Project Summary/Relevance

Obese women BMI>=30kg/m2 are at elevated risk for cesarean delivery, with rates up to 5 times higher than normal weight women. Cesarean deliveries are most often indicated for obese women because of abnormally slow labor progression, a complication known as labor dystocia. In clinical practice, expectations of labor progress are not individualized by degree of maternal obesity, but instead are standardized based on the average rate of cervical dilation among healthy-weight women (about 1cm/hour). As a result, obese women are at increased risk of cesarean delivery simply because they do not proceed through labor as expected by the nurses and doctors who provide their intrapartum care. When obese women experience cesarean delivery, they are significantly more likely to experience maternal morbidity and mortality than their normal weight counterparts. Therefore, the optimal labor care of obese women is an important national healthcare priority.
This project involves the creation of BMI-individualized partograms with data from the newly-released, multi-site Consortium of Safe Labor study and development of a web phone partogram application that would allow clinicians caring for obese women during labor to view a woman's cervical dilation progress on a graph that represents normal and abnormally slow labor progression according to that woman's BMI. Although obese women are known by researchers to proceed through labor more slowly than normal weight women, this information is not typically used by clinicians to guide their care of obese women. The proposed study will make a unique contribution to science by providing a tool to clinicians who are caring for obese women during labor that will provide evidence-based guidance on BMI-individualized normal labor progress. Thus, this project will, for the first time, provide a tool that could help decrease the rates of unnecessary interventions in the labors of obese women (artificial rupture of membranes or oxytocin augmentation initiated to speed labor progress) and help improve outcomes (decrease practice of unplanned cesarean delivery for slow labor progress among obese women).
This project will utilize interval-censored regression, as used in other investigations of labor progression times, to estimate the time required for progress from one centimeter of dilation to the next. Median and 95th percentiles will be calculated for women who achieved full cervical dilation (10 centimeters), differentiated by parity and maternal BMI. Using these times, updated BMI-individualized partograms for women successfully achieving second stage labor will be created and used to build the web application.

Research Strategy

I. Significance

Obese women (BMI>=30kg/m2), who now comprise 31.8 percent of women 20-39 years of age in the United States 1, are at particular risk for cesarean delivery due to abnormally slow labor progress, known clinically as labor dystocia 2-4. For each 1 kg/m2 increase in maternal BMI at the time of labor, there is a 2-5% increase in the risk for cesarean delivery 4. Obese women's heightened risk for cesarean is magnified in the current healthcare environment, where cesarean delivery is common,5,6 and results in a range of poor maternal and neonatal outcomes, and increased healthcare costs 7-11. Multiple efforts aimed at decreasing cesarean deliveries in the U.S.

are ongoing, including recommendations for optimal labor management6,12-16. However, these recommendations do not provide guidance on the optimal labor management of obese women, who have the highest risks for unplanned cesarean delivery4,17. Obese women are more likely to end their full-term pregnancies with cesarean delivery in large part due to labor dystocia, or the slow, abnormal progression of labor7,10,22,25,33,46–48. Approximately sixty percent of unplanned cesarean deliveries done on mixed-weight women with vertex-presenting babies are performed for the indication of labor dystocia49. In a 2009 prospective study of over 200,000 nulliparous Swedish women in spontaneous labor, the risk of cesarean for the indication of labor dystocia disorder was increased 4-fold among morbidly obese women when compared to normal-weight women25. For each 10 kg of maternal pre-pregnant weight, the rate of cervical dilation in a prospective study of 509 term nulliparous women was found to decrease by 0.4cm/hr23. It was initially theorized that obese women's slow labors were caused by soft-tissue obstruction of late labor and birth4, but more recent studies point to a slowing in the active phase of the first stage of obese women's labors, from 4 to 10 centimeters of cervical dilation7,10,22,33,47,48. Once obese women reach the second stage of labor (full cervical dilation to birth), they appear to achieve vaginal birth as frequently as normal-weight women50,51. Obese women are more likely than normal-weight women to have slightly larger babies, yet in studies controlling for maternal diabetes, this increased fetal weight was not associated with additional diagnoses of labor arrest/slowing or shoulder dystocia22,27. In a case control investigation comparing the labors of obese and normal-weight women, the sub-set of obese women giving birth to babies weighing less than 3500g still had significantly more labor arrest (arrest in 18.8% of labors) than their lean counterparts carrying the same size babies (arrest in 5.0% of labors)22. Expectations for labor progress are based on findings from large studies showing the median time required for women to make cervical change during labor18,19. Secondary analyses of these studies showed that there is a dose-dependent slowing of labor with elevations in maternal BMI 20. When a laboring woman's cervix dilates more slowly than these median rates, the most common tool used by clinicians to speed labor progress is synthetic oxytocin. Synthetic oxytocin is also used to induce contractions in women undergoing labor induction. Unfortunately, obese women show decreased response to synthetic oxytocin when used for either induction or augmentation of spontaneous labor21-24. Current labor management guidelines do not recommend different labor progression standards by maternal BMI 25. Thus, obese women are more likely than normal-weight women to end labor with unplanned cesarean delivery as a result of their slow labor progress and decreased response to synthetic oxytocin4. Moreover, when obese women end labor with cesarean, they are more likely than normal weight women to experience significant morbidity and mortality7-11. Therefore, this population is a particularly important target for nation-wide efforts to decrease the use of cesarean delivery.

