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Sonographic Evaluation of the Mechanism of Active Labor (SonoLabor study): observational study protocol regarding the implementation of the sonopartogram

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Sonographic Evaluation of the Mechanism of Active Labor (SonoLabor study): observational study protocol regarding the implementation of the sonopartogram

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Abstract

Methods / Analysis: This is a prospective observational study performed in three university hospitals, with an unselected population of women admitted in labor at term. Clinical and US evaluations will be performed assessing fetal head position, descent and rotation. Specific US parameters regarding fetal head position, progression and rotation will be recorded so as to develop nomograms in a similar way that partograms were developed. The primary outcome is to develop nomograms for the longitudinal US assessment of labor in unselected nulliparous and multiparous women with occiput anterior position of the fetal head. The secondary aims are to assess the particularities of the sonopartogram in occiput posterior deliveries and to develop standard deviations based on the US pilot study findings. Finally, we will investigate the capability of the US labor monitoring to predict the outcome of delivery.

Ethics and dissemination: All protocols and the informed consent form comply with the Health Ministry and professional society ethics guidelines. University Ethics Committees approved the study protocol. The trial results will be published in peer-reviewed journals and at conference presentations. The study will be implemented and reported in line with the STROBE statement.

Trial registration number: ClinicalTrials.gov Registry: NCT02326077.

Keywords: intrapartum ultrasound, labor monitoring, prenatal diagnosis, fetal medicine, maternal medicine, ultrasonography.

Strengths and limitations of this study

Strengths

- The multicentre design on representative population and the blinded clinical / imagistic assessment aims to intercept the potential sources of bias.
- Sonographic and clinical evaluation of the labor progression in any cephalic presentation (not only with occiput anterior position).

Limitations

- The high number of laboring women necessary to investigate the characteristics of each clinical situation aimed in the study design.
- The concept of normality is population-based and depends on various management attitudes (for example epidural analgesia, active management of labor), different characteristics of the partogram are observed[1] that may affect generalizability.

Introduction

Studies show that clinical digital pelvic estimations of fetal head position, station and progression in the pelvic canal are poorly reproducible, and therefore unreliable[2-17]. This may have major consequences on the decision of the appropriate delivery mode, because digital examination is less reliable especially in clinical situations when obstetrical interventions are more likely to be needed[7,18-22]. Severe complications may occur secondary to failed instrumental delivery and Caesarean extraction with the fetal head deeply impacted in the maternal pelvis. Many studies provided sonographic data regarding the fetal head descend / progression (FHPr) in the second stage of labor and proposed several easily measurable and reliable parameters, capable to predict the vaginal or operative

outcome of the delivery with occiput anterior positions[24-29]. The literature regarding US evaluation in the first stage of labor is much less, but based on available data US evaluation appears to be useful for the prognosis of labor[30,31]. Given the increasing evidence regarding the advantages offered by the use of US in labor, our group concluded that the development of a *sonopartogram*, as an adjuvant to or a replacement of traditional labor monitoring, may be the answer to many of decision problems on the mode of delivery[,32,33].

There is little information in the literature regarding the ultrasonographic monitoring of the entire active labor mechanism[34-36,42]. A recent proof-of-concept study showed that the sonopartogram is feasible in most cases[34]. However, a study of the paired clinical and sonographic assessments of labor in a large unselected population has not yet been conducted. Furthermore, there are no nomograms for the ultrasound monitoring of labor. Nowadays, the use of ultrasound in labor is generally limited to research settings and a relatively small-number of women has been studied. Therefore, efforts should be made to describe the value of an objective partogram in practice, especially because of the important medico-legal liability issues related to labor and delivery.

Our study is the first to present a multicentre longitudinal assessment of the mechanism of both stages of active labor, in a representative population using concomitant blinded clinical and sonographic evaluations in unselected low-risk parturients at term. The aim of this paper is to describe the protocol of the current study.

Objectives

The primary objective of this study is the development of sono-nomograms for the longitudinal US assessment of labor in unselected nulliparous and multiparous women at term with occiput anterior position of the fetal head.

The secondary objectives of the study are:

- to compare the US pattern of labor evolution in nulliparous and multiparous women.
- to study the influence of occiput position, body mass index, parturient age on the mechanism of delivery evaluated by US.
- to compare the labor clinical trend from our study data with the Friedman studies[35,36] and other recent research on the partogram[1].
- to compare and correlate the US findings (sonopartogram data) with the classical clinical partogram parameters.
- to investigate the correlations between the data of the participating centres.
- to analyse the temporal variation of the sonographic measurements in spontaneous vaginal delivery versus obstructed labor in primiparae versus multiparae and in fetuses with occiput anterior versus those with persistent occiput posterior.
- to evaluate the capability of the US technique to predict the outcome of delivery.

Methods and analysis

Study design and setting

This is an observational cohort prospective study, which will take place in three tertiary maternity hospitals (University Emergency Clinical County Hospital Craiova, Alexandra University Hospital of Athens and Ippokrateion Hospital Thessaloniki), with more than 4000 deliveries per annum. The study aims to record almost simultaneously blinded US and clinical features of low-risk women in labor at term, with singleton eutrophic cephalic presentation pregnancies.

Figure 1

Participants

All pregnant women admitted in active labor at term are considered eligible for the study. They are included in the study consecutively, depending on the availability of the US operators involved. Cases planned for elective caesarean section, or involving imminent intention to deliver, with non-cephalic presentation, intra-uterine death, multiple pregnancies or resulting neonates weighting less than 2500g or more than 4000g will be excluded from the study. Also, we will exclude women with previous cervical surgery (eg. cone biopsy, cervical cerclage), those younger than 18 years, or those considered in the opinion of the researcher as having language or learning impairment.

Women are defined as being in labor in the presence of regular uterine contractions occurring at a frequency of at least 2 every 10 minutes associated with a cervical dilatation of 3-4 cm or more[39], regardless of whether they underwent Oxytocin augmentation or epidural anaesthesia.

Gestational age is determined by the last menstrual period if confirmed by early US dating or by the first sonographic evaluation alone if fetal biometry was not consistent with the menstrual dating by more than one week.

Procedures

Recruitment

During their usual consultation in the labor ward, in an eligible case, the physician on duty provides brief information about the research and invites the patient to take part in the study. If the patient shows interest in the study and meets the inclusion criteria, a face-to-face appointment with the ultrasound operator is arranged. The details of the study and its potential benefits are explained thoroughly to the patient. If the patient agrees to participate in the study, written informed consent is obtained.

Interventions

All pregnant women that meet the inclusion criteria are assessed clinically by the physician on duty. The managing clinician is a senior consultant not involved in the study.

Clinical examinations are performed just before the US assessments and recorded as follows (Figure 1):

- cervical dilation in centimetres,
- head station in relation to the ischial spines - to determine FHPr and
- occiput position – to determine fetal head position (FHPo) and occiput rotation during labor. Occiput position was classified as occiput anterior (OA), occiput posterior (OP), left or right occiput transverse (LOT or ROT), left or right occiput anterior (LOA or ROA), or left or right occiput posterior (LOP or ROP)[39,40].

In women in active labor, transabdominal and transperineal **ultrasound evaluations** are performed by obstetricians with appropriate training in US in labor, with minimum 1 year of experience in the field. Mobile and compact US machines are used: Logic e (GE Healthcare, China), GE Voluson P6, Samsung R7 and ALOKA f31 equipped with 2–5-MHz transabdominal 2D convex transducers.

The following planes are obtained and stored on the system's hard disk drive for off-line analysis (Figure 1):

1. transabdominal suprapubic transverse plane (used for FHPo determination),
2. transabdominal transversal and longitudinal planes (used to determine the spine position),
3. infrapubic or translabial sagittal plane in the in semi-recumbent position, with legs flexed (used to evaluate FHPr parameters),

4. transperineal transverse plane, at the level of the ischial tuberosity, applying firm pressure without creating discomfort, and the transducer moved and angled until the shortest distance to the fetal skull was visualized (used to evaluate the fetal head to perineum distance (HPD)),
5. infrapubic transverse plane (used to visualise the cerebral midline rotation to the antero-posterior axis of the maternal pelvis - rotation angle or midline angle (MLA) in the 2nd stage of labor).

Using the measurement techniques described in the literature, the assessments are performed offline by the respective examiner (Figure 1, 2, 3):

- FHPo parameters (Figure 2): occiput position[6], midline angle (MLA) in advanced labor[26]. The clinical and US findings of the FHPo are recorded on a data sheet depicting a circle, like a clock, divided into 24 sections, each of 15°. The position of the occiput (OA, OP, LOA, ROA, LOP, ROP) is determined transabdominally in the 1st stage of labor[6] and transperineally[26] in the 2nd stage, measured using the MLA parameter. At the initial assessment, the digital evaluation is considered to be correct if the FHPo was within±45◦ of the US determination. Because of ethical issues, the design of the study stated that the attending obstetrician was informed in case of clinical and US discordance when instrumental or operative delivery was attempted.
- FHPr parameters (Figure 3): progression angle (PA)[27,28], progression distance (PD)[23], head direction angle (HDA)[23,25] and head to perineum distance (HPD)[41].
- Cervical dilation is evaluated only clinically, as the evaluation of this parameter is best achieved with digital assessment[42].
- The caput (Figure 3) is measured as the maximum distance between the leading part of the skull and the fetal skin in the sagittal or transverse planes.
- Moulding (Figure 3) is diagnosed when the skull bones were seen overlapping in the sagittal or transverse planes.

Figure 2

Figure 3

US scans are performed hourly until complete dilation (1st phase of active labor) and at every 15 minutes after complete dilation (2nd phase). The purpose of the apparently high number of examinations was to obtain accurate information in each labor in terms of correlation of FHPr, FHPo and cervical dilatation. In a previous study in our clinic this methodology proved acceptable for the parturients[43]. The frequent evaluations in the second stage are meant to offer a better analysis of this critical stage of labor.
Notation of time delivery is used to calculate the time interval from each scan to delivery.

The sonographer and the clinician are blinded to each other's findings (except FHPo) as the specific measurements are performed afterwards, offline and labor management is conducted by the Labor and Delivery department personnel.
Labor characteristics are recorded: mode and time of delivery, neonatal Apgar score and birth weight, whether labor was spontaneous or induced, use of oxytocin or epidural anaesthesia, occipital position at delivery. Maternal characteristics are retrieved from the hospital records: age, height, weight, ethnicity, parity, gestational age.

The US labor assessments should not be biased by confounders that influence the quality of the clinical evaluations in labor (obesity, anterior placenta, caput, moulding), because the visualization of the fetal skull and pubic symphysis is easily achievable even in such conditions. To ensure protocol fidelity, all sonographers have completed an one-day workshop and participated in group supervision sessions that were held weekly in the first month of the study.

The information provided to the clinician regarding the US determination of the FHPo in case of clinical – imagistic discordance before instrumental or operative delivery, could represent a theoretically bias of the study. However, many tertiary centres already use the US determination of the FHPo in such situations, and this aspect does not interfere with the objectives of our study.

Outcome measures

Primary outcome

The primary objective of this study is the elaboration of nomograms for the longitudinal US assessment of labor in unselected nulliparous and multiparous. The nomograms represent the evolution of the progression markers (PA, DA, PD, HPD) in relation with time and cervical dilatation.

Secondary outcomes

- to compare the US pattern of labor evolution in nulliparous and multiparous women.
- to study the influence of occiput position, body mass index, parturient age on the mechanism of delivery evaluated by US.
- to compare the labor clinical trend from our study data with the Friedman studies[35,36] and other recent research on the partogram[1].
- to compare and correlate the US findings (sonopartogram data) with the classical clinical partogram parameters.
- to investigate the correlations between the data of the participating centres.
- to analyse the temporal variation of the sonographic measurements in spontaneous vaginal delivery versus obstructed labor in primiparae versus multiparae and in fetuses with occiput anterior versus those with persistent occiput posterior.
- to evaluate the capability of the US technique to predict the outcome of delivery.

Data collection and management, Quality control

To ensure the acquisition of accurate data and for study monitoring purposes, the following procedures are followed:

- The initial workshop established standardised procedures regarding data collection, encoding of the clinical and ultrasound data and electronic storage;
- The principal investigators held training sessions to provide instructions on the protocol and study procedures for the sonographers at the beginning of the study;
- Periodic meetings are held with study site personnel, in order to discuss issues related to the conduct of the study;
- The principal investigators in the three centres are available for consultation by telephone at request;
- Interim analyses monthly - the data manager evaluates the data with the statistics personnel and conducts a quality review of the database. The results of the interim analyses are discussed between the principal investigators, who decide whether to continue, stop, or modify the trial.

Statistical methods

Sample size estimation

Although several studies have investigated the clinical course of labor, until present we do not have data regarding the nomograms for US evolution of labor. The number of patients enrolled in the clinical partogram studies varies widely. However, the Friedman's study that still serves as the basis of how most physicians define normal labor, enrolled 500 primiparous at term[37,38]. On the other hand, we have a recent large, but retrospective study that analysed the clinical labor records of more than 62,000 women from 19 hospitals across the U.S. and concluded that these criteria created 50 years ago may no longer be applicable to contemporary obstetric populations and for current obstetric management[1].

Regarding imaging studies, the prospective researches on the trend of the labor progress using intrapartum transperineal US, gathered less than 100 cases each[34,36,44].

The primary outcome of our study will be centile charts for each US progression marker in relation to time. Our statistical goal was that the sample size should be large enough to yield precise estimates predictions of extreme centiles. We estimate the sample size in relation to the precision and accuracy of a single centile and regression based reference limits[45,46].

According to previously published studies the overall rate of occiput posterior deliveries in nulliparous is around 7.2%, whereas for the multiparous deliveries the rate is around 4%. A suitable statistical power (two-tailed type of null hypothesis with default statistical power goals $P \geq 95\%$ and type I error $\alpha = 0.05$ level of significance) can be achieved if we have at least 102 patients in the case of nulliparous deliveries, and 57 multiparous deliveries, respectively, with occiput anterior positions.

Such population groups are not achievable during our present research. However, we hope that the publication of our protocol and the preliminary results with preliminary standard deviation results will trigger and help similar studies and a meta-analysis that will achieve the necessary size for this purpose.

Statistical analysis

The statistical analyses will be performed by IBM SPSS Statistics for Windows, Version 22.0. (Armonk, NY: IBM Corp.).

Descriptive statistics will be produced for all study variables (mother's age, height, weight, parity, gestational age, neonatal Apgar score and birth weight, mode and time of delivery, whether labor was spontaneous or induced, use of oxytocin or epidural anaesthesia, occiput position, progression angle, progression distance, head direction angle, head to perineum distance). Continuous variables will be presented as the mean and standard deviation (SD) or mean (95% confidence intervals). Categorical data will be presented as frequency and percentage.

