetus by characterizing changes in autonomic regulation while accounting for variability attributable to fetal movement as measured by the Toitu movement recording device. Ultimately, we would like to learn whether in utero autonomic nervous system (ANS) function may serve as an additional marker of neurobehavioral outcomes in CHD survivors.

Assessing neurodevelopmental outcomes in fetuses with CHD has many potential benefits. Early identification of CHD fetuses at risk for neurodevelopmental compromise may impact the prenatal and postnatal care of these infants. In addition, identifying these possible fetal markers can allow physicians to provide more informed anticipatory guidance and prenatal counseling to parents. Knowledge of the impact of fetal cardiac lesions diagnosed by fetal echocardiography on quality of life and possible neurodevelopmental outcomes is lacking. Identifying at-risk CHD fetuses could also inform decisions

regarding fetal surgery. Knowledge of the potential risks and benefits of fetal intervention on quality of life and fetal outcomes would be valuable in targeting the patients most likely to benefit.

In addition to the impact on fetal life, knowledge of the neurodevelopmental markers in CHD fetuses and their correlation with infant development could impact early childhood management. By identifying those at greater risk, infants may be more likely to receive interventional services such as Early Intervention to realize their developmental potential.

B. Study Design and Statistical Analysis

Fetuses that have been diagnosed with HLHS, TGA, or TOF are the subjects of this prospective observational cohort study. Participants were less than 24 weeks gestational age at enrollment without evidence of multiple gestation, chromosomal abnormalities, structural brain malformations, placental insufficiency, intrauterine growth retardation or sustained cardiac arrhythmia. IRB approval has been obtained for this study. Verbal and written informed consent was obtained from participants.

Fifty CHD fetuses were enrolled in the study with sufficient power of 80% to detect difference in means of 0.56 (effect size of 0.7) and 90% power to detect a difference in means of 0.64 (effect size of 0.8) when using the standard deviation of RMSSD of 0.8 as found in initial studies in fetal baboons (10). An alpha of 0.05 was used.

Differences between the CHD and normal fetal groups will be compared using Student's t-test as well as nonparametric testing such as the Wilcoxon Rank Sum test where applicable. Results will be analyzed using SPSS.

C. Study Procedure-

Data for this study has already been collected in the following manner:

The Monica AN24 was the fetal electrocardiogram (fECG) monitor used to measure fetal autonomic regulation. Placed on the maternal abdomen, this monitor provides non-invasive and more accurate measures of fetal heart rate (FHR), heart rate variability (HRV), and fetal movement compared to Doppler FHR monitors (Figure 1). Fetal movement signals were derived from the Toitu monitor, which was placed on the maternal abdomen along with the Monica. fECG and movement measurements have been obtained from enrolled participants at 3 gestational ages: 19-27, 28-33, and 34-38 weeks. Mothers were asked to have a meal 1.5 hours prior to testing and to avoid caffeine. All measurements were recorded between 11:00 and 13:00 hours to minimize the potential impact of circadian rhythms. Fetal and maternal HR data was collected for over 50 minutes in a recumbent, left lateral position to ensure that quiet and active fetal sleep states were obtained. The fECG and movement data was then downloaded and reviewed via the Monica and GMark software. Software differentiates maternal and fetal heart rate to extract the fECG data and analyzes HRV data at 1000Hz.

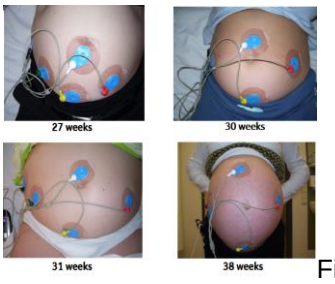

Figure 1: Monica electrode placement.

From the data obtained from fECG, 3 measures of fetal autonomic regulation will be calculated: 1. Variability will be measured by the ratio of the interquartile range of FHR over the heart rate 2. FHR standard deviation 3. The percentage of consecutive changes in the R-R interval that sustained through 2 consecutive increases or decreases in FHR. These results will then be coupled to the Toitu movement

signal in order to account for variability in fECG recordings that result from fetal movement. These results will be compared to the 18 month infant Bailey development scores obtained from the same cohort of CHD fetuses.

D. Study Drugs- There were no study drugs used in this study.

E. Medical Device

The Monica AN24 abdominal fetal electrocardiogram (fECG) monitor is a commercially available device used only for research studies. The Monica has not yet been FDA approved and pending review of an FDA application for clinical use, but has been used in multiple research studies to assess fetal autonomic activity. This monitor is a small wireless device that can be worn around the mother's neck and is connected to five electrodes placed on the maternal abdomen. These electrodes create four distinct channels that record ECG activity. The recording provides data on FHR, HRV and fetal movement with a signal sample rate of 1000Hz. This high frequency allows for FHR accuracy up to 1 ms; as compared to the 4Hz sampling rate of current conventional Doppler fetal monitors. The improved accuracy of the fetal ECG recording allows the true beat-to-beat variability to be determined, which provide an indirect measure of parasympathetic activity.

