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Noninvasive Monitoring of Uterine Electrical Activity and Fetal Heart Rate: A New External Monitoring Device

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Introduction:

Monitoring of fetal heart rate and uterine contractions are crucial to determining fetal well-being and labor progress. The current methods available for monitoring fetal heart rate and contraction frequency and intensity are either externally applied (i.e. Doppler ultrasound for determining the fetal heart rate and tocodynamometry for measuring contractions) or require invasive insertion in the presence of cervical dilation and rupture of membranes (i.e. fetal scalp electrode for determining fetal heart rate and intrauterine pressure catheter for measuring contractions). While the invasive devices represent the

"gold standard" for monitoring, their invasive nature comes with limitations of when they can be used and has risks of infection, etc.[i]

The noninvasive devices have limitations in their accuracy. Although the tocodynamometer is noninvasive, it can only be used to measure contraction frequency. Additionally, it is difficult to obtain an accurate tracing in patients that are obese or in pain and unable to lie still. The fetal Doppler averages the last three beats, which limits its accuracy. Both are limited in that maintaining proper placement on the maternal abdomen is limited in the presence of both maternal and fetal movement.

Obesity during pregnancy presents significant challenges to monitoring uterine activity and fetal heart rates with the usual external devices. The tocodynamometer works by through a button on the underside of the device that is pressed when the uterus becomes firm and moves anteriorly in the maternal abdomen during a contraction. The ability of the uterus to "push" this button becomes more limited the greater the amount of adipose tissue interposed between it and the button. Additionally, with obesity keeping the tocodynamometer and the Doppler ultrasound device (used to monitor the fetal heart rate noninvasively) in their proper positions in order to obtain useable tracing becomes a significant obstacle.

For these reasons developing a device that is noninvasive but has similar accuracy to a fetal scalp electrode and an intrauterine pressure catheter is of paramount importance.

Obstetrical triage visits are most often secondary to uterine contractions either at term or preterm[ii]. It is however challenging to determine whether a patient is in active labor and in need of admission[iii]. The predictive value of current objective and non-objective methodologies of term or preterm deliveries remain poor. The ability to determine true labor from contractions that do not lead to cervical change becomes important in a busy triage, such as those at Montefiore, and is especially important in preterm gestations when interventions such us betamethasone injections, magnesium sulfate for

neuroprotection and tocolysis can lead to decrease fetal morbidity. Women who are not in labor are at risk of medical interventions (e.g. oxytocin and cesarean birth) that can lead to increased risk of morbidity and mortality for mothers and babies[iv],[v], [vi], [vii].

The EUM300 (electrical uterine myography)(OB Tools, Israel) is an FDA approved monitor intended for the evaluation of electrical signals originating in the uterus, thus providing a tool for measuring uterine activity as well as fetal heart rate. It is an external, non-invasive device that uses electrodes placed on the abdomen. The electrical traces can be displayed on screen in real time and data are stored and can be retrieved for later analysis.

The EUM300 was tested and found to be reliable as a non-invasive method for evaluating contractions. It is safe and effective in monitoring uterine contractions[Error! Bookmark not defined.], [viii]. It is able to quantify uterine electrical activity and therefore to measure the strength of uterine contractions noninvasively. Thus, it has the potential to differentiate productive v. nonproductive contractions (as determined by cervical change). Although, there are yet no published studies using the EUM to assess fetal heart rate, fetal heart rate has also been accurately acquired using maternal abdominal sensors associated with this device[ix].

Purpose:

We propose to perform a study to validate the accuracy and clinical usefulness of the EUM device by comparing it with simultaneous use of current methods (both external or internal devices) among obese patients and patients with normal body mass indexes (BMI). Our goal is to show that the EUM device is a noninvasive tool of similar utility to the fetal scalp electrode and the IUPC, and superior the traditionally used noninvasive devides (Doppler ultrasound and tocodynamometer).