Data will be first tested for normality and equal variance. The maternal, labor, and neonatal characteristics of women will be compared using $\chi 2$, Fisher exact test, and the Wilcoxon rank sum test where applicable.

Pearson's correlations and regressions will be used for the evaluation of correlation between ultrasound parameters and between US and time to delivery and digital vaginal examination for various clinical situations (nulliparous and multiparous, foetuses with OA and those with persistent OP position). Reference ranges (90% range between 5th and 95th centiles) and the 95% confidence interval will be constructed for each ultrasound parameter and displayed in graphic form. Predictive ability of the nomogram will be assessed by calculating sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratio, by plotting receiver-operating characteristics (ROC) curve.

To identify factors that predict spontaneous or obstructed labor, all analyses will use appropriate (that is, logistic or linear) regression models, with results presented as point estimates (odds ratios or difference in means), 95% confidence intervals and p values. Further secondary analyses will involve planned subgroup analyses and will use multivariable regression models. In all models, predictors will be selected for inclusion in stepwise regression. Based on the probabilities predicted by the logistic models, receiver operating characteristic (ROC) curves will be constructed and we will calculate and report the area under the curve, sensitivity and specificity rates with 95% confidence interval in predicting mode of delivery.

The induction–delivery interval within 24 hours will be evaluated using Kaplan–Meier survival analyses and Cox regression analyses. Women undergoing a Cesarean section or if time to delivery is more than 24 hours are excluded. In the Cox regression analyses, fetal head–perineum distance, occiput position and parity will be tested as possible predictive factors. In additional analyses, we will adjust for maternal age, BMI, gestational age, and birth weight as possible confounders.

Reporting of adverse events

Prenatal ultrasonography appears to be a safe investigation method, as until today there has been no study reported suggesting otherwise (Statement approved by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) Board in September 2011 and by the World Federation of Ultrasound in Medicine and Biology (WFUMB) Council in August 2011)[47]. US is routinely used in everyday clinical practise for assessment of neonates, including cranial and cerebral examination. However US involves energy exposure and that requires further investigation.

Regarding the perception of laboring women about US there have been no reports in the literature of US causing discomfort.

All adverse events reported spontaneously by patients or observed by the obstetricians will be recorded. When an adverse event occurs, the treating physician will take all necessary and appropriate measures to ensure the safety of the patient.

Ethical considerations and dissemination

Ethics approval of the study protocol was obtained from the Ethics Committees of the universities in the three centres. The trial is registered in the ClinicalTrials.gov Registry: NCT02326077.

Informed consent

The US operator on duty is responsible for explaining the procedure to the participants and for obtaining an informed written consent from all women accepting to take part in the study.

Regarding the unforeseen complications or health damage that may occur during or after labor, the management of labor and delivery is made exclusively based on the traditional clinical evaluation, by senior physicians. The US study protocol is only observational, without any obstruction for the clinical manoeuvres. On the other hand, it is made clear to all participants that US is considered safe in the third trimester and after birth, both for the mother and the baby.

Compensation and insurance for harmed patients

There will be no special financial compensation; however, any negligence on the part of the physician may be covered by the doctors' liability insurance.

Declaration of interests

The investigators do not have any financial and other competing interests nor any relationships with companies that may have a financial interest in the information obtained during the study. All investigators comply with the policy on conflicts of interest in research and relevant conflict of interest guidelines.

Dissemination

The results of the study will be disseminated at national and international research conferences and as published articles in peer-reviewed journals. The study will be implemented and reported in line with the STROBE statement.

Discussion

It has been widely shown before that despite the significant progress in the last decades in maternal-fetal medicine, labor management remained unchanged, based on traditional clinical "blind" evaluations (Leopold manoeuvers, digital clinical evaluation) which have been proved by many studies to be subjective and inexact. In our view, clinical skills should not be abandoned and ultrasonography should only complement clinical examination and not replace it. However, nowadays more than ever, an objective method of assessing labor is needed, given the rates of fetal and maternal trauma at birth and because of the increasing amount of medico-legal liability issues related to labor and delivery. The SonoLabor study aims to provide new objective evidence regarding the evaluation of the mechanism of labor with US.

The SonoLabor study differs from previous studies as it aims to assess all stages of labor, rather than just the second stage of labor in order to elaborate nomograms for the longitudinal US assessment of labor in unselected low-risk population, an important issue of the future sonopartograms. We identified only one pilot study in the literature that aimed to assess the application of sonopartogram[34]. A unique point of our protocol is the comparative evaluation of the US parameters for various clinical situations. This may facilitate the use of different nomograms in labor, adapted to the clinical characteristics of the laboring woman. Another strength of our study is the multicentre design that is useful to achieve a proper study size and also an opportunity to compare the data recorded in different settings.

Although published six decades ago, Friedman's curve remains the only method for routine labor management today. Clinical studies showed that the pattern of labor progression and the present characteristics of the partogram differ significantly from the traditional Friedman curve[1]. Therefore, our study aims to develop curves for labor monitoring which will be not only objective, but also but also adapted to contemporary practice.

The challenge and limitation of this study is the achievement of a sufficient study size for the secondary objectives of the research. In order to produce specific sonopartograms regarding the maternal characteristics and occiput position, an important number of patients would be required, that is not achievable during our present research. However, preliminary data will be published on this matter. We also hope that the dissemination of our study protocol will serve to future larger studies that will help to collect or complete the necessary data.

We are also aware that the participating sites in this study have certain experience in the intrapartum US assessment. Thus, the results might not be generalizable to other settings. Nevertheless, previous research demonstrated that intrapartum US is reproducible[48] and the learning curve is much easier for US than clinical examination, even for younger and less experienced colleagues[49]. The results of the current study will hopefully

improve the evidence-based understanding of the mechanism of labor and establish an objective solution for the labor monitoring, complementary to the traditional clinical examination.

Ethics approval and consent to participate

Ethics approval of the study protocol was obtained from the Ethics Committees of the universities in the three centres. The trial is registered in the ClinicalTrials.gov Registry: NCT02326077.

Informed consent

The US operator on duty is responsible for explaining the procedure to the participants and for obtaining an informed written consent from all women accepting to take part in the study.

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Availability of data and material (Disemination)

The results of the study will be disseminated at national and international research conferences and as published articles in peer-reviewed journals. The study will be implemented and reported in line with the STROBE statement.

Competing interests

The authors and their relations have no financial connections with companies that may have an interest in the submitted work, and no non-financial interests that may be relevant to the article.

Funding

The potential funding sources will play no role in data collection, analysis and interpretation, in the writing of the reports, or the decision to submit the paper for publication.

Authors' contributions

ID, AP and TS conceived and designed the study and supervise the study implementation. ID and TS drafted the protocol of the study. CN, NL, CD and AA revised and refined the study protocol and study implementation and provided final approval of the version to be published. CM provided methodological and statistical expertise and conducts the statistical analysis. ID and AD drafted a post PhD salary grant proposal that was accepted. DR, CO, FM, CP, ZL and GD are responsible for study management, staff training, and supervision. ID and AP are the directors of the two sites and provided clinical expertise and on-site management of the study. All authors critically reviewed and approved the final version of the manuscript.

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Current study status

The SonoLabor study recruited patients during January - December 2016 for a pilot study of 168 deliveries. Data analysis was be completed in January 2017 and the results were communicated at the 27th World Congress on Ultrasound in Obstetrics and Gynecology[33]. Then the project was discontinued, due to the lack of resources.

Competing interests

The authors and their relations have no financial connections with companies that may have an interest in the submitted work, and no non-financial interests that may be relevant to the article.

Details of ethics approval

Ethics Research Committees of University of Medicine and Pharmacy and University of Athens approved the study protocol. Women will provide written consent.

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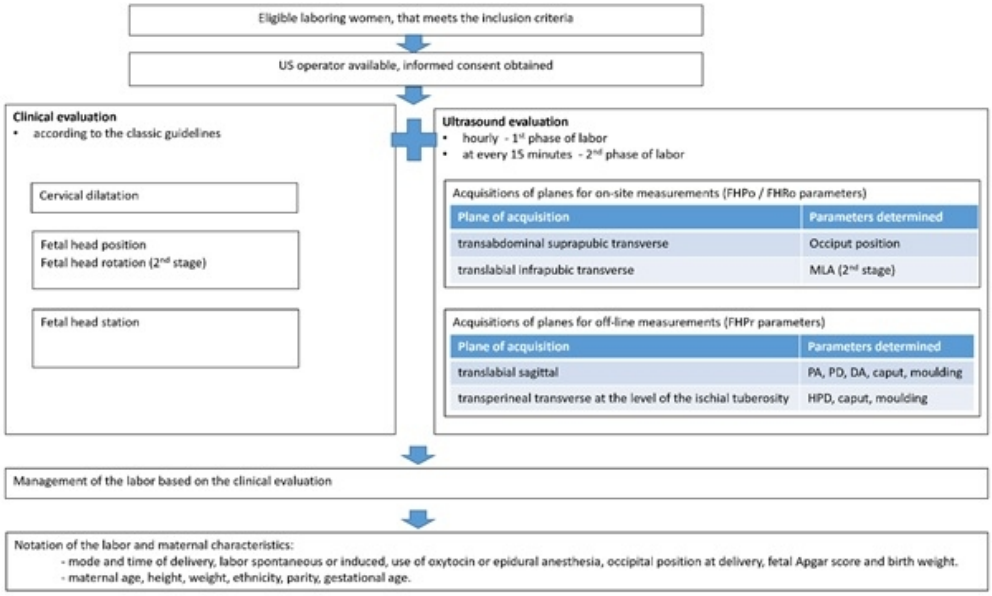
Figure 1. Implementation of the SONOLABOR study.

Figure 2. Ultrasound determination of the foetal head position and rotation.
A: Example of the orientation of the probe in the transabdominal suprapubic transverse plane. B: FHPo determination in the plane described in image A. C: Orientation of the probe placed above the perineum for the infrapubic transverse plane aquisition. D: Visualization of the cerebral midline in relation with the antero-posterior axis of the maternal pelvis and the measurement of rotation angle or midline angle (MLA).
OA, occiput anterior; OP, occiput posterior, LOT, left occiput transverse; ROT, right occiput transverse; LOA left occiput anterior; ROA right occiput anterior; LOP, left occiput posterior; ROP, right occiput posterior.

Figure 3. Ultrasound determination of the foetal head progression in the infrapubic translabial sagittal plane (A-C), and infrapubic transversal plane (D), caput and molding (E, F). A: measurement of the progression angle between the long axis of the pubic symphysis and a line extending from its most inferior portion tangentially to the fetal skull. B: measurement of the direction angle as the angle between the major longitudinal axis of fetal head (perpendicular to the biparietal diameter) and the infrapubic line. C: measurement of the progression distance as the minimal distance between the infrapubic line and the leading part of the fetal skull. D: measurement of the head to perineum distance as the shortest distance from the skin surface of the perineum to the outer bony limit of the fetal skull. E: caput (star), with the correct measurement of the progression angle marked in blue, tangent to the foetal calvaria and not to the skin. F: moulding of the cranian bones, marked with arrow.



Implementation of the SONOLABOR study.

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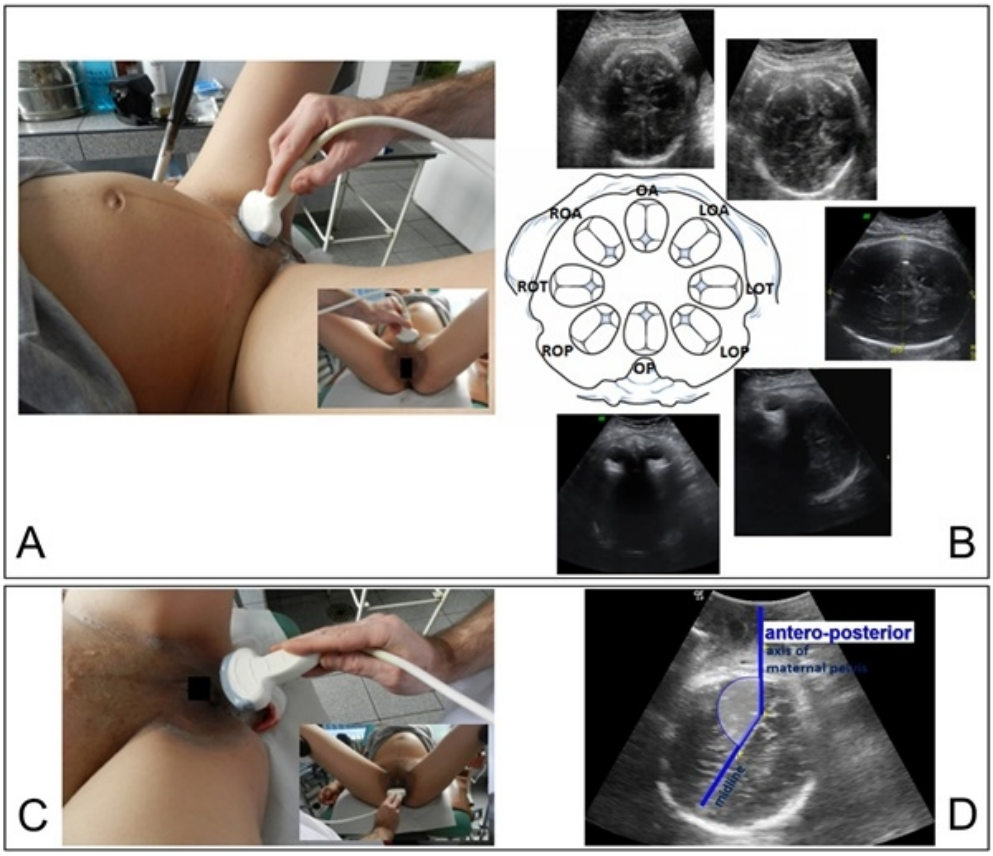