Preliminary data by Dr. Williams suggests that fECG recordings have improved data capture using the Monica. Among 10 fetal cases that underwent fECG recording with fECG and Doppler, good FHR data was found in 76.6% of Doppler recordings and 72.1% of fECG recordings ($p=0.004$). Unlike Doppler based fetal monitors, information regarding fECG waveform and cardiac intervals is provided with Monica. In addition, Monica does not require transducer gel, belts or repositioning following fetal movement.

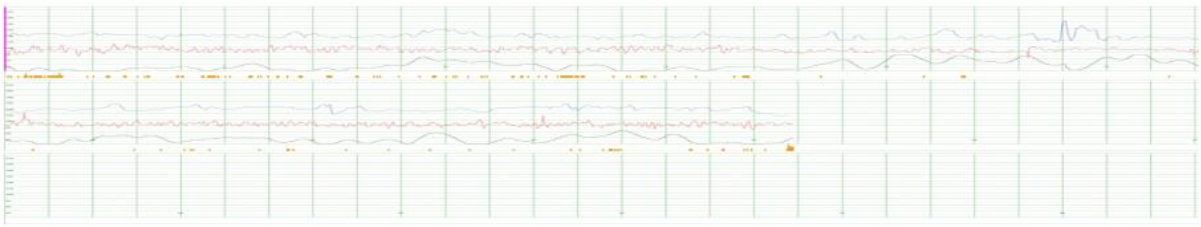

Figure 2: Monica AN24 fECG recording with fetal (blue) and maternal (red) heart rate demonstrated along with uterine activity (green).

Other research studies have also used Monica AN24. Over 800 recordings on 500 mothers beginning from 20 weeks gestation were conducted by Monica Healthcare. In an independent study in the Netherlands, Graatsma et al found fECG signals in >60% of 15 hour recording in 123 of 150 pregnant women between 20 and 40 weeks gestation. A high correlation between fECG and simultaneous scalp electrode recordings of FHR was found in 22 women during labor ($r=0.99$, $p<0.01$) (11). No association was found between maternal BMI and signal quality. Over 75 fECG recordings have been obtained locally by Dr. Fifer's lab and 300 recordings at participating centers in the Prenatal Alcohol Stillbirth and SIDS (PASS) network (12).

F. Study Questionnaires- No questionnaires were used.

G. Study Subjects- Study subjects were based on patients referred from CHONY. Pregnant women were extended an offer to participate in the study. Pregnant women were not be asked to participate during the first visit when the CHD diagnosis was made, but rather at the second visit. We reinforced the voluntary nature of their participation in the study and that their medical care would not be affected by their decision to participate.

Inclusion Criteria:

- < 24 wks gestational age (GA) at enrollment

- Control fetuses with normal fetal echo
- CHD fetuses with HLHS, TGA or TOF

Exclusion Criteria:

- Multiple gestation
- Chromosomal abnormalities
- Structural brain malformations
- Placental insufficiency
- Intrauterine growth retardation
- Sustained cardiac arrhythmia

H. Recruitment of Subjects- Pregnant women referred to the CHONY Pediatric Cardiology Heart Station for fetal echocardiogram and meet eligibility criteria were recruited for this study.

I. Confidentiality of Study Data- All data was de-identified. Only the principle investigator, Dr. Ismee Williams, has access to a file that identifies study subjects.

J. Potential Conflict of Interest- There were no conflicts of interest to report.

K. Location of the Study - Dr. Williams recorded all measurements in the Pediatric Clinical Research Center on Vanderbilt Clinic 3rd Floor.

L. Potential Risks- No adverse events are expected for this study because there was no intervention offered.

M. Potential Benefits- Potential advantages to the individual will include early identification of learning disabilities that would render the individual eligible for Early Intervention, a service that has been demonstrated to enhance developmental outcome. There are no measurable risks associated with this study.

N. Alternative Therapies- No alternative therapies are available.

O. Compensation to Subjects- Pregnant women participating in the study were offered a financial incentive of $100 to defray the cost of transportation.

P. Costs to Subjects- The cost of transportation to the study site was the only predicted cost in this study.

Q. Minors as Research Subjects- This study includes fetuses and infants up until 2 years of age in order to assess neurodevelopmental outcomes.

R. Radiation or Radioactive Substances- Not applicable

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