Objectives:

1. Compare the contraction tracings obtained using the EUM device vs. those obtained using the intrauterine pressure catheter vs. those obtained from external tocodynamometer among current obese patients (BMI greater than 30 kg/m^2) and nonobese patients using simultaneously obtained, 30 minute tracings with regards to the frequency of contractions, the duration of contractions, maximum height of the contractions, the total Montevideo units recorded, the timing of the contractions, and the amount of discontinuous tracings from the devices. Of the variables mentioned, the Montevideo units will only be comparable between the IUPC tracings and the EUM device.

2. Compare the fetal heart rate tracing obtained via the EUM device vs. external fetal Doppler vs. fetal scalp electrode (simultaneously obtained, 30 minute tracings will be compared) among obese patients and nonobese patients with regards to the amount of discontinuous/uninterpretable tracing, average fetal heart rate, baseline heart rate, the number accelerations, the number of decelerations, the timing of the accelerations, the timing of decelerations, the maximum fetal heart rate achieved during acceleration, the lowest fetal heart rate achieved during deceleration, and compare the degree of variability in the tracing.

3. Compare tracings of productive vs. non-productive contractions in patients presenting to triage to rule out labor (30 minutes of simultaneously obtained tracings of external tocodynamometer and EUM device will be compared) with regards to the frequency of contractions, the duration of contractions, maximum height of contractions, the timing of the contractions and the amount of discontinuous tracings from both devices, as well as changes in cervical exam on the basis of body mass index. Productive contractions are those that cause a change in cervical exam of 1 cm or more, any change in station or change in effacement of 50% or more.

Materials and Methods:

This will be a prospective observational study of women presenting for care to Montefiore Medical Center. Patient enrollment will occur during their obstetric triage encounter or on admission to labor and delivery. Patients will be approached if they meet the enrollment criteria. Once informed consent is obtained and the standard methods of fetal and labor assessment are in place the electrodes of the EUM will be attached to the abdominal skin surface. The electrodes will remain in place until delivery or discharge from the hospital if the patient is found not to be in labor and is discharged undelivered.

Patients will be monitored simultaneously with the EUM device and currently used methods (external or internal devices) as clinically indicated by the standard of care. Providers will be blinded to the results of the EUM device and will continue care as per current guidelines using the information obtained from the current monitoring methods. Data from the EUM devices will be captured on a study laptop computer as will data generated by the currently used fetal/uterine monitor to allow for comparison of the two systems. Each patient will serve as her own control for comparison as the data obtained from the two monitoring systems simultaneously will be compared. Patients will be monitored for 30 minutes once they consent in the labor and delivery triage rooms or labor and delivery rooms. Patients will also be asked to complete a device experience and satisfaction survey comparing the methods of monitoring. Assuming the number of minutes of unreadable tracing for the EUM is less than the Doppler by 1 minute, the standard deviation of difference in minutes by the two devices is 3 minutes, and there are 2 obstetrician readings per subject, to reach a power of 80% with 0.05 significance level, 39 patients will be needed for our primary outcome as listed below. It is anticipated that within 6-12 months, this number can be reached with recruiting efforts at both Weiler and North campus. To maximize recruitment, the co-investigator will be present daily on L&D and triage to recruit patients.

Maternal demographics to be obtained will include maternal age, ethnicity, BMI, gestational age, current medications, mode of delivery, birth weight, Apgar scores,

newborn outcome, medical history and any antenatal complications, past surgical history, and postpartum course.

Primary Outcomes:

- Continuity in readings of fetal heart rate (as measured in the number of minutes without a readable tracing in a 30 minute sample tracing) between EUM and fetal scalp electrode and external fetal heart rate monitoring from the same patient
- Continuity in readings of contractions (as measured in the number of minutes without a readable tracing in a 30 minute sample tracing) between EUM, IUPC and external tocodynamometer from the same patient

Secondary Outcomes:

- Compare average frequency of contractions between the monitoring systems
- Compare duration of contraction between the monitoring systems
- Compare maximum height of the contraction between the monitoring systems
- Compare total Montevideo units obtained between the monitoring systems
- Compare the timing of the contraction between the monitoring systems
- Compare average fetal heart rate between the monitoring systems
- Compare baseline heart rate between the monitoring systems
- Compare the number accelerations between the monitoring systems
- Compare the number of decelerations between the monitoring systems
- Compare the timing of the accelerations between the monitoring systems
- Compare the timing of decelerations between the monitoring systems
- Compare the maximum fetal heart rate achieved during acceleration between the monitoring systems
- Compare the lowest fetal heart rate achieved during deceleration between the monitoring systems
- Compare the degree of variability in the tracing between the monitoring systems. Degree of variability will be defined as the correlation between the tracings. The tracings will be broken down into 4 minute intervals and defined as minimal, moderate or marked variability and compared with each other for accuracy and

consistency. Most accurate will be the internal monitor in each case, i.e. fetal scalp electrode.