Biological Basis of Myometrial Dysfunction in Obese Women

Studies examining the contraction strength and frequency of myometrial cells suggest several biological changes associated with obesity may be responsible for the observed slowing of obese women's active labor. During pregnancy, most obese women have higher levels of adipokines, cholesterol, and free fatty acid (FFA) than normal-weight pregnant women. Both leptin and cholesterol have an inhibitory effect on in vitro spontaneous and oxytocin-induced contractions26,27. Elevated FFA in pregnancy may also contribute to slow labor in obese women by

causing high levels of oxidative stress and low pH levels in and around the uterus28-30. Without the ability to balance these abnormal levels during labor, lower pH and oxidative stress are thought to cause myometrial damage that results in unorganized and ineffective uterine smooth muscle contractions leading to labor dystocia31. There is currently no known treatment for these physiologic changes affecting labor in obese women. Moreover, few clinicians are aware that obese women's labor physiology is shown to be altered by numerous research studies.

BMI-Individualized Partograms

Using labor progression calculations from a large, multi-site study20, median and 90th percentile labor traverse times were used to construct BMI-individualized partograms in keeping with both traditional and newer partogram development methods 32,33. Women in the labor progression study used to construct these partograms (the Consortium of Safe Labor Study) were exposed to a range of intrapartum interventions, including augmentation with synthetic oxytocin, induction of labor, continuous electronic fetal monitoring, AROM, and epidural analgesia 20,34. Subjects also had medical co-morbidities, including diabetes and hypertension and were either nulliparous or multiparous. Thus, the data on labor duration reflected the intrapartum situations typical for both obese and normal-BMI women today, and lend external validity to the BMI-individualized partograms constructed using these data. The sample was limited to women with a term, singleton fetus in a cephalic presentation. However, these partograms were constructed using labor traverse times in a publication from the CSL that included both women who achieved full cervical dilation and others who did not20. Thus, labor progression times in these BMI-individualized partograms are longer than labor progression intervals calculated only from women achieving full cervical dilation. Since these BMI-individualized partograms will be used to guide clinicians to recognize the limits of normal labor progress by maternal BMI, the first step in our project to create a web application of the BMI-individualized partograms will be to re-configure labor progression intervals using only women who achieved full cervical dilation. This information is available in the newly-released CSL dataset. On the partograms, a blue 'dystocia line' was drawn on to represent the labor progression of only the slowest 10% of women, in keeping with the physiologic partogram recently published 33. Women progressing through labor more slowly than the dystocia line are identified for possible intervention to speed labor progress. These four partograms cover ranges of BMI: normal (BMI < 25 kg/m2), overweight (BMI 25.1-29.9), obese (BMI 30-40), and morbidly obese (BMI > 40). Once traverse times were calculated, they were rounded to the nearest quarter hour for the creation of the dystocia line of each partogram. To use the BMI-individualized partogram, the intrapartum provider calculates the maternal BMI using height and weight of the laboring woman at time of admission to hospital for birth. Once the correct partogram is obtained using this BMI, and the woman is determined to be at least 4 cm dilated in active phase labor, the time, cervical dilation and fetal station are plotted on the partogram. The amniotic sac may be intact or ruptured at onset of partogram use. After the time of first cervical exam is plotted, subsequent times may be inserted in the remaining hour boxes of the partogram. As labor progresses, further cervical exams should be plotted on the partogram and tracked against the blue 'dystocia line' as first described by Neal/Lowe in their physiologic partogram 33. When a woman's labor progress crosses the dystocia line into the red area of the partogram, the provider is instructed to do a thorough assessment of the woman and fetus, and consider using augmentation of labor with synthetic oxytocin or other