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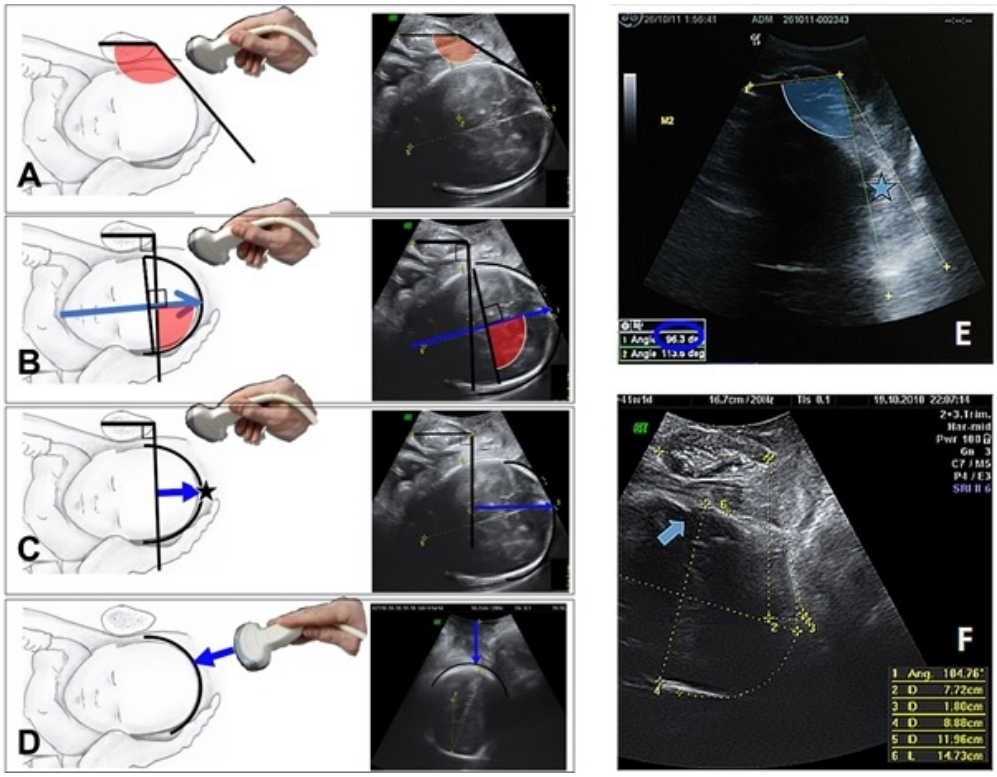

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51x39mm (300 x 300 DPI)

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Sonographic Evaluation of the Mechanism of Active Labor (SonoLabor study): observational study protocol regarding the implementation of the sonopartogram

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Sonographic Evaluation of the Mechanism of Active Labor (SonoLabor study): observational study protocol regarding the implementation of the sonopartogram

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Abstract

Introduction

Over the last decades, a large body of literature have shown that intrapartum clinical digital pelvic estimations of fetal head position, station and progression in the pelvic canal are less accurate, compared to US scan. Given the increasing evidence regarding the advantages of using US to evaluate the mechanism of labor, our study protocol aims to develop sonopartograms for fetal cephalic presentations. They will allow for a more objective evaluation of labor progression than the traditional labor monitoring, which could enable more rapid decisions regarding the mode of delivery.

Methods / Analysis: This is a prospective observational study performed in three university hospitals, with an unselected population of women admitted in labor at term. Both clinical and US evaluations will be performed assessing fetal head position, descent and rotation. Specific US parameters regarding fetal head position, progression and rotation will be recorded to develop nomograms in a similar way that partograms were developed. The primary outcome is to develop nomograms for the longitudinal US assessment of labor in unselected nulliparous and multiparous women with fetal cephalic presentation. The secondary aims are to assess the sonopartogram differences in occiput anterior and posterior deliveries, to compare the labor trend from our research with the classic and other recent partogram models and to investigate the capability of the US labor monitoring to predict the outcome of spontaneous vaginal delivery.

Ethics and dissemination: All protocols and the informed consent form comply with the Ministry of Health and the professional society ethics guidelines. University Ethics Committee approved the study protocol. The trial results will be published in peer-reviewed journals and at the conferences presentations. The study will be implemented and reported in line with the STROBE statement.

Trial registration number: ClinicalTrials.gov Registry: NCT02326077.

Keywords: intrapartum ultrasound, labor monitoring, prenatal diagnosis, fetal medicine, maternal medicine, ultrasonography.

Strengths and limitations of this study

Strengths

- The multicentre design on representative population and the blinded clinical / ultrasound assessment aims to intercept the potential sources of bias.
- Sonographic and clinical evaluation of the labor progression in any cephalic presentation (not only with occiput anterior position).

Limitations

- The high number of laboring women needed to investigate the characteristics of each clinical situation targeted in the study design.
- The concept of normality is population-based and depends on various management attitudes (for example epidural analgesia, active management of labor), different characteristics of the partogram are observed that may affect generalizability.

Introduction

Over the last decades, a large body of literature have shown that clinical digital pelvic estimations of fetal head position, station and progression in the pelvic canal are not accurate during the first[1] and second stage of labor[1-6], poorly reproducible when compared to US[7-9], poorly reliable[10-12], experience-dependent[1,4] and often inexact in challenging labor circumstances, such as: prolonged first stage of labor[13], cases with arrested cervical dilation[14], obstructed labor[15], fetal head engagement[10,16], posterior and transverse occiput locations[6,14], or caput [4]. This may imply significant consequences on the decision of the appropriate delivery mode, because digital examination is less reliable especially when obstetrical interventions are more likely to be needed[15,17-21]. Previous studies that used sonographic evaluation in prolonged labor cases have demonstrated the potential to decrease the rate of late Cesarean extractions, and the various approaches proposed in the literature were considered by our study design. Many studies provided sonographic data regarding the fetal head descent / progression (FHPr) in the second stage of labor and proposed several easily measurable and reliable parameters, capable to predict the vaginal or operative outcome of the delivery with occiput anterior positions[22-28]. The literature regarding US evaluation in the first stage of labor is lesser, but based on available data US evaluation appears to be useful for the prognosis of labor[29,30,31].

Given the increasing evidence regarding the advantages offered by using US in labor, our group concluded that the development of a *sonopartogram*, as an adjuvant to or a replacement of traditional labor monitoring, provides the setting for a more objective evaluation of labor progression, which could enable more rapid decisions regarding the mode of delivery[32,33].

There is few information in the literature regarding the ultrasonographic monitoring of the entire active labor mechanism[34-36]. A recent proof-of-concept study showed that the sonopartogram is feasible in most cases[34]. However, a study of the paired clinical and sonographic assessments of labor in a large, unselected population has not yet been conducted. Furthermore, there are no nomograms for the ultrasound monitoring of labor. Nowadays, the use of ultrasound in labor is generally limited to research settings and a relatively small number of women has been studied. Therefore, efforts should be made to describe the value of an objective partogram in practice, especially because of the important medico-legal liability issues related to labor and delivery.

This study is designed to produce an original multicentre longitudinal assessment of the mechanism of active labor, including both stages, in a representative population, using concomitant blinded clinical and sonographic evaluations in unselected low-risk parturient women at term. The aim of this paper is to describe the protocol of the study.

Objectives

The primary objective of this study is the development of sono-nomograms for the longitudinal US assessment of labor in unselected nulliparous and multiparous women at term with fetal cephalic presentation.

The secondary objectives of the study are:

- to compare the US pattern of labor evolution in nulliparous and multiparous women.
- to study the influence of occiput position, body mass index, parturient age on the mechanism of delivery evaluated by US.
- to compare the labor trend from our study with the Friedman studies[37,38] and other recent research on the partogram[39].
- to compare and correlate the US findings (sonopartogram data) with the classical clinical partogram parameters regarding the fetal head position and descent during active labor
- to investigate the correlations between the data of the participating centres.

- to analyse the temporal variation of the sonographic measurements in spontaneous vaginal delivery versus obstructed labor in primiparae versus multiparae and in fetuses with occiput anterior versus those with persistent occiput posterior.
- to evaluate the capability of the US technique to predict the outcome of vaginal delivery.

Methods and analysis

Study design and setting

This is an observational cohort prospective study, which will take place in three tertiary maternity hospitals (University Emergency County Hospital Craiova, Alexandra University Hospital of Athens and Ippokrateion Hospital Thessaloniki), with more than 4000 deliveries per annum. The study aims to record simultaneously the labor progress by clinical and US evaluations in low-risk women in labor at term, with singleton cephalic presentation.

Patient and Public Involvement

We conducted a previous study[40] during the development of this research question, where we evaluated the acceptability of the method and found that the vast majority of laboring women (98%) agree with the supplementary US investigation protocol and the demographic characteristics did not influence the rate of acceptance. Most of the women (93% of accepters and 75% of decliners) had little difficulty deciding whether or not to have the scan protocol. All women who were scanned during labor found it an acceptable experience, and only 21% of women without epidural anesthesia rated the perceived difficulty as "mild" or "discomforting". Women rated having the intrapartum scan as being significantly less difficult than having a cervical smear, transvaginal scan or having a digital clinical evaluation. Two-thirds (67%) of the patients expressed increased confidence while being able to follow along the medical personnel the fetal head progression on the ultrasound screen. Almost all of the consenting women (97%) who had the intrapartum US scans and all the 4 decliners said they would definitely or probably agree such ultrasound monitoring in a future labor, if this technique is proven useful for the labor outcome.

Participants

All pregnant women admitted in active labor at term are considered eligible for the study. They will be included in the study consecutively, depending on the availability of the US operators involved. Cases planned for elective caesarean section, or involving imminent intention to deliver, with non-cephalic presentation, intra-uterine death, multiple pregnancies or resulting neonates weighting less than 2500g or more than 4000g will be excluded from the study. Also, we will exclude women with previous cervical surgery (e.g. cone biopsy, cervical cerclage), those younger than 18 years, or those considered in the opinion of the researcher as having language or learning impairment.

Women will be admitted in the first stage of labor when there are regular painful contractions and there is a progressive cervical dilatation from 4 cm, and the second stage will be established based on the finding of full dilatation of the cervix[41] regardless of whether the parturients underwent artificial rupture of the membranes, Oxytocin augmentation or epidural anaesthesia.

Gestational age will be determined by the last menstrual period in women with regular menses, confirmed with US dating, preferably during the first trimester. If the first trimester biometry is not consistent with the menstrual dating by more than one week, gestational age will be established based on the sonographic evaluation alone. In women with irregular menses, the gestational age will be determined solely based on the first fetal biometry evaluation in pregnancy.

Procedures

Recruitment

During their usual consultation in the labor ward, in an eligible case, the physician on duty provides brief information about the research and invites the patient to take part in the study. If the patient shows interest in the study and meets the inclusion criteria, a face-to-face appointment with the ultrasound operator is arranged. The details of the study and the potential benefits that may result following the completion of the objectives will be explained thoroughly to the patient. The only direct benefit of the laboring women that participate in the study would be the communication between the obstetrician and sonographer regarding fetal head position when instrumental delivery is attempted, as presented in the Interventions section. If the patient agrees to participate in the study, written informed consent will be obtained.

Interventions

All pregnant women that meet the inclusion criteria will be assessed clinically by the physician on duty. The managing clinician is a senior consultant not involved in the study.

Clinical examinations will take place in women in active labor just before the US assessments (Figure 1). The clinician will note the observations on a specially designed partogram-like sheet that will be used for women in labor who agree to participate in the study. The following labor characteristics has to be noted before US assessment:

- ***cervical dilation*** in centimetres,
- ***fetal head descent or progression (FHPr)*** – determined by the evaluation of head station in relation to the ischial spines,
- ***fetal head position (FHPo)*** – the evaluation of occiput position in both stages and rotation in the second stage. Occiput position will be classified as occiput anterior (OA), occiput posterior (OP), left or right occiput transverse (LOT or ROT), left or right occiput anterior (LOA or ROA), or left or right occiput posterior (LOP or ROP)[5,42].
- Presence of ***caput*** and / or ***molding***, with the approximate diameter.

Clinical examination will be followed by transabdominal and transperineal **ultrasound evaluations** conducted by obstetricians with appropriate training in US in labor, with minimum 1 year of experience in the field. Mobile and compact US machines will be used: Logic e (GE Healthcare, China), GE Voluson P6, Samsung R7, BenQ T3300 and ALOKA f31 equipped with 2–5 and 2-6 MHz 2D convex transducers.

The objectives of US evaluations are like those of clinical assessment, and aimed to record the mechanism of labor by specific measurements. In Table 1 we present the sonographic measurements, in relation to the acquisition planes and the features of labor mechanism that are involved. The respective images will be stored on the system's hard disk drive for off-line analysis and measurements that will be performed according to the techniques described in the literature, by the sonographer who performed the evaluation.

Table 1. Acquisition of US planes, and ultrasound measurements performed offline, according previous literature

Labor mechanism feature	Acquisition plane	Ultrasound measurements
Fetal head position (FHPo) in the first stage of labor	Transabdominal suprapubic transverse plane	• Occiput position (Figure 2)

		Both clinical and US findings of the FHPo are recorded on a data sheet depicting a circle, like a clock, divided into 24 sections, each of 15º, and the position of the occiput is assigned as anterior (OA), posterior (OP), left anterior (LOA), right anterior (ROA), left posterior (LOP), right posterior (ROP), right transverse (ROT), left transverse (LOT)[5,42]
Fetal head position (FHPo) in the second stage of labor, evaluation of head rotation	Transperineal infrapubic transverse plane (Figure 3), with visualization of the cerebral midline	• Occiput position • Midline angle (MLA) (Figure 3) The position of the occiput (OA, OP, LOA, ROA, LOP, ROP) is determined in a similar fashion transperineally in the 2nd stage of labor. Midline angle (MLA) is calculated[25] based on the visualization of the cerebral midline in relation to the antero-posterior axis of the maternal pelvis - rotation angle or midline angle (MLA).
Fetal head descent / progression (FHPr)	Transperineal translabial sagittal plane	• Progression angle (PA)[26,27], • Progression distance (PD)[22], • Head direction angle (HDA)[23,24] (Figure 4).
	Transperineal translabial transverse plane, at the level of the ischial tuberosity, applying firm pressure without creating discomfort, and the transducer moved and angled until the shortest distance to the fetal skull is visualized	• Head to perineum distance (HPD)[43] (Figure 4).
Caput and molding	Transperineal sagittal and transverse plane	• Caput (Figure 5) is measured as the maximum distance between the leading part of the skull and the fetal skin in the sagittal or transverse planes. • Molding (Figure 5) is diagnosed when the skull bones were seen overlapping in the sagittal or transverse planes.

Because of ethical issues, the design of the study states that the attending obstetrician should be informed in case of clinical and US discordance when instrumental or operative delivery is attempted. The digital evaluation is considered to be correct if the FHPo is within±45◦ of the US determination.

Cervical dilation will be evaluated only clinically, as the evaluation of this parameter is best achieved with digital assessment[31].

Timing: clinical and US scans are performed hourly until complete dilation (1st phase of active labor) and at every 15 minutes after complete dilation (2nd phase). The purpose of the apparently high number of examinations was to obtain accurate information in each labor in terms of correlation of FHPr, FHPo and cervical dilatation. In a previous study in our clinic this methodology proved acceptable for the parturients[40]. The frequent evaluations in the second stage are meant to offer a better analysis of this critical stage of labor. Notation of time delivery will be used to calculate the time interval from each scan to delivery.