- Compare patient satisfaction between the monitoring systems

Inclusion criteria:

1) Maternal age >18 years old
2) Singleton pregnancy
3) Gestational age of 24 completed weeks or greater based on the estimated due date as calculated from last menstrual period or early ultrasound
4) Category I (reassuring) fetal heart rate tracing at time of enrollment

Exclusion criteria:

1) Fetal anomaly or chromosome defect
2) Allergy to silver
3) Woman with implanted electronic device of any kind
4) Irritated skin or open wound on the abdominal wall

Recruitment Mechanisms:

Clinicians will ask patients during their obstetric triage encounter or on admission to labor and delivery after they meet enrollment criteria whether they are interested in the study. Informed consent will then be obtained by the research clinicians.

Informed Consent:

Copies of the informed consent and a brochure detailing the device will be distributed to offices at Montefiore where prenatal care is provided to allow patients to provide provisional consent in advance of presenting to the labor and delivery unit. If at that time the patient refuses participation, it will be documented in the patient's chart and the patient will not be approached a second time. Patient's providing provisional consent will be given a second opportunity to provide consent or to refuse at the time they present

to the labor and delivery unit and are eligible to initiate the protocol. If at the time they are approached for actual involvement in the protocol, they are in too much pain to have the informed consent discussion and provide consent, they will not be considered for participation.

Patient consent will occur on admission to the obstetrical triage or labor and delivery unit. Because patients presenting to our units may be in pain and pain may compromise cognition and judgment, at the time of actual enrollment, the principal investigator or his or her designee will assess the capacity of the patient to provide ethically and legally adequate informed consent and will document that finding in the research record. If the patient is capable of providing informed consent the patient will be: engaged in the discussion of the risks and benefits of the protocol, reminded of his or her prior provisional consent (if it had been obtained) and asked to consent to or to refuse participation.

Device Description:

The EUM300 is composed of three units: Disposable electrode, Maternal unit and Interface unit.

Disposable electrode applied part – Proprietary bio-compatible patch electrode array with nine Ag/AgCl and hydrogel connections. Electrode is made by US based manufacturers: Lead-Lok, Sandpoint, ID and Molex, Naperville, IL.

Maternal Unit – The maternal unit is connected via a proprietary connector to the electrode. The EMG signals are amplified by an analog front-end. OB-Tools Algorithm runs on a DSP board and the result – Fetal Heart Rate and Uterine Activity are transmitted via Bluetooth. The unit contains a 4.2V Li-Ion rechargeable battery. The battery allows 24h of work and must be charged away from the patient.

Interface unit – Wall mount unit translates the information received from a paired Bluetooth Maternal unit. In this setup the EUM is used as a secondary system, one that

is not involved with clinical decisions. In this case a PC computer receives the bluetooth transmission from the maternal unit and saves it into an Excel readable file. A primary monitor that is used for clinical decisions may also be connected to the PC and its data is recorded into the same file for comparison. The file format is a simple 6 column format: Date, Time, EUM UA, EUM FHR, Monitor UA, Monitor FHR. The file can be read and analyzed using Excel, Matlab and other statistical tools.

Data management:

Data collected in this study protocol will be extracted from the secure password protected clinical computer programs utilized by Montefiore for patient care: ASOBGYN/ EPFweb/EPIC. Information extracted for study use will be maintained in a locked office on a password protected computer and not accessible to others. Once the clinical information obtained on a patient is completed the information will be de-identified. Patient confidentiality will be maintained at all times.

Statistics:

Routine parametric and non parametric statistical analysis will be performed. Given that each patient serves as her own control (since we will be comparing the EUM device to the routinely used devices simultaneously), we will be able to limit the number of women enrolled.