methods (ambulation, pain control, etc.) in the attempt to correct delayed labor progress.

II. Innovation

This proposal brings together cutting edge technology and scientific expertise in labor dysfunction to confront labor dystocia, one of the most impactful conditions affecting maternal morbidity and mortality—and obesity. The BMI-individualized partogram in a web application format is introduced as a bedside tool to aid in labor management for nulliparous women birthing in hospital settings. BMI has been shown by researchers to exert a dose-dependent slowing of labor progress, especially during early active phase labor35. This slow labor progress results in women of higher BMI being more likely to end labor with an unplanned cesarean delivery secondary to labor dystocia 3. Meta-analysis of labor trials using partograms demonstrated that providers using partograms with more liberal timing used less labor interventions, including unplanned cesarean delivery 36. It is anticipated that the use of BMI-individualized partograms will encourage intrapartum providers to allow more time for women of higher BMI to labor before turning to medical interventions, especially cesarean delivery. These BMI-individualized partograms in a web application format are proposed for use in hospital settings with women of mixed risk status who present at term with a single fetus in cephalic presentation, in active labor after either spontaneous or induction onset. These partograms may be updated in the future with the results of labor progression data from users of the application providing labor duration data separating spontaneous and induced labors, categorized by BMI. These partograms also may be further individualized with the addition of maternal age effects on labor duration (a demographic variable which will also be collected by application users), as this is another factor correlated with the diagnosis of labor dystocia 37. With greater percentages of childbearing women having higher BMIs and intrapartum interventions being used commonly across all BMI categories, individualized partograms built with datasets from contemporary populations, such as those whose labors are tracked with this app, may offer providers valuable tools for labor management of women to optimize perinatal outcomes.

Web Applications & Pregnancy

Web and mobile apps are established and accepted both with the medical community and in the field of pregnancy. Examples of web applications used widely include Epocrates for medical reference, special-purpose tools like Figure 1 for image sharing, and apps geared toward complex conditions like iBGStar Diabetes Manager. In the context of intrapartum management, the Yale Labor Curve Assistant provides generalized partograms to practitioners, but does not address customization for women of different BMI ranges. Patients are also accustomed to using apps in pregnancy. Notably, Ovia Fertility and Pregnancy are used by women to track fertility and then to receive education on normal changes from week to week during pregnancy. The proposed BMI-individualized web app builds on a foundation of web applications for medical uses and in pregnancy, thus increasing its acceptability by clinicians.

III. Approach

Preliminary studies

Nicole Carlson, PI of this project, completed an NIH-funded pre-doctoral project in 2015 where she gained experience using data documenting labor onset and progression from large databases to analyze labor processes and outcomes such as will be required for the proposed project. In that research, Dr. Carlson found that maternal delivery obesity (BMI ≥ 30 kg/m2) (OR 2.09, 95% CI [1.17, 3.75]) and AA race (OR 2.35, 95% CI [1.53, 3.60]) were significantly associated with unplanned cesarean delivery when included in analyses adjusting for intrapartum provider type, chorioamnionitis, labor management, gestational age, and neonatal birthweight. She also constructed the BMI-individualized partograms in paper format that will be updated, then used to build the proposed web application.