Ultrasound images will be saved and stored on ultrasound hard disk during labor, then transferred by the sonographer to a designated PC storage unit after birth. The images will be reviewed during the following week, by the same sonographer, who will also and input the offline measurements results into the database.

The sonographer and the clinician are blinded to each other's findings (except FHPo, during the circumstances mentioned above) as the specific measurements are performed afterwards, offline and labor management is conducted by the Labor and Delivery department personnel. During labor, the available sonographer cannot be completely blinded to clinical findings, as he/she will perform the scans at certain time intervals, depending on the labor stage, that is established by the clinician's cervical dilatation assessment. However, the sonographer will only record the images. The clinician will note the observations on a partogram-like sheet that is not available for the sonographer, who in turn, will perform the measurements offline, after birth.

Labor characteristics will be recorded by the clinician on the study datasheet: mode and time of delivery, neonatal Apgar score and birth weight, whether labor was spontaneous or induced, use of oxytocin or epidural anaesthesia, occipital position at delivery. Maternal characteristics will be retrieved from the hospital records (patient files) by the personnel involved in data centralization: age, height, weight, ethnicity, parity, gestational age.

The US labor assessments should not be biased by confounders that influence the quality of the clinical evaluations in labor (obesity, anterior placenta, caput, moulding), because the visualization of the fetal skull and pubic symphysis is easily achievable even in such conditions. To ensure protocol fidelity, all sonographers will have completed a one-day workshop and will participate in group supervision sessions programmed weekly in the first month of the study. This approach proved to be successful during the previous pilot study conducted in our center.

The information provided to the clinician regarding the US determination of the FHPo in case of clinical – sonographic discordance before instrumental or operative delivery, could represent a theoretically bias of the study. However, many tertiary centres already use the US determination of the FHPo in such situations, and this aspect does not interfere with the objectives of our study.

Outcome measures

Primary outcome

The primary objective of this study is the elaboration of nomograms for the longitudinal US assessment of labor in unselected nulliparous and multiparous with fetal cephalic presentation. The nomograms represent the evolution of the progression markers (PA, DA, PD, HPD) in relation with time and cervical dilatation.

Secondary outcomes

- to compare the US pattern of labor evolution in nulliparous and multiparous women.
- to study the influence of occiput position, body mass index, parturient age on the mechanism of delivery evaluated by US.
- to compare the labor clinical trend from our study data with the Friedman studies[35,36] and other recent research on the partogram[39].
- to compare and correlate the US findings (sonopartogram data) with the classical clinical partogram parameters:
    - correlation of the FHPo determined by US with FHPo clinically estimated (by digital vaginal evaluation);
    - correlations between the US FHPr parameters and between US and clinical (head station) FHPr parameters;
    - the concordance between the fetal head station evaluations derived from US measurements and clinical digital estimations.
- to investigate the correlations between the data of the participating centres.
- to analyse the evolution of the sonographic measurements in spontaneous vaginal delivery versus obstructed labor cases, in primiparae versus multiparae, and in occiput anterior deliveries versus those with persistent occiput posterior.
- to evaluate the capability of the US technique to predict the labor outcome (vaginal or Cesarean birth) in both nulliparous and multiparous

Data collection and management, Quality control

To ensure protocol fidelity, the sonographers will have completed a one-day workshop and will participate in group supervision sessions, programmed weekly in the first month of the study. This approach proved to be successful during the previous pilot study conducted in our center. The following procedures are to be followed:

- At the initial workshop will be established the standardised procedures regarding data collection, encoding of the clinical and ultrasound data and electronic storage;
- The principal investigators will organize training sessions to provide instructions on the protocol and study procedures for the sonographers at the beginning of the study;
- Periodic meetings will take place with study site personnel to discuss issues related to the conduct of the study;
- The principal investigators in the three centres will be available for consultation by telephone at request;
- Interim analyses monthly - the data manager will evaluate the data with the statistics personnel and will conduct a quality review of the database. The results of the interim analyses will be discussed between the principal investigators, who decide whether to continue, stop, or modify the trial.
- All the collected data will be anonymized. The data will be collected by the research team, processed and stored in the www.zenodo.org research depository.

Statistical methods

Sample size estimation

Although several studies have investigated the clinical course of labor, until present we do not have data regarding the nomograms for US evolution of labor. The number of patients enrolled in the clinical partogram studies varies

widely. However, the Friedman's study that still serves as the basis of how most physicians define normal labor, enrolled 500 primiparous at term[37,38]. On the other hand, we have a recent large, but retrospective study that analyzed the clinical labor records of more than 62,000 women from 19 hospitals across the U.S. and concluded that these criteria created 50 years ago may no longer be applicable to contemporary obstetric populations and for current obstetric management[39].

Regarding imaging studies, the prospective research on the trend of the labor progress using intrapartum transperineal US, gathered less than 100 cases each[34,36,44].

The primary outcome of our study will be centile charts for each US progression marker in relation to time.

An important challenge of our study is to achieve a sufficient number of OP cases in both nulliparous and multiparous women. According to the Central Limit Theorem and the Large Enough Sample Condition, a sample size of at least 30 items is sufficient for describing a 'normal' behaviour of the sample, even if it is not governed by the Gaussian distribution. By looking at the *t*-table we can see that when using around 30 degrees of freedom, the value of *t* become approximately equal to the value of the *z* statistics[45] . Taking into account previously published studies, the overall rate of occiput posterior deliveries in nulliparous is around 7.2%, whereas for the multiparous deliveries is around 4%. Only in 65% of these cases, the outcome is vaginal birth. This implies that the corresponding sample size is 642 primiparous women, and 1154 multiparous women with both OP and AP who give their consent to participate in the study. Using this sample size, we achieve a suitable statistical power two-type of null hypothesis with default statistical power goals $P \geq 95\%$ and type I error $\alpha = 0.05$ level of significance.

In our pilot study, a cervical dilatation of more than 4 cm was noted in 16.34% of the primiparous and 37.5% of the multiparous that were admitted in the hospital with labor criteria. In such cases, data from the beginning of labor will not be available for calculation. In order to achieve the sample mentioned above with patients registered from the beginning of labor, we adjusted the study size to include 767 primiparous women and 1846 multiparous women.

Statistical analysis

The statistical analyses will be performed by IBM SPSS Statistics for Windows, Version 22.0. (Armonk, NY: IBM Corp.).

Descriptive statistics will be produced for all study variables (mother's age, height, weight, parity, gestational age, mode and time of delivery, whether labor was spontaneous or induced, use of oxytocin or epidural anaesthesia, occiput position, progression angle, progression distance, head direction angle, head to perineum distance). Continuous variables will be presented as the mean and standard deviation (SD) or median, if appropriate. Categorical data will be presented as frequency and percentage.

Data will be first tested for normality and equal variance.

Clinical obtained data from our study will be compared with similar data from other partograms. The results between groups (maternal, labor and neonatal characteristics of women assessed by classical clinical partograms or a more recent partogram and our sonopartogram) will be compared using Chi-square test or Fisher exact test (for categorical variables), and Student t-test or Mann Whitney test where applicable (for continuous variables) with a statistical significance level set at $p < 0.05$.

We will analyze the agreement between sonopatogram and clinical partogram in estimating fetal head position and fetal head station. For the fetal head position, we will assess the level of agreement between US and digital VE using Cohen's kappa statistics. Correlation coefficient (Pearson's correlation or the Spearman rank correlation or Kendall's rank correlation if appropriate) and linear regression will be employed for analyzing the strength of association between the fetal head station estimated by digital vaginal examination and the ultrasound parameters (HPD, PA, PD and HDA).

Pearson's correlation and regressions will be used for the evaluation of correlation between ultrasound parameters (PA, PD, HAD and HPD) and between US and time to delivery and digital vaginal examination (head station) for various clinical situations (nulliparous and multiparous, fetuses with OA and those with persistent OP position).

Reference ranges (90% range between 5th and 95th centiles) and the 95% confidence interval will be constructed for each ultrasound parameter and evolution in time will be display in graphic form separately for nulliparous and for multiparous. Predictive ability of each ultrasound parameters for vaginal delivery will be assessed by calculating sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratio and by plotting receiver-operating characteristics (ROC) curve.

In order to identify factors that predict vaginal birth, for each subgroup population (nulliparous and multiparous) all analyses will use appropriate (that is, logistic or linear) regression models, with results presented as point estimates (odds ratios or difference in means), 95% confidence intervals and p values. Further secondary analyses will involve planned subgroup analyses and will use multivariable regression models. In all models, predictors (like maternal age, gestational age, clinically assessed cervical dilatation, maternal BMI) will be selected for inclusion in regression. We plan to include in our model covariates such as HPD, PA, PD, HDA and OP position. Based on the probabilities predicted by the logistic models, receiver operating characteristic (ROC) curves will be constructed and we will calculate and report the area under the curve, sensitivity and specificity rates with 95% confidence interval in predicting vaginal mode of delivery.

The time from the ultrasound examination at the beginning of active phase of labor to vaginal delivery will be evaluated with Kaplan–Meier and Cox regression analysis. Data for women with Cesarean section will be censored. In the Cox regression analyses, fetal head position and fetal head station parameters will be tested as possible predictive factors. In additional analyses, we will adjust for maternal age, BMI, gestational age and parity as possible confounders.

Reporting of adverse events

Prenatal ultrasonography appears to be a safe investigation method, as until today there has been no study reported suggesting otherwise (Statement approved by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) Board in September 2011 and by the World Federation of Ultrasound in Medicine and Biology (WFUMB) Council in August 2011)[46]. US is routinely used in everyday clinical practice for assessment of neonates, including cranial and cerebral examination. However, US involves energy exposure and that requires further investigation.

Regarding the perception of laboring women about US, there have been no reports in the literature of US causing discomfort.

All adverse events reported spontaneously by patients or observed by the obstetricians will be recorded. When an adverse event occurs, the treating physician will take all necessary and appropriate measures to ensure the safety of the patient.

Ethical considerations and dissemination

Ethics approval of the study protocol was obtained from the Ethics Committees of the universities in the three centres. The trial is registered in the ClinicalTrials.gov Registry: NCT02326077, approved by the University of Medicine and Pharmacy Of Craiova Committee of Ethics and Academic and Scientific Deontology No: 18/26.02.2016.

Informed consent

The US operator on duty will be responsible for explaining the procedure to the participants and for obtaining an informed written consent from all women accepting to take part in the study.

Regarding the unforeseen complications or health damage that may occur during or after labor, the management of labor and delivery is made exclusively based on the traditional clinical evaluation, by senior physicians. The US study protocol is only observational, without any obstruction for the clinical manoeuvres. On the other hand, it is made clear to all participants that US is considered safe in the third trimester and after birth, both for the mother and the baby.

Compensation and insurance for harmed patients

There will be no special financial compensation; however, any negligence on the part of the physician may be covered by the doctors' liability insurance.

Declaration of interests

The investigators do not have any financial and other competing interests nor any relationships with companies that may have a financial interest in the information obtained during the study. All investigators comply with the policy on conflicts of interest in research and relevant conflict of interest guidelines.

Dissemination

The results of the study will be disseminated at national and international research conferences and as published articles in peer-reviewed journals. The study will be implemented and reported in line with the STROBE statement.

Discussion

It has been widely shown before that despite the significant progress in the last decades in maternal-fetal medicine, labor management remained unchanged, based on traditional clinical "blind" evaluations (Leopold manoeuvers, digital clinical evaluation) which have been proved by many studies to be subjective and inexact. In our view, clinical skills should not be abandoned and ultrasonography should only complement clinical examination and not replace it. However, nowadays more than ever, an objective method of assessing labor is needed, given the rates of fetal and maternal trauma at birth and because of the increasing amount of medico-legal liability issues related to labor and delivery. The SonoLabor study aims to provide new objective evidence regarding the evaluation of the mechanism of labor with US.

The SonoLabor study differs from previous studies as it aims to assess all stages of labor, rather than just the second stage of labor to elaborate nomograms for the longitudinal US assessment of labor in unselected low-risk population, an important issue of the future sonopartograms. We identified only one pilot study in the literature that aimed to assess the application of sonopartogram[34]. A unique point of our protocol is the comparative evaluation of the US parameters for various clinical situations. This may facilitate the use of different nomograms in labor, adapted to the clinical characteristics of the laboring woman. Another strength of our study is the multicentre design that is useful to achieve a proper study size and an opportunity to compare the data recorded in different settings.

Although published six decades ago, Friedman's curve remains the only method for routine labor management today. Clinical studies showed that the pattern of labor progression and the present characteristics of the partogram differ significantly from the traditional Friedman curve[39]. Therefore, our study aims to develop curves for labor monitoring which will be not only objective, but also but also adapted to contemporary practice.

The challenge and limitation of this study is the achievement of a sufficient study size for the secondary objectives of the research. In order to produce specific sonopartograms regarding the maternal characteristics and occiput position, an important number of patients would be required, that may not achievable during our present research. However, preliminary data will be published on this matter. We also hope that the dissemination of our study protocol will serve to future larger studies that will help to collect or complete the necessary data.

We are also aware that the participating sites in this study have certain experience in the intrapartum US assessment. Thus, the results might not be generalizable to other settings. Nevertheless, previous research demonstrated that intrapartum US is reproducible[47] and the learning curve is much easier for US than clinical examination, even for younger and less experienced colleagues[48]. The results of the current study will hopefully improve the evidence-based understanding of the mechanism of labor and establish an objective solution for the labor monitoring, complementary to the traditional clinical examination.

Ethics approval and consent to participate

Ethics approval of the study protocol was obtained from the Ethics institutional committees in the centres involved. The trial is registered in the ClinicalTrials.gov Registry: NCT02326077, with the approval from University of Medicine and Pharmacy Of Craiova Committee of Ethics and Academic and Scientific Deontology No: 18/26.02.2016.

Informed consent

The US operator on duty is responsible for explaining the procedure to the participants and for obtaining an informed written consent from all women accepting to take part in the study.

Regarding the unforeseen complications or health damage that may occur during or after labor, the management of labor and delivery is made exclusively based on the traditional clinical evaluation, by senior physicians. The US study protocol is only observational, without any obstruction for the clinical manoeuvres. The only potential sonographic intervention in the clinical assessment of labor is due to the ethical issues regarding the neonatal outcome when instrumental delivery is attempted. Thus, the attending obstetrician will be informed in case of clinical and US discordance.

On the other hand, it is made clear to all participants that US is considered safe in the third trimester and after birth, both for the mother and the baby.

Availability of data and material (Dissemination)

The results of the study will be disseminated at national and international research conferences and as published articles in peer-reviewed journals. The study will be implemented and reported in line with the STROBE statement.

Competing interests

The authors and their relations have no financial connections with companies that may have an interest in the submitted work, and no non-financial interests that may be relevant to the article.