To assess the improvement in continuity of readings in EUM, continuity in readings will be compared between EUM, Doppler, and FSE from the same patients. Assuming the number of minutes of unreadable tracing for the EUM is less than the Doppler by one minute, the standard deviation of difference in minutes by the two devices is three minutes, and there are two obstetrician readings per subject, to reach a power of 80% with 0.05 significance level, 39 patients will be needed for our primary outcome as listed below.

Regarding assessment of contractions, continuity in readings will be compared between EUM and IUPC in the same patients. To assess the improvement in continuity of readings in EUM, continuity in readings (yes or no) will be compared between EUM and

IUPC from the same patients. A McNemar test will be used to compare the proportion of continuity between these two methods. With N=55 patients, the study will have at least 80% to detect an odds ratio of 3.2 associated with continuity between EUM and IUPC with a two-sided type I error rate of not more than 5%, assuming 50% of discordant pairs. It is acknowledged that the study has only adequate power to detect a substantial difference between EUM and Doppler, and between EUM and IUPC however, anything below this level would be of less clinical interest and the result we obtain from this study will be used to design more definitive studies in the future. Thus, the number of patients required to address each of the aims of the study is as below:

1. Fetal heart rate monitoring: EUM device v. external monitor v. FSE n = 39
2. Contraction monitoring: EUM device v. external monitor n = 55 obese and n = 55 nonobese subjects; EUM device v. intrauterine pressure catheter n = 55 obese and n = 55 nonobese subjects.
3. Productive v. non-productive contractions: EUM device v. external monitor n = 55 subjects.

Because many of these patients will overlap due to the fact that they will serve as their own control and will be monitored simultaneously for fetal heart rate and change in cervical exam, it is anticipated that the maximum number of patients required in this study will not be more than 220 patients since 55 obese and 55 non-obese patients will be needed and additional patients may be needed to evaluate productive contractions. In addition to comparing the continuity in readings, in assessing contractions, we will also compare average frequency of contractions, the duration of contraction, maximum height of the contraction, the total Montevideo units obtained, the timing of the contraction and the amount of discontinuous tracings from the devices. In assessing fetal heart rate, we will compare average fetal heart rate, baseline heart rate, the number accelerations, the number of decelerations, the timing of the accelerations, the timing of decelerations, the maximum fetal heart rate achieved during acceleration, the lowest fetal heart rate achieved during deceleration, and compare the degree of variability in the tracing. A continuous outcome will be compared using a paired t-test.

As each patient is serving as its own control, missing data is unlikely to be an issue in this study once the patient consents. If the monitoring is less than 30 minutes, these patients will not be used in analysis due to concern for completeness and accuracy.

Safety assessment:

Safety and tolerability will be assessed by recording of adverse events. Adverse events will be reported. Adverse events will be assessed in terms of their seriousness, severity, and relationship to the study device. To date more than 800 patients have used the device in clinical trials and there have been no safety events reported with the use of the device to date.

Potential benefits:

There is no immediate benefit to the subject from her participation in this study. The study results will support the development of the EUM300pro system, which may have clinical importance in providing the care provider with more continuous and accurate monitoring of fetal heart rate and contractions in a less invasive way. These parameters will aid the medical staff in making timely clinical decisions and increasing the chances of attaining a successful treatment and/or delivery.

Potential risks:

No severe or serious events are anticipated with the use of the EUM300 system. There is a potential for an allergic reaction to the EUM adhesive.

Alternatives:

Patients may choose not to participate in the study or withdraw from the study at any time for any reason without compromise or change in their care.

Adverse Events:

Definition of Adverse Events (AE)

An AE is any reaction, side effect, or other untoward event (signs, symptoms, and changes in laboratory data) associated with the use of a test article (drug, biologic, or device),

whether or not the event is considered related to the test article. All AE occurring after the administration of study treatments will be recorded. AE will be ascertained on the basis of volunteered symptoms and clinical observation and assessment at study visits. AE and concomitant medication information will be recorded during study visits on the appropriate case report form (CRF) page, and every effort will be made to capture information regarding AE and concomitant medications between visits. All AE considered to be related to study treatment, and all serious AEs (SAE) will be followed until resolved or until a stable status has been achieved.