Methods: Overview

Individualized Partogram Updates

Existing BMI-individualized partograms (pictured in this Research Strategy above) will be updated to picture labor progression intervals of women who achieve full cervical dilation (10 cm cervical dilation) and to separate women who are parous or nulliparous (had previous birth or not). This information is available in the newly-released CSL dataset, which the PI has applied to receive from the NIH in 6/2016 (N=228,668 deliveries). We will first focus on a sample of CSL women with singleton pregnancies, had term live birth (>36 6/7 weeks), and vertex presentation of fetus, as used in CSL labor progression analysis by Zhang and colleagues18. Unlike previous CSL analyses, we will exclude women who ended labor with cesarean delivery for labor dystocia, thereby creating labor curves using times that are normal for women who achieved 10 cm cervical dilation20. Although CSL analysis of labor times by BMI reported by Kominiarek and colleagues used this sample exclusion for their graphical depiction of labor curves, they only reported tabular data on labor progression times for women who had both vaginal delivery and cesarean for labor progression difficulty. Our rationale for this plan is to produce partograms that better identify women whose labor progression is abnormally slow for the pathway to vaginal delivery. We then plan to replicate statistical methods used in the CSL analysis, which estimated duration of labor by running interval-censored regression analysis18, to produce time intervals for women to progress from centimeter to centimeter in labor.

Limitations

Although these BMI-individualized partograms offer an evidence-based tool for use in labor management, there are limitations inherent in this project. Induced labor requiring cervical ripening is known to lengthen first stage labor when compared to women with spontaneous onset of labor34 38. Given that higher maternal BMIs are associated with induction of labor39, it is important that these partograms allow providers to track the progression of induced labor. However, the Consortium of Safe Labor study that provided the traverse times for these partograms included both induced and spontaneous labors20. Thus, although the traverse times used to build these partograms might be slightly fast when used to track the labors of women who are being induced, we anticipate these traverse times will still be useful for providers of

intrapartum care to obese women. We plan to further individualize future partograms for labor onset, allowing clinicians to receive labor progression data for both BMI and labor onset type (spontaneous or induced) in the future. These first individualized partograms will serve to introduce clinicians to this type of individualized labor tracking tool. If acceptable and useful to clinicians, we plan to incorporate further individualization into the base program after the time period of this project application.

Another limitation of the BMI-individualized partograms is that, although partogram instructions recommend assessment of women who pass over the dystocia line for possible augmentation of labor, correct dosages and timelines for synthetic oxytocin in the obese woman are not known 21,24. The unique physiology of the obese woman in labor may require other strategies for augmenting labor that have not yet been described, including ambulation, pain relief measures, etc. The BMI-individualized partograms presented here can therefore only help providers become aware of labor difficulties, not recommend how best to address those difficulties. Finally, the initial set of partograms developed for web application use will only be individualized for parity and maternal BMI. Although other characteristics, including maternal age, estimated fetal birthweight, gestational age, and maternal race, have been shown to affect the speed of labor progress18,40, quantification of labor progress for women with differences in these variables will not initially be possible in the proposed partograms. However, if the web application is successful, information on labor progress for women with differences in these variables can be incorporated from the CSL data, and used to individualize partograms further.

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Protection of Human Subjects

Risk to Human Subjects

The web application planned in this project will be based on data from the multi-site Consortium of Safe Labor (CSL) study on labor progression to guide clinician decision-making in labor20, and will only use de-identified information about these human subjects, thus not requiring IRB protocols for creation of the partograms. All women who were the subjects of the CSL study ended labor with healthy maternal and neonatal outcomes18. Moreover, the labor progression findings from the CSL study are recommended by the American College of Obstetricians and Gynecologists and the Society for Maternal Fetal Medicine for practicing clinicians25. Therefore, the labor progression data from the CSL that will be used to update these BMI-individualized partograms will be based on best evidence and best recommendations. In fact, the plan in this application to update the BMI-individualized partograms using cervical progression times from only women who achieved full cervical dilation will shorten the time intervals in these partograms compared to the labor progression times published in 2010-11 that included some women’s labor timing who did not achieve full dilation18,20. Thus, these updated BMI-individualized partograms will offer more conservative labor management guidance than times already publicized.