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The potential funding sources will play no role in data collection, analysis and interpretation, in the writing of the reports, or the decision to submit the paper for publication. A funded PhD project provided the resources for a

previous pilot study. Currently, the study has no outside funding. The project will take place as part of PhD and postdoctoral studies, and we will use the opportunities to apply for future research funding.

Authors' contributions

IDG AP and TS conceived and designed the study and will supervise the study implementation. IDG drafted the protocol of the study. DL, DG, CML DR, PC, ZL, NM and TD revised and refined the study protocol for an optimal implementation and provided final approval of the version to be published. CML, BS and SR provided methodological and statistical expertise and will conduct the statistical analysis. IDG and DR drafted a PhD salary grant proposal for a previous approved pilot study. DG, DR, PC, ZL, NR, RD and FM will be responsible for study management, staff training and supervision and data centralization. IDG, AP and TD are the directors of the sites and they will provide clinical expertise and on-site management of the study. All authors critically reviewed and approved the final version of the manuscript.

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Current study status

The SonoLabor study recruited patients during January - December 2016 for a pilot study of 168 deliveries. Data analysis was completed in January 2017 and the results were communicated at the 27th World Congress on Ultrasound in Obstetrics and Gynecology[33]. Then the project was discontinued, due to the lack of resources.

Given the birth flow in the centres involved, the sample size required, the acceptability previously recorded and the disponible sonographers for intrapartum US evaluations, we should expect that the study should be completed during a two-years period of time.

Competing interests

The authors and their relations have no financial connections with companies that may have an interest in the submitted work, and no non-financial interests that may be relevant to the article.

Details of ethics approval

Ethics Research Committees of University of Medicine and Pharmacy and University of Athens approved the study protocol. Women will provide written consent.

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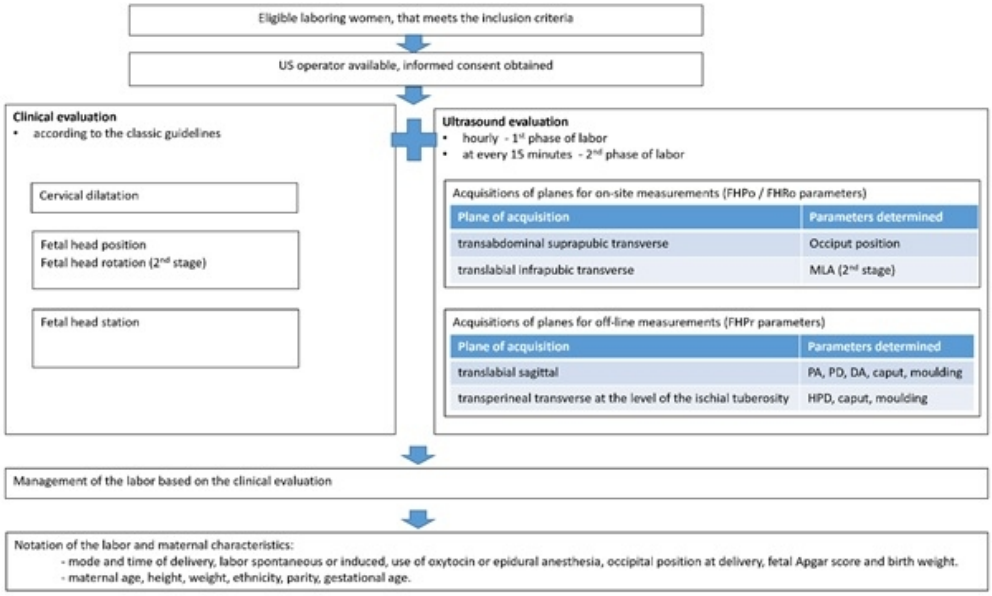
Figure 1. Implementation of the SONOLABOR study.

Figure 2. Ultrasound determination of the occiput position in the first stage of labor.
A: Example of the probe orientation in the transabdominal suprapubic transverse plane. B: FHPo determination in the plane described in image A, based on the identification of cranium or cerebral structures: occiput (Oc), thalamus (T), interhemispheric septum (S), orbits (O).
OA, occiput anterior; OP, occiput posterior, LOT, left occiput transverse; ROT, right occiput transverse; LOA left occiput anterior; ROA right occiput anterior; LOP, left occiput posterior; ROP, right occiput posterior.

Figure 3. Ultrasound determination of the occiput position in the second stage of labor.
A: Example of the probe orientation in the transperineal infrapubic transverse plane. B: Schematization of the structures visualized and the measurement of the midline angle between the midline (falx cerebri) and the anteroposterior axis of the maternal pelvis. C-H: Presentation of an example with midline angle measurement and evolution during anterior rotation of a transverse occiput. Occiput position is identified based on the visualization of the cerebral midline (interhemispheric septum, S) and choroid plexus (Px) direction (divergent posteriorly), or thalami aspect (triangular, with the base anteriorly). Midline angle gradually decreases during the anterior occiput rotation from the transverse position (C,D), as it reaches right anterior (E,F) and anterior (infrapubic) (G,H) positions.

Figure 4. Ultrasound determination of the fetal head descent/progression (FHPr). Placement of the transducer in the infrapubic translabial sagittal plane (A) and infrapubic transverse plane (B). C: measurement of the progression angle between the long axis of the pubic symphysis and a line extending from its most inferior portion tangentially to the fetal skull. D: measurement of the direction angle as the angle between the major longitudinal axis of the fetal head (perpendicular to the biparietal diameter) and the infrapubic line. E: measurement of the progression distance as the minimal distance between the infrapubic line and the leading part of the fetal skull (star). F: measurement of the head to perineum distance as the shortest distance from the skin surface of the perineum to the outer bony limit of the fetal skull.

Figure 5. A,B: Presentation of caput (star) in transperineal transverse (A) and sagittal evaluation (B). C: Molding of the cranium bones indicated with the arrow.



Implementation of the SONOLABOR study.

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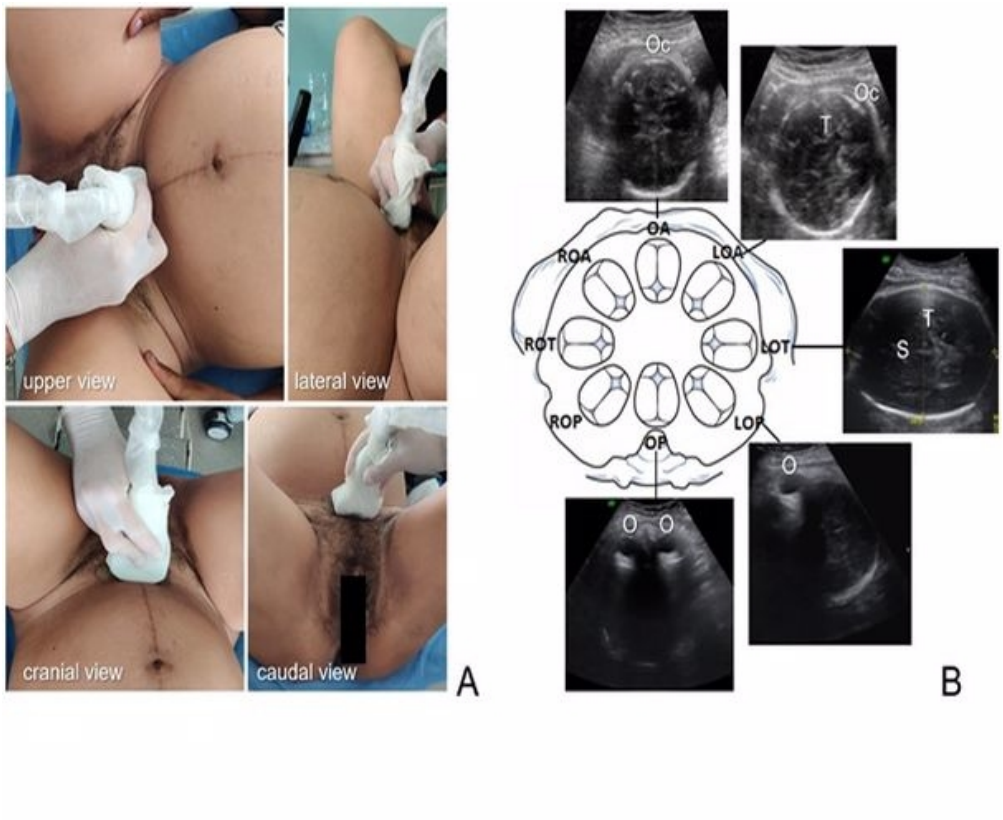

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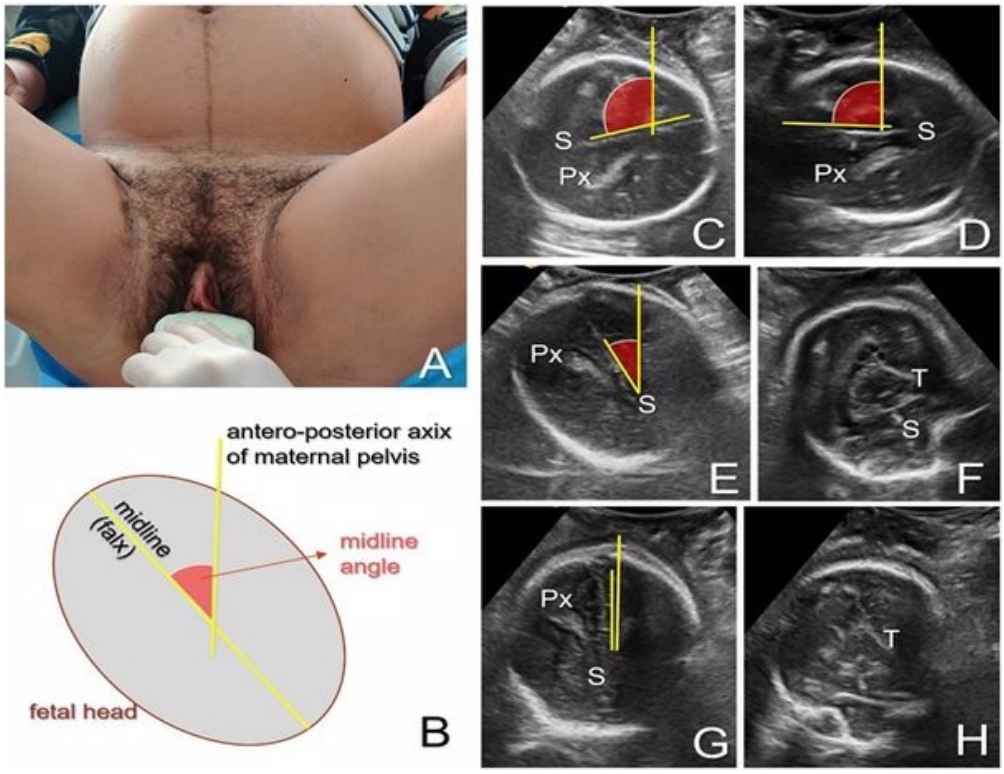

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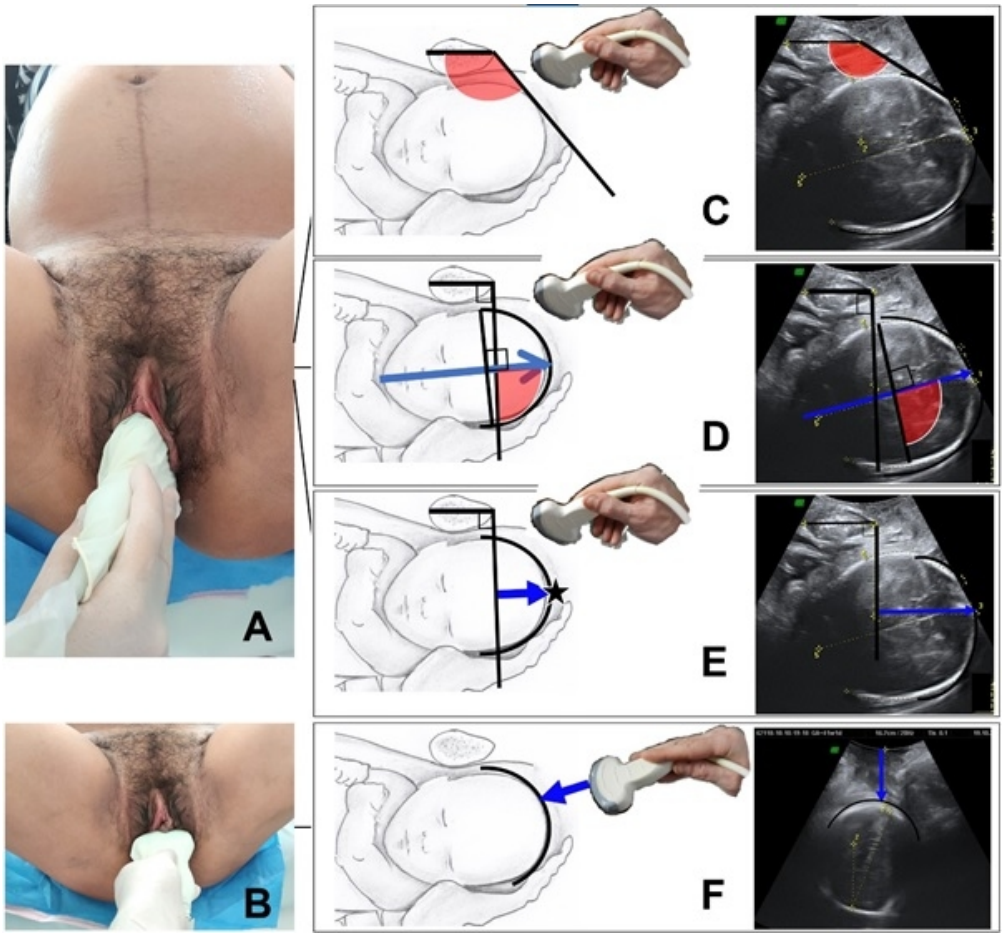

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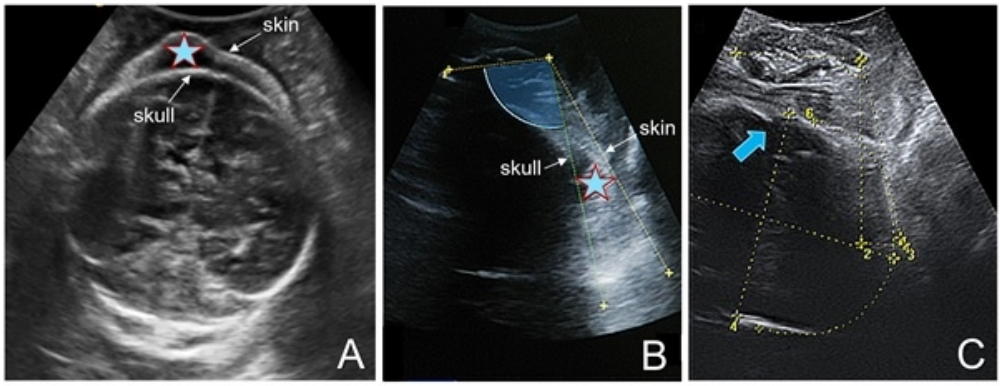

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Sonographic Evaluation of the Mechanism of Active Labor (SonoLabor study): observational study protocol regarding the implementation of the sonopartogram

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Sonographic Evaluation of the Mechanism of Active Labor (SonoLabor study): observational study protocol regarding the implementation of the sonopartogram

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Abstract

Introduction

Over the last decades, a large body of literature have shown that intrapartum clinical digital pelvic estimations of fetal head position, station and progression in the pelvic canal are less accurate, compared to US scan. Given the increasing evidence regarding the advantages of using ultrasound (US) to evaluate the mechanism of labor, our study protocol aims to develop sonopartograms for fetal cephalic presentations. They will allow for a more objective evaluation of labor progression than the traditional labor monitoring, which could enable more rapid decisions regarding the mode of delivery.

Methods / Analysis: This is a prospective observational study performed in three university hospitals, with an unselected population of women admitted in labor at term. Both clinical and US evaluations will be performed assessing fetal head position, descent and rotation. Specific US parameters regarding fetal head position, progression and rotation will be recorded to develop nomograms in a similar way that partograms were developed. The primary outcome is to develop nomograms for the longitudinal US assessment of labor in unselected nulliparous and multiparous women with fetal cephalic presentation. The secondary aims are to assess the sonopartogram differences in occiput anterior and posterior deliveries, to compare the labor trend from our research with the classic and other recent partogram models and to investigate the capability of the US labor monitoring to predict the outcome of spontaneous vaginal delivery.

Ethics and dissemination: All protocols and the informed consent form comply with the Ministry of Health and the professional society ethics guidelines. University Ethics Committee approved the study protocol. The trial results will be published in peer-reviewed journals and at the conferences presentations. The study will be implemented and reported in line with the STROBE statement.

Trial registration number: ClinicalTrials.gov Registry: NCT02326077.

Keywords: intrapartum ultrasound, labor monitoring, prenatal diagnosis, fetal medicine, maternal medicine, ultrasonography.

Strengths and limitations of this study

Strengths

- The multicentre design on representative population and the blinded clinical / ultrasound assessment aims to intercept the potential sources of bias.
- The SonoLabor study differs from previous studies as it aims to assess all stages of labor, rather than just the second stage of labor to elaborate nomograms for the longitudinal US assessment of labor in unselected low-risk population, an important issue of the future sonopartograms.
- Sonographic and clinical evaluation of the labor progression in any cephalic presentation (not only with occiput anterior position).
- Our study aims to develop curves for labor monitoring which will be not only objective, but also but also adapted to contemporary practice. Clinical studies showed that the pattern of labor progression and the present characteristics of the partogram differ significantly from the traditional Friedman curve

Limitations

The high number of laboring women needed to investigate the characteristics of each clinical situation targeted in the study design. In order to produce specific sonopartograms regarding the maternal characteristics and occiput position, an important number of patients would be required, that may not achievable during our present research. We hope that the publication of our study protocol, dissemination of the results and the storage of the anonymized collected data in a research depository will serve to future larger studies that will help to collect or complete the necessary data.

- The concept of normality is population-based and depends on various management attitudes (for example epidural analgesia, active management of labor), different characteristics of the partogram are observed that may affect generalizability.

Introduction

Over the last decades, a large body of literature has shown that clinical digital pelvic estimations of fetal head position, station and progression in the pelvic canal are not accurate during the first[1] and second stage of labor[1-6], poorly reproducible when compared to US[7-9], poorly reliable[10-12], experience-dependent[1,4] and often inexact in challenging labor circumstances, such as: prolonged first stage of labor[13], cases with arrested cervical dilation[14], obstructed labor[15], fetal head engagement[10,16], posterior and transverse occiput locations[6,14], or caput [4]. This may imply significant consequences on the decision of the appropriate delivery mode, because digital examination is less reliable especially when obstetrical interventions are more likely to be needed[15,17-21]. Intrapartum sonographic evaluation may not provide a solution for all these conditions mentioned above, but previous studies have demonstrated the potential to decrease the rate of late Cesarean extractions in prolonged labor cases, and the various approaches proposed in the literature were considered by our study design. Many studies provided sonographic data regarding the fetal head descent / progression (FHPr) in the second stage of labor and proposed several easily measurable and reliable parameters, capable to predict the vaginal or operative outcome of the delivery with occiput anterior positions[22-28]. The literature regarding US evaluation in the first stage of labor is lesser, but based on available data US evaluation appears to be useful for the prognosis of labor[29,30,31].

Given the increasing evidence regarding the advantages offered by using US in labor, our group concluded that the development of a *sonopartogram*, as an adjuvant to or a replacement of traditional labor monitoring, provides the setting for a more objective evaluation of labor progression, which could enable more rapid decisions regarding the mode of delivery[32,33]. Intrapartum US evaluation is not meant to change the standard principles for labor mechanism evaluation, but to provide accurate evaluation of the main parameters involved: fetal head position and rotation, fetal head progression and engagement.

The SonoLabor study aims to provide new objective evidence regarding the evaluation of the mechanism of labor with US. There is few information in the literature regarding the ultrasonographic monitoring of the entire active labor[34-36]. A recent proof-of-concept study showed that the sonopartogram is feasible in most cases[34]. However, a study of the paired clinical and sonographic assessments of labor in a large, unselected population has not yet been conducted. Furthermore, there are no nomograms for the ultrasound monitoring of labor. Nowadays, the use of ultrasound in labor is generally limited to research settings and a relatively small number of women has been studied. Therefore, efforts should be made to describe the value of an objective partogram in general practice.

This study is designed to produce an original multicentre longitudinal assessment of the mechanism of active labor, including both stages, in a representative population, using concomitant blinded clinical and sonographic evaluations in unselected low-risk parturient women at term. A unique point of our protocol is the comparative evaluation of the US parameters for various clinical situations. This may facilitate the use of different nomograms in labor, adapted to the clinical characteristics of the laboring woman. Another strength of our study is the

multicentre design that is useful to achieve a proper study size and an opportunity to compare the data recorded in different settings.

The aim of this paper is to describe the protocol of the study.

Objectives

The primary objective of this study is the development of nomograms for ultrasound measured variables during labor in unselected nulliparous and multiparous women at term with fetal cephalic presentation.

The secondary objectives of the study are:

- to compare the US pattern of labor evolution in nulliparous and multiparous women.
- to study the influence of occiput position, body mass index, parturient age on the labor progression evaluated by US.
- to correlate the labor trend from our study with the Friedman studies[37,38] and other recent research on the partogram[39] regarding the progression of labor by means of objective US evaluation.
- to correlate the US and standard clinical findings regarding the mechanism of labor, e.g., fetal occiput position and head descent during active labor.
- to investigate the correlations between the data of the participating centres.
- to analyse the temporal variation of the sonographic measurements in spontaneous vaginal delivery versus obstructed labor in nulliparae versus multiparae.
- to analyse the evolution of the sonographic measurements in spontaneous vaginal delivery versus obstructed labor in fetuses with occiput anterior versus those with persistent occiput posterior.
- to investigate the value of combined US measurements to predict the outcome of vaginal delivery.

Methods and analysis

Study design and setting

This is an observational cohort prospective study, which will take place in three tertiary maternity hospitals (University Emergency County Hospital Craiova, Alexandra University Hospital of Athens and Ippokrateion Hospital Thessaloniki), with more than 4000 deliveries per annum. The study aims to record simultaneously the labor progress by clinical and US evaluations in women in labor at term, with singleton cephalic presentation. We will include low-risk pregnancies, according the criteria defined in the Participants section.

Patient and Public Involvement

We conducted a previous study[40] during the development of this research question, where we evaluated the acceptability of the method and found that the vast majority of laboring women (98%) agree with the supplementary US investigation protocol and the demographic characteristics did not influence the rate of acceptance. Most of the women (93% of accepters and 75% of decliners) had little difficulty deciding whether or not to have the scan protocol. All women who were scanned during labor found it an acceptable experience, and only 21% of women without epidural anesthesia rated the perceived difficulty as "mild" or "discomforting". Women rated having the intrapartum scan as being significantly less difficult than having a cervical smear, transvaginal scan or having a digital clinical evaluation. Two-thirds (67%) of the patients expressed increased confidence while being able to follow along the medical personnel the fetal head progression on the ultrasound screen. Almost all of the consenting

women (97%) who had the intrapartum US scans and all the 4 decliners said they would definitely or probably agree such ultrasound monitoring in a future labor, if this technique is proven useful for the labor outcome.

Participants

All pregnant women admitted in active labor at term are considered eligible for the study. They will be consecutively included in the study, depending on the availability of the US operators involved in the study. We will try to attract a large team of collaborators, in order to investigate as many eligible cases as possible. Cases planned for elective caesarean section, or involving imminent intention to deliver, with non-cephalic presentation, intra-uterine death, multiple pregnancies or resulting neonates weighting less than 2500g or more than 4000g will be excluded from the study. Also, we will exclude women with previous cervical surgery (e.g. cone biopsy, cervical cerclage), those younger than 18 years, or those considered in the opinion of the researcher as having language or learning impairment.

Following the clinical evaluation, women will be admitted in the first stage of labor when there are regular painful contractions and there is a progressive cervical dilatation from 4 cm, and the second stage will be established based on the finding of full dilatation of the cervix[41] regardless of whether the parturients underwent artificial rupture of the membranes, Oxytocin augmentation or epidural anaesthesia.

Gestational age will be determined by the last menstrual period in women with regular menses, confirmed with US dating, preferably during the first trimester. If the first trimester biometry is not consistent with the menstrual dating by more than one week, gestational age will be established based only on the sonographic evaluation. In women with irregular menses, the gestational age will be determined solely based on the first fetal biometry evaluation in in the first half of pregnancy.

Procedures

Recruitment

During their usual consultation in the labor ward, in an eligible case, the physician on duty provides brief information about the research and invites the patient to take part in the study. If the patient shows interest in the study and meets the inclusion criteria, a face-to-face appointment with the ultrasound operator is arranged. The details of the study and the potential benefits of the research will be thoroughly explained to the patient. The only direct benefit of the laboring women that participate in the study would be the communication between the obstetrician and sonographer regarding fetal head position when instrumental delivery is attempted, as presented in the Interventions section. If the patient agrees to participate in the study, written informed consent will be obtained.

Interventions

All pregnant women that meet the inclusion criteria will be assessed clinically by the physician on duty. The managing clinician is a senior consultant not involved in the study.

Clinical examinations will take place in women in active labor just before the US assessments (Figure 1). The clinician will note the observations on a specially designed partogram-like sheet that will be used for women in labor who agree to participate in the study. The following labor parameters must be noted before US assessment:

- ***cervical dilation*** in centimetres,
- ***fetal head position (FHPo)*** – the evaluation of occiput position in both labor stages. Occiput position will be classified as occiput anterior (OA), occiput posterior (OP), left or right occiput transverse (LOT or ROT), left or right occiput anterior (LOA or ROA), or left or right occiput posterior (LOP or ROP)[5,42],

- ***fetal head progression (FHPr)*** – determined by the evaluation of head station in relation to the ischial spines,
- Presence of ***caput***, with the approximate diameter,
- Presence of ***molding*** and grading: closure of sutures with no overlap (grade 1), reducible bones overlap (grade 2) and irreducible overlap (grade 3).

Clinical examination will be followed by transabdominal and transperineal **ultrasound evaluations** conducted by obstetricians with appropriate training in US in labor, with minimum 1 year of experience in the field. Mobile and compact US machines will be used: Logic e (GE Healthcare, China), GE Voluson P6, Samsung R7, BenQ T3300 and ALOKA f31 equipped with 2–5 and 2-6 MHz 2D convex transducers.

The objectives of US evaluations are similar to those of standard clinical assessment. The purpose of US evaluations is to document the progression of labor using objective measurements for the main parameters involved in the mechanism of labor:

- ***fetal head position (FHPo)***, by determining occiput position,
- ***fetal head rotation*** in the second stage of labor, by measuring the midline angle (MLA),
- **fetal head descent or progression (*FHPr*)**, by evaluating the relation between the fetal head and maternal landmarks, using specific measurements: progression angle (PA), progression distance (PD), head direction angle (HDA), head to perineum distance (HPD),
- ***caput*** measurement, if present,
- ***molding*** notation, if present.

In Table 1 we present the sonographic measurements, in relation to the acquisition planes and the features of labor mechanism that are involved. The images will be stored on the hard disk drive of the system for off-line analysis and the measurements will be performed by the sonographer who evaluated the case, according to the techniques described in the literature[5,22-27,42,43] (Table 1).

Table 1. Acquisition of US planes, and ultrasound measurements performed offline, according previous literature

Labor mechanism feature	**Acquisition plane**	**Ultrasound measurements**
Fetal head position (FHPo) in the first stage of labor	Transabdominal suprapubic transverse plane	• Occiput position (Figure 2) Both clinical and US findings of the FHPo are recorded on a data sheet depicting a circle, like a clock, divided into 24 sections, each of 15º, and the position of the occiput is assigned as anterior (OA), posterior (OP), left anterior (LOA), right anterior (ROA), left posterior (LOP), right posterior (ROP), right transverse (ROT), left transverse (LOT)[5,42] The position of the occiput is determined based on the identification of the midline, thalami, choroid plexus, cerebellum, orbits or occiput.
Fetal head position (FHPo) in the second stage of labor, evaluation of head rotation	Transperineal infrapubic transverse plane (Figure 3), with visualization of the cerebral midline	• Occiput position • Midline angle (MLA) (Figure 3)

		The position of the occiput (OA, OP, LOA, ROA, LOP, ROP) is determined in a similar fashion transperineally in the 2nd stage of labor. Midline angle (MLA) is calculated[25] based on the visualization of the cerebral midline in relation to the antero-posterior axis of the maternal pelvis - rotation angle or midline angle (MLA).
Fetal head descent / progression (FHPr)	Transperineal translabial sagittal plane	• Progression angle (PA)[26,27] (Figure 4), as the angle between the longitudinal axis of the pubic symphysis and the line running from the anterior edge of the pubic symphysis tangentially to the leading edge of the fetal skull. • Progression distance (PD)[22] (Figure 4), as the minimal distance between a vertical line from inferior apex of the symphysis (infrapubic line) and the leading edge of the fetal skull. • Head direction angle (HDA)[23,24] (Figure 4), as the direction of the line perpendicular to the widest diameter of the fetal head, with respect to the infrapubic line.
	Transperineal translabial transverse plane, at the level of the ischial tuberosity, applying firm pressure without creating discomfort, and the transducer moved and angled until the shortest distance to the fetal skull is visualized	• Head to perineum distance (HPD)[43], as the shortest distance from the outer bony limit of the fetal skull to the skin surface of the perineum (Figure 4).
Caput and molding	Transperineal sagittal and transverse plane	• Caput (Figure 5) is measured as the maximum distance between the leading part of the skull and the fetal skin in the sagittal or transverse planes. • Molding (Figure 5) is diagnosed when the skull bones were seen overlapping in the sagittal or transverse planes.

Because of ethical issues, the design of the study states that the attending obstetrician should be informed in case of clinical and US discordance when instrumental or operative delivery is attempted. The digital evaluation is considered to be correct if the FHPo is within±45◦ of the US determination.

Cervical dilation will be evaluated only clinically, as the evaluation of this parameter is best achieved with digital assessment[31].

Timing: clinical and US scans are performed hourly until complete dilation (1st phase of active labor) and at every 15 minutes after complete dilation (2nd phase). The purpose of the apparently high number of examinations was

to obtain accurate information in each labor in terms of correlation of FHPr, FHPo and cervical dilatation. In a previous study in our clinic this methodology proved acceptable for the parturients[40]. The frequent evaluations in the second stage are meant to offer a better analysis of this critical stage of labor. Notation of time delivery will be used to calculate the time interval from each scan to delivery.

Ultrasound images will be saved and stored on ultrasound hard disk during labor, then transferred by the sonographer to a designated PC storage unit after birth. The images will be reviewed during the following week, by the same sonographer, who will also and input the offline measurements results into the database.

The sonographer and the clinician are blinded to each other's findings (except FHPo, during the circumstances mentioned above) as the specific measurements are performed afterwards, offline and labor management is conducted by the Labor and Delivery department personnel. During labor, the available sonographer cannot be completely blinded to clinical findings, as he/she will perform the scans at certain time intervals, depending on the labor stage, that is established by the clinician's cervical dilatation assessment. However, the sonographer will only record the images. The clinician will note the observations on a partogram-like sheet that is not available for the sonographer, who in turn, will perform the measurements offline, after birth.

Labor characteristics will be recorded by the clinician on the study datasheet: mode and time of delivery, neonatal Apgar score and birth weight, whether labor was spontaneous or induced, use of oxytocin or epidural anaesthesia, occipital position at delivery. Maternal characteristics will be retrieved from the hospital records (patient files) by the personnel involved in data centralization: age, height, weight, ethnicity, parity, gestational age.

The US labor assessments should not be biased by confounders that influence the quality of the clinical evaluations in labor (obesity, anterior placenta, caput, moulding), because the visualization of the fetal skull and pubic symphysis is easily achievable even in such conditions. To ensure protocol fidelity, all sonographers will have completed a one-day workshop and will participate in group supervision sessions programmed weekly in the first month of the study. This approach proved to be successful during the previous pilot study conducted in our center. The information provided to the clinician regarding the US determination of the FHPo in case of clinical – sonographic discordance before instrumental or operative delivery, could represent a theoretically bias of the study. However, many tertiary centres already use the US determination of the FHPo in such situations, and this aspect does not interfere with the objectives of our study.

Outcome measures

Primary outcome

The primary objective of this study is the elaboration of nomograms for the longitudinal US assessment of labor in unselected nulliparous and multiparous with fetal cephalic presentation. The nomograms represent the evolution of the progression markers (PA, DA, PD, HPD) in relation with time and cervical dilatation.

Secondary outcomes

- to compare the US pattern of labor evolution in nulliparous and multiparous women.
- to study the influence of occiput position, body mass index, parturient age on the mechanism of delivery evaluated by US.
- to compare the labor clinical trend from our study data with the Friedman studies[35,36] and other recent research on the partogram[39].
- to correlate the US findings with classical clinical estimations:
    - correlation of the FHPo determined by US with FHPo clinically estimated (by digital vaginal evaluation);

- correlations between the US FHPr parameters and between US and clinical (head station) FHPr parameters;
- the concordance between the fetal head station evaluations derived from US measurements and clinical digital estimations.

- to investigate the correlations between the data of the participating centres.
- to analyse the evolution of the sonographic measurements in spontaneous vaginal delivery versus obstructed labor cases, in nulliparae versus multiparae, and in occiput anterior deliveries versus those with persistent occiput posterior.
- to evaluate the capability of the US technique to predict the labor outcome (vaginal or Cesarean birth) in both nulliparous and multiparous

Data collection and management, Quality control

To ensure protocol fidelity, the sonographers will have completed a one-day workshop and will participate in group supervision sessions, programmed weekly in the first month of the study. This approach proved to be successful during the previous pilot study conducted in our center. The following procedures are to be followed:

- At the initial workshop will be established the standardised procedures regarding data collection, encoding of the clinical and ultrasound data and electronic storage;
- The principal investigators will organize training sessions to provide instructions on the protocol and study procedures for the sonographers at the beginning of the study;
- Monthly meetings will take place between study site personnel to discuss issues related to the conduct of the study and supplementary convocations will be announced whenever necessary;
- The principal investigators in the three centres will be available for consultation by telephone at request;
- Interim analyses monthly - the data manager will evaluate the data with the statistics personnel and will conduct a quality review of the database. The results of the interim analyses will be discussed between the principal investigators, who decide whether to continue, stop, or modify the trial.
- All the collected data will be anonymized. The data will be collected by the research team, processed and stored in the www.zenodo.org research depository.

Statistical methods

Sample size estimation

Although several studies have investigated the clinical course of labor, until present we do not have data regarding the nomograms for US evolution of labor. The number of patients enrolled in the clinical partogram studies varies widely. However, the Friedman's study that still serves as the basis of how most physicians define normal labor, enrolled 500 nulliparous at term[37,38]. On the other hand, we have a recent large, but retrospective study that analyzed the clinical labor records of more than 62,000 women from 19 hospitals across the U.S. and concluded that these criteria created 50 years ago may no longer be applicable to contemporary obstetric populations and for current obstetric management[39].

Regarding imaging studies, the prospective research on the trend of the labor progress using intrapartum transperineal US, gathered less than 100 cases each[34,36,44].

The primary outcome of our study will be centile charts for each US progression marker in relation to time.

An important challenge of our study is to achieve a sufficient number of OP cases in both nulliparous and multiparous women. According to the Central Limit Theorem and the Large Enough Sample Condition, a sample size of at least 30 items is sufficient for describing a 'normal' behaviour of the sample, even if it is not governed by

the Gaussian distribution. By looking at the *t*-table we can see that when using around 30 degrees of freedom, the value of *t* become approximately equal to the value of the *z* statistics[45]. Taking into account previously published studies, the overall rate of occiput posterior deliveries in nulliparous is around 7.2%, whereas for the multiparous deliveries is around 4%. Only in 65% of these cases, the outcome is vaginal birth. This implies that the corresponding sample size is 642 nulliparous women, and 1154 multiparous women ~~with both OP and OA~~ who give their consent to participate in the study. Using this sample size, we achieve a suitable statistical power two-type of null hypothesis with default statistical power goals $P \geq 95\%$ and type I error $\alpha = 0.05$ level of significance.
In our pilot study, a cervical dilatation of more than 4 cm was noted in 16.34% of the nulliparous and 37.5% of the multiparous that were admitted in the hospital with labor criteria. In such cases, data from the beginning of labor will not be available for calculation. In order to achieve the sample mentioned above with patients registered from the beginning of labor, we adjusted the study size to include 767 nulliparous women and 1846 multiparous women.

Statistical analysis

The statistical analyses will be performed by IBM SPSS Statistics for Windows, Version 22.0. (Armonk, NY: IBM Corp.).

Descriptive statistics will be produced for all study variables (mother's age, height, weight, parity, gestational age, mode and time of delivery, whether labor was spontaneous or induced, use of oxytocin or epidural anaesthesia, occiput position, progression angle, progression distance, head direction angle, head to perineum distance). Continuous variables will be presented as the mean and standard deviation (SD) or median, if appropriate. Categorical data will be presented as frequency and percentage.

Data will be first tested for normality and equal variance.

Clinical obtained data from our study will be compared with similar data from other partograms. The results between groups (maternal, labor and neonatal characteristics of women assessed by classical clinical partograms or a more recent partogram and our sonopartogram) will be compared using Chi-square test or Fisher exact test (for categorical variables), and Student t-test or Mann Whitney test where applicable (for continuous variables) with a statistical significance level set at $p < 0.05$.

We will analyze the agreement between sonopatogram and clinical partogram in estimating fetal head position and fetal head station. For the fetal head position, we will assess the level of agreement between US and digital VE using Cohen's kappa statistics. Correlation coefficient (Pearson's correlation or the Spearman rank correlation or Kendall's rank correlation if appropriate) and linear regression will be employed for analyzing the strength of association between the fetal head station estimated by digital vaginal examination and the ultrasound parameters (HPD, PA, PD and HDA).

Pearson's correlation and regressions will be used for the evaluation of correlation between ultrasound parameters (PA, PD, HAD and HPD) and between US and time to delivery and digital vaginal examination (head station) for various clinical situations (nulliparous and multiparous, fetuses with OA and those with persistent OP position).

Reference ranges (90% range between 5th and 95th centiles) and the 95% confidence interval will be constructed for each ultrasound parameter and evolution in time will be display in graphic form separately for nulliparous and for multiparous. Predictive ability of each ultrasound parameters for vaginal delivery will be assessed by calculating sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratio and by plotting receiver-operating characteristics (ROC) curve.

In order to identify factors that predict vaginal birth, for each subgroup population (nulliparous and multiparous) all analyses will use appropriate (that is, logistic or linear) regression models, with results presented as point estimates (odds ratios or difference in means), 95% confidence intervals and p values. Further secondary analyses will involve planned subgroup analyses and will use multivariable regression models. In all models, predictors (like maternal age, gestational age, clinically assessed cervical dilatation, maternal BMI) will be selected for inclusion in regression. We plan to include in our model covariates such as HPD, PA, PD, HDA and OP position. Based on the probabilities predicted by the logistic models, receiver operating characteristic (ROC) curves will be constructed and we will calculate and report the area under the curve, sensitivity and specificity rates with 95% confidence interval in predicting vaginal mode of delivery.

The time from the ultrasound examination at the beginning of active phase of labor to vaginal delivery will be evaluated with Kaplan–Meier and Cox regression analysis. Data for women with Cesarean section will be censored. In the Cox regression analyses, fetal head position and fetal head station parameters will be tested as possible predictive factors. In additional analyses, we will adjust for maternal age, BMI, gestational age and parity as possible confounders.

Reporting of adverse events

Prenatal ultrasonography appears to be a safe investigation method, as until today there has been no study reported suggesting otherwise (Statement approved by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) Board in September 2011 and by the World Federation of Ultrasound in Medicine and Biology (WFUMB) Council in August 2011)[46]. US is routinely used in everyday clinical practice for assessment of neonates, including cranial and cerebral examination. However, US involves energy exposure and that requires further investigation.

Regarding the perception of laboring women about US, there have been no reports in the literature of US causing discomfort.

All adverse events reported spontaneously by patients or observed by the obstetricians will be recorded. When an adverse event occurs, the treating physician will take all necessary and appropriate measures to ensure the safety of the patient.

Ethical considerations and dissemination

Ethics approval and consent to participate

Ethics approval of the study protocol was obtained from the Ethics Committees of the universities in the three centres. The trial is registered in the ClinicalTrials.gov Registry: NCT02326077, approved by the University of Medicine and Pharmacy of Craiova Committee of Ethics and Academic and Scientific Deontology No: 18/26.02.2016.

Informed consent

The US operator on duty will be responsible for explaining the procedure to the participants and for obtaining an informed written consent from all women accepting to take part in the study.

Regarding the unforeseen complications or health damage that may occur during or after labor, the management of labor and delivery is made exclusively based on the traditional clinical evaluation, by senior physicians. The US study protocol is only observational, without any obstruction for the clinical manoeuvres. The only potential sonographic intervention in the clinical assessment of labor is due to the ethical issues regarding the neonatal

outcome when instrumental delivery is attempted. Thus, the attending obstetrician will be informed in case of clinical and US discordance.

On the other hand, it is made clear to all participants that US is considered safe in the third trimester and after birth, both for the mother and the baby.

Compensation and insurance for harmed patients

There will be no special financial compensation; however, any negligence on the part of the physician may be covered by the doctors' liability insurance.

Declaration of interests

The investigators do not have any financial and other competing interests nor any relationships with companies that may have a financial interest in the information obtained during the study. All investigators comply with the policy on conflicts of interest in research and relevant conflict of interest guidelines.

Availability of data and material (Dissemination)

The results of the study will be disseminated at national and international research conferences and as published articles in peer-reviewed journals. The study will be implemented and reported in line with the STROBE statement.

The anonymized collected data will be stored in the www.zenodo.org research depository.

Authors' contributions

IDG AP and TS conceived and designed the study and will supervise the study implementation. IDG drafted the protocol of the study. DL, DG, CML DR, PC, ZL, NM and TD revised and refined the study protocol for an optimal implementation and provided final approval of the version to be published. CML, BS and SR provided methodological and statistical expertise and will conduct the statistical analysis. IDG and DR drafted a PhD salary grant proposal for a previous approved pilot study. DG, DR, PC, ZL, NR, RD and FM will be responsible for study management, staff training and supervision and data centralization. IDG, AP and TD are the directors of the sites and they will provide clinical expertise and on-site management of the study. All authors critically reviewed and approved the final version of the manuscript.

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The potential funding sources will play no role in data collection, analysis and interpretation, in the writing of the reports, or the decision to submit the paper for publication. A funded PhD project provided the resources for a previous pilot study. Currently, the study has no outside funding. The project will take place as part of PhD and postdoctoral studies, and we will use the opportunities to apply for future research funding.

Competing interests

The authors and their relations have no financial connections with companies that may have an interest in the submitted work, and no non-financial interests that may be relevant to the article.

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Current study status

The SonoLabor study recruited patients during January - December 2016 for a pilot study of 168 deliveries. Data analysis was completed in January 2017 and the results were communicated at the 27th World Congress on Ultrasound in Obstetrics and Gynecology[33]. Then the project was discontinued, due to the lack of resources.

Given the birth flow in the centres involved, the sample size required, the acceptability previously recorded and the disponible sonographers for intrapartum US evaluations, we should expect that the study should be completed during a two-years period of time.

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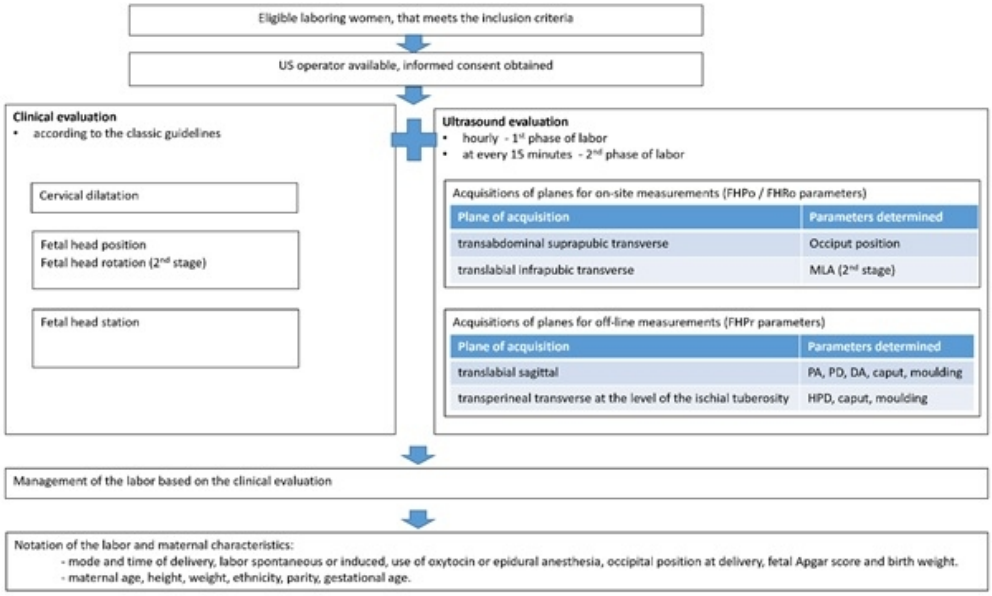
Figure 1. Implementation of the SONOLABOR study.

Figure 2. Ultrasound determination of the occiput position in the first stage of labor.
A: Example of the probe orientation in the transabdominal suprapubic transverse plane. B: FHPo determination in the plane described in image A, based on the identification of cranium or cerebral structures: occiput (Oc), thalamus (T), interhemispheric septum (S), orbits (O).
OA, occiput anterior; OP, occiput posterior, LOT, left occiput transverse; ROT, right occiput transverse; LOA left occiput anterior; ROA right occiput anterior; LOP, left occiput posterior; ROP, right occiput posterior.

Figure 3. Ultrasound determination of the occiput position in the second stage of labor.
A: Example of the probe orientation in the transperineal infrapubic transverse plane. B: Schematization of the structures visualized and the measurement of the midline angle between the midline (falx cerebri) and the anteroposterior axis of the maternal pelvis. C-H: Presentation of an example with midline angle measurement and evolution during anterior rotation of a transverse occiput. Occiput position is identified based on the visualization of the cerebral midline (interhemispheric septum, S) and choroid plexus (Px) direction (divergent posteriorly), or thalami aspect (triangular, with the base anteriorly). Midline angle gradually decreases during the anterior occiput rotation from the transverse position (C,D), as it reaches right anterior (E,F) and anterior (infrapubic) (G,H) positions.

Figure 4. Ultrasound determination of the fetal head descent/progression (FHPr). Placement of the transducer in the infrapubic translabial sagittal plane (A) and infrapubic transverse plane (B). C: measurement of the progression angle between the long axis of the pubic symphysis and a line extending from its most inferior portion tangentially to the fetal skull. D: measurement of the direction angle as the angle between the major longitudinal axis of the fetal head (perpendicular to the biparietal diameter) and the infrapubic line. E: measurement of the progression distance as the minimal distance between the infrapubic line and the leading part of the fetal skull (star). F: measurement of the head to perineum distance as the shortest distance from the skin surface of the perineum to the outer bony limit of the fetal skull.

Figure 5. A,B: Presentation of caput (star) in transperineal transverse (A) and sagittal evaluation (B). C: Molding of the cranium bones indicated with the arrow.



Implementation of the SONOLABOR study.

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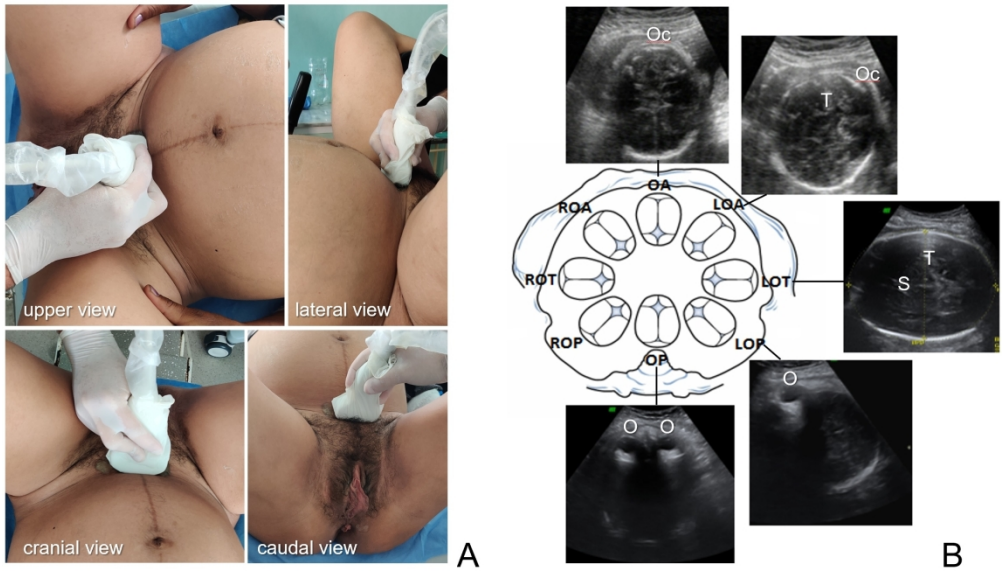

Caption : Figure 2. Ultrasound determination of the occiput position in the first stage of labor.A: Example of the probe orientation in the transabdominal suprapubic transverse plane. B: FHPo determination in the plane described in image A, based on the identification of cranium or cerebral structures: occiput (Oc), thalamus (T), interhemispheric septum (S), orbits (O).OA, occiput anterior; OP, occiput posterior, LOT, left occiput transverse; ROT, right occiput transverse; LOA left occiput anterior; ROA right occiput anterior; LOP, left occiput posterior; ROP, right occiput posterior.

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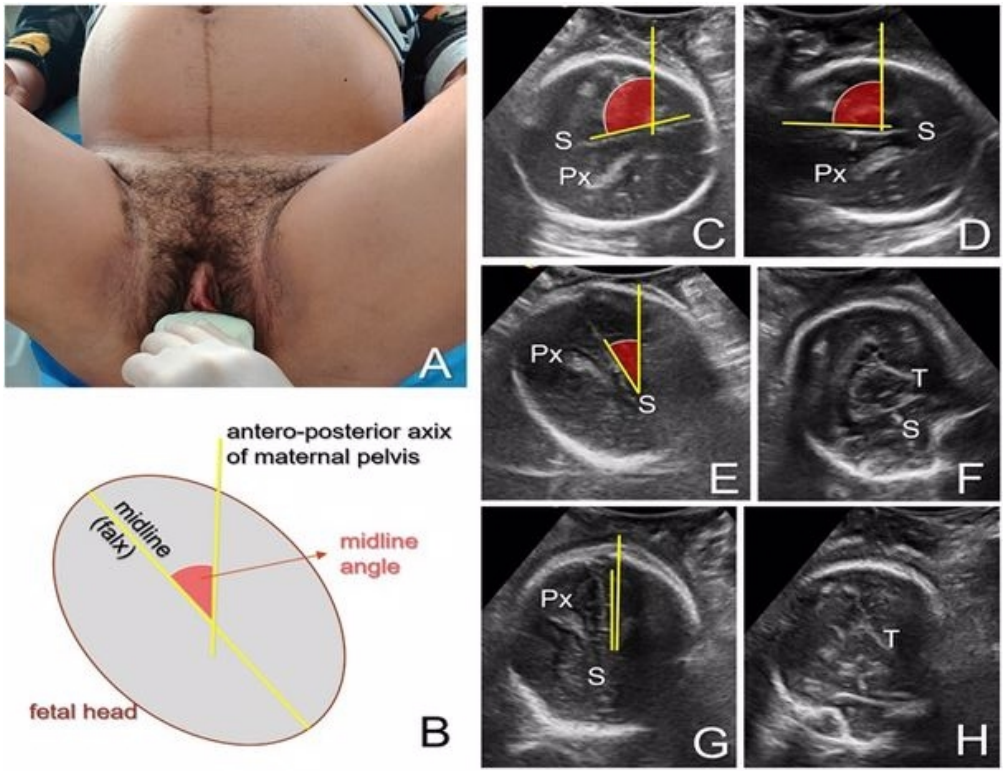

Figure 3. Ultrasound determination of the occiput position in the second stage of labor.
A: Example of the probe orientation in the transperineal infrapubic transverse plane. B: Schematization of the structures visualized and the measurement of the midline angle between the midline (falx cerebri) and the anteroposterior axis of the maternal pelvis. C-H: Presentation of an example with midline angle measurement and evolution during anterior rotation of a transverse occiput. Occiput position is identified based on the visualization of the cerebral midline (interhemispheric septum, S) and choroid plexus (Px) direction (divergent posteriorly), or thalami aspect (triangular, with the base anteriorly). Midline angle gradually decreases during the anterior occiput rotation from the transverse position (C,D), as it reaches right anterior (E,F) and anterior (infrapubic) (G,H) positions.

51x39mm (300 x 300 DPI)

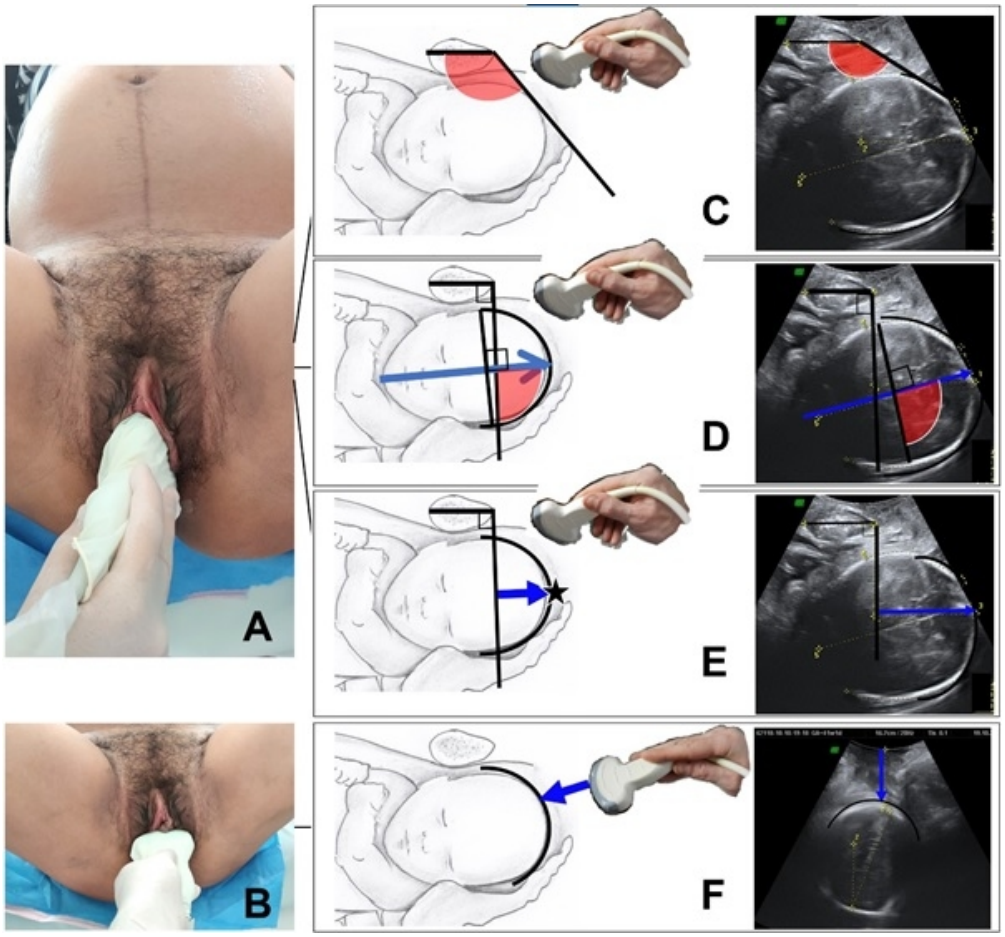

Figure 4. Ultrasound determination of the fetal head descent/progression (FHPr). Placement of the transducer in the infrapubic translabial sagittal plane (A) and infrapubic transverse plane (B). C: measurement of the progression angle between the long axis of the pubic symphysis and a line extending from its most inferior portion tangentially to the fetal skull. D: measurement of the direction angle as the angle between the major longitudinal axis of the fetal head (perpendicular to the biparietal diameter) and the infrapubic line. E: measurement of the progression distance as the minimal distance between the infrapubic line and the leading part of the fetal skull (star). F: measurement of the head to perineum distance as the shortest distance from the skin surface of the perineum to the outer bony limit of the fetal skull.

50x47mm (300 x 300 DPI)

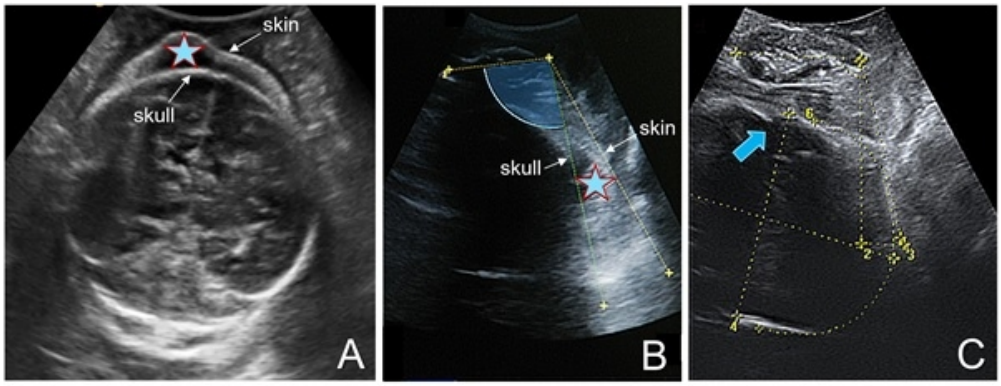

Figure 5. A,B: Presentation of caput (star) in transperineal transverse (A) and sagittal evaluation (B