Relationship

The relationship between an AE and the study intervention will be determined by the Investigator on the basis of his or her clinical judgment and the following definitions:

- Associated: There is a reasonable possibility that the AE may have been caused by the study device. This definition applies to those AEs that are considered definitely[a], probably[b], and possibly[c] related to the use of the study device.
    a. Likely Related: An AE that: follows a reasonable temporal sequence from using the study device; follows a known response pattern to the study device; and, when appropriate to the protocol, is confirmed by improvement after stopping the study device (positive dechallenge) and by reappearance of the reaction after repeat exposure (positive rechallenge); and cannot be reasonably explained by known characteristics of the participant's clinical state or by other therapies.
    b. Probably Related: An AE that: follows a reasonable temporal sequence from administration of the study device; follows a known response pattern to the study device; and, when appropriate to the protocol, is confirmed by improvement after dechallenge; and cannot be reasonably explained by the known characteristics of the participant's clinical state or by other therapies.
    c. Possibly Related: An AE that: follows a reasonable temporal sequence from administration of the study device and follows a known response pattern to the study device but could have been produced by the participant's clinical state or by other therapies.

- Not Related: An AE for which sufficient information exists to indicate that the etiology is unrelated to the study device. Two or more of the following variables apply:
  a. The AE does not follow a reasonable temporal sequence after administration of the study device.
  b. The AE is readily explained by the participant's clinical state or other therapies.
  c. Negative dechallenge - the AE does not abate upon dose reduction or cessation of therapy (assuming that it is reasonable to expect abatement of the AE within the observed interval).

Severity

The intensity of an AE will be assessed as follows:

- None
- Mild: does not interfere with routine activities, can perform daily functions
- Moderate: interferes with routine activities, can perform daily functions, but with concerted effort
- Severe: participant is unable to perform routine activities

Outcome

The outcome of an AE will be assessed as follows:

- Resolved
- Unresolved
- Resolved with sequelae
- Worsening
- Death

Serious Adverse Events definition and reporting

All serious adverse events require additional detailed reports and follow-up. A serious adverse experience is any adverse experience that is fatal or life-threatening, is permanently disabling, requires or prolongs inpatient hospitalization, or is a congenital anomaly, cancer, or the result of an overdose.

All serious adverse events, whether or not device related or expected, must be reported by the Investigator to the Sponsor within one working day by fax or E-mail (initial report). A written report, which includes a full description of the event, will be sent to the Sponsor within 5 working days. This includes serious adverse events that occur any time after the inclusion of the patient in the study until 30 days after using the study device.

Reports of SAEs related to the study device, will be evaluated and assessed by the sponsor's medical advisors.

All serious adverse events must be reported to the appropriate Institutional Review Board or ethical committee in accordance with local laws and regulations.

Removal of a subject from the study due to adverse experiences whether by the Investigator or by the subject's own volition, should be reported promptly to the Medical Monitor.

Studies completed using EUM:

1. Rosen H, Salzer L, Hiersch L, Aviram A, Ben-Haroush A, Yogev Y. Uterine electric activity during the third stage of labor; a look into the physiology of a deserted stage. J Matern Fetal Neonatal Med. 2013 Oct 22. [Epub ahead of print]
2. Aviram A, Melamed N, Hadar E, Raban O, Hiersch L, Yogev Y. Effect of Prostaglandin E2 on Myometrial Electrical Activity in Women Undergoing Induction of Labor. Am J Perinatol. 2013 Aug 5. [Epub ahead of print]
3. Hadar E, Melamed N, Aviram A, Raban O, Saltzer L, Hiersch L, Yogev Y. Effect of an oxytocin receptor antagonist (atosiban) on uterine electrical activity. Am J Obstet Gynecol. 2013 Oct;209(4):384.e1-7.
4. Most O, Langer O, Kerner R, David GB, Calderon I. Can myometrial electrical activity identify patients in preterm labor? Am J Obstet Gynecol. 2008 Oct;199(4):378.e1-6.

5. Hiersch L, Salzer A, Aviran A, et al. Factors affecting uterine electrical activity during the active phase of labor prior to rupture of membranes. J Matern Fetal Med, 1-4, Sep 2014.

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[i] Hadar E, Biron-Shental T, Gavish O, et al. A comparison between electrical uterine monitor, tocodynamometer, and intrauterine pressure catheter for uterine activity in labor. J Matern Fetal Neonatal Med, 1-8, Sep 2014

[ii] Bennett TA, Kotelchuck M, Cox CE, Tucker MJ, Nadeau DA. Pregnancy-associated hospitalizations in the United States in 1991 and 1992: a comprehensive view of maternal morbidity. Am J Obstet Gynecol. 1998; 178:346–54

[iii] Lauzon L, Hodnett E. Labour assessment programs to delay admission to labour wards. Cochrane Database Syst Rev. 2001

[iv] Klein MC, Kelly A, Kaczorowski J, Grzybowski S. The effect of family physician timing of maternal admission on procedures in labour and maternal and infant morbidity. J Obstet Gynaecol Can. 2003; 26:641–5.

[v] . Hemminki E, Simukka R. The timing of hospital admission and progress of labour. Eur J Obstet Gynecol Reprod Biol. 1986; 22:85–94.

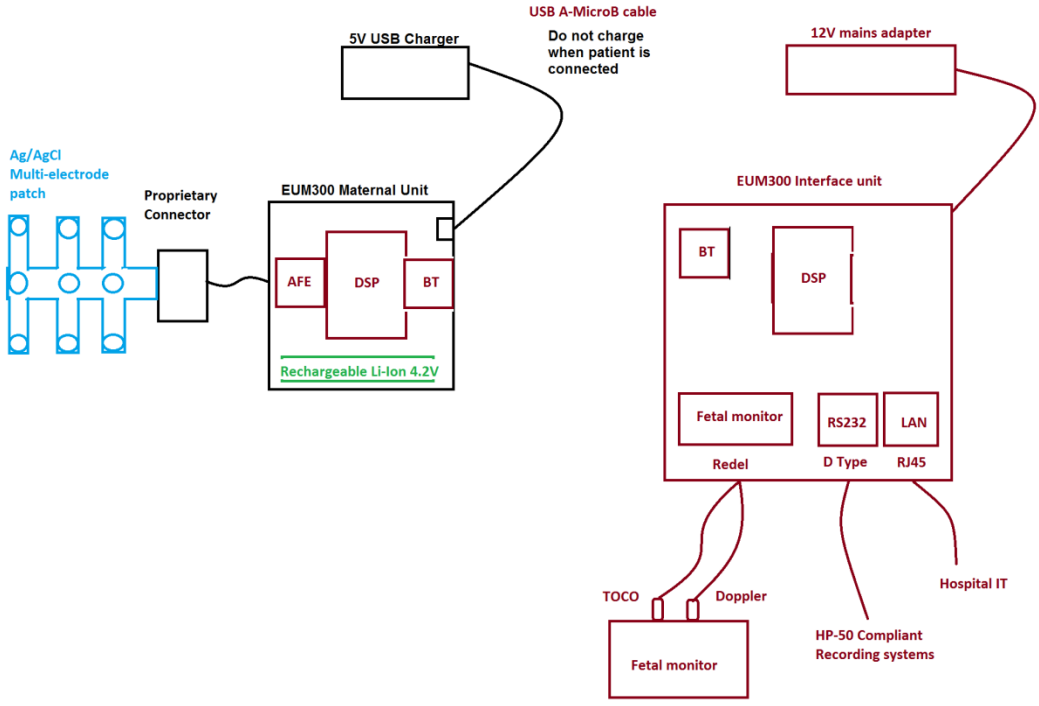
[vi] Holmes P, Oppenheimer LW, Wen SW. The relationship between cervical dilatation at initial presentation in labour and subsequent intervention. BJOG. 2001; 108:1120–4.

[vii] . Jackson DJ, Lang JM, Ecker J, Swartz WH, Heeren T. Impact of collaborative management and early admission in labour on method of delivery. J Obstet Gynecol Neonatal Nurs. 2003; 32:147–57.

[viii] Haran G, Elbaz M, Fejgin MD, Biron-Shental T. A comparison of surface acquired uterine electromyography and intrauterine pressure catheter to assess uterine activity. Am J Obstet Gynecol. 2012 May;206(5):412.e1-5.

[ix] Clifford, G, Sameni R, Ward J, Robinson J, Wolfberg AJ. Clinically accurate fetal ECG parameters acquired from maternal abdominal sensors. Am J Obstet Gynecol 2011;205:47.e-1-5.

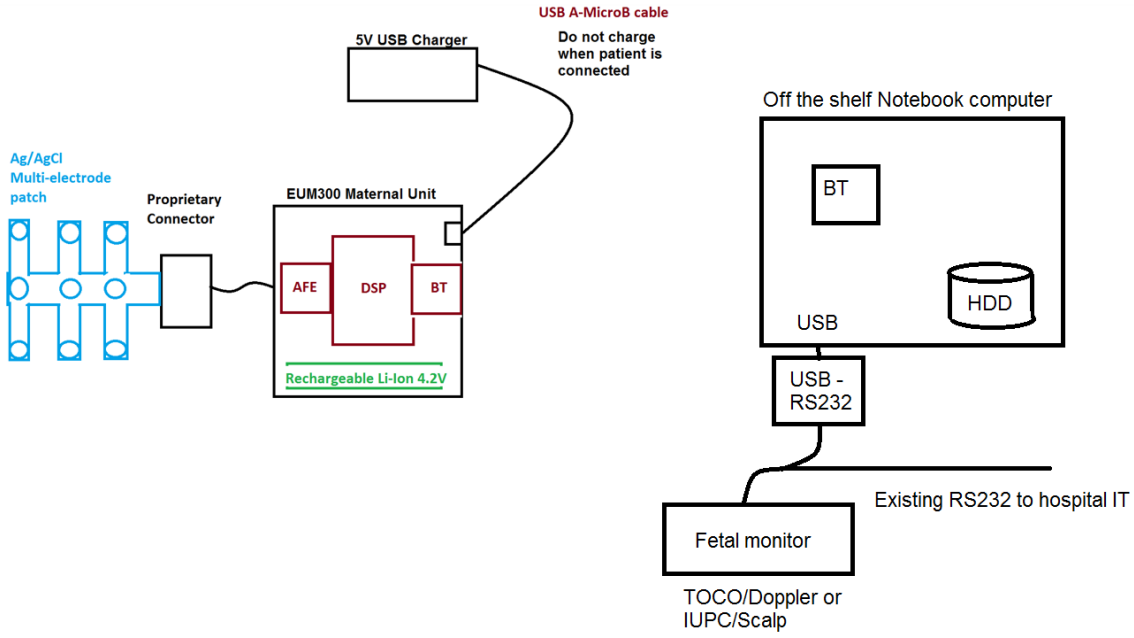
Option 1 – normal EUM300 setup



AFE – Analog Frontend
DSP – Digital Signal Processing board
BT – Bluetooth
LAN – Local Area Network
RS232 – Industry standard HP-50 Communication protocol

UA – Uterine activity
FHR – Fetal Heart Rate

Option 2 - EUM300 with dedicated notebook



The proposed setup eliminates the need to install the interface unit during the clinical evaluation time frame and minimize the required changes to the delivery room setup. The maternal unit will transmit the uterine activity/fetal heart rate information to an off-the–shelf computer equipped with Bluetooth V4.0 (e.g., Lenovo IdeaPad U41-70). An existing fetal monitor transmits similar information using HP-50 protocol over RS232 physical connection. The RS232 is likely to be connected to existing hospital IT. A simple Y connection is the only change needed to the delivery room. The RS232 transmissions will also be received by an off-the-shelf USB-RS232 adaptor.

A computer program will record both the EUM300 and the fetal monitor into a common file (CSV format in order to be able to be analyzed by either Matlab or Excel). Program may also present the four signals (EUM Uterine, EUM FHR, monitor Uterine, monitor FHR) in real time. Other features may be: Dialog to provide the file information with patient ID, name, gestational age, etc.