Sources of Materials

The proposed project will involve the development of BMI-individualized partograms using de-identified data from the Consortium of Safe Labor study (CSL), an NIH-sponsored, multi-site investigation of laboring women41. The study will use BMI, pregnancy, and labor progression variables contained in the CSL database. Women to be included in this project will meet the

following criteria: o Delivered at term gestation (at or beyond 37 completed weeks gestation) o Delivered a singleton fetus o Fetus was in a head-down position at the start of labor o Had no medical indication for cesarean delivery prior to the onset of labor o Achieved 10cm dilation (full cervical dilation)

The CSL data that will be used to update these BMI-individualized partograms and build the proposed web application are completely de-identified and thus involve no issues for protection of human subjects. Construction of the web application for the partograms will not involve human subjects. Once the web application for the BMI-individualized partograms is complete, they will be made available to clinicians after testing with small groups of nurse-midwives, labor and delivery nurses, and obstetricians. This phase of the proposed project will involve human subjects for product evaluation, and thus will require human subjects protection planning.

Potential Risks

Since the labor progression data that will be used to update BMI-individualized partograms was already de-identified by the NIH, the proposed project to create a web application of these partograms will not involve risks to human subjects. We also do not anticipate risks from this project to the clinicians who will provide product evaluations, as we will not collect identifying information on these product testers, and testing of the application will not pose risks to these testers.

Adequacy of Protection Against Risks

Recruitment & Informed Consent

Once the proposed web application is complete, clinicians who wish to use this application will be referred to the CSL website at the NIH, and cautioned that this application is not intended to replace the judgement of clinicians or to be taken as medical consultation, which is similar language used on other web partograms that do not individualize by maternal BMI42.

Protections Against Risk

We plan to submit to the Emory IRB for Exempt status, once we initiate web application development and in expectation of our first product evaluation session with clinicians. We plan to have clinician product testers receive Informed Consent in written format and complete HIPAA waivers before their evaluation activities. Although we do not anticipate risk from serving as a product tester of the web application, we plan to secure Emory IRB approval and recommendations before proceeding with that step of the project. As the partograms will be built on retrospective clinical data, this project can have no influence and can add no risk to the women who were the subject of the CSL study.

Potential Benefits of the Proposed Research to Human Subjects and Others

The proposed web application will put evidence-based information on normal labor progression of women across a range of maternal BMIs in the hands of clinicians. Several potential benefits of the

proposed project include: 1) Clinicians using the web application will have more accurate labor progression standards upon which to decide on correct timing of labor interventions (oxytocin, artificial rupture membranes, etc.), 2) Clinicians using the web application will be better able to educate and reassure laboring women and their families about the normalcy of their laboring process rather than maintain unrealistic expectations of cervical progress, 3) Clinicians will be less likely to move toward unplanned cesarean delivery for the indication of slow labor progress in women with elevated BMI.

Importance of the Knowledge to be Gained

Gaps exist in our knowledge of the effectiveness of different management strategies (alone and in combination) in the intrapartum care of otherwise healthy obese women at term gestation with a head-down, singleton fetus. The knowledge to be gained from the proposed study is important because both the rate of cesarean delivery and the incidence of obesity are high in the childbearing population in the U.S. Obese women experience cesarean delivery rates approximately 3-5 times higher than their normal weight counterparts4, a reality that is unexplained by simply weight alone. Likewise, obese women are significantly more likely to experience morbidity and mortality following surgical delivery than similar normal weight women11. Obese women are known to be over-represented among lower socio-economic and ethnic minority groups in the U.S1. Thus, this project is important in its potential to produce a tool for use at the bedside that can be used to promote health by preventing unnecessary surgical intervention and its accompanying risk for morbidity and mortality, preventing future pregnancy complications associated with past cesarean delivery, and eliminating health disparities through a better guidance labor management in obese women.

Inclusion of Women and Minorities

The proposed project involves use of CSL data on the labors of women, including some racial and ethnic minority women. No men were included in the CSL study, as this study profiled labor progress. In the publication based on CSL data that produced the first labor traverse times individualized by maternal BMI (N=118,978 women)20, distribution of subjects by race and ethnicity were as follows:

Nulliparous women (N=57,462) Multiparous women (N=61,516 women) White race 29,243 (50.9%) 32,480 (52.8%) Black race 11,768 (20.5%) 12,447 (20.2%) Hispanic race 9,940 (17.3%) 11,548 (18.8%)

We plan to use data on the same women from the CSL dataset to update and transform our BMI-individualized partograms as a web application.

Inclusion of Children

The proposed project is built upon CSL data that did not include women less than 18 years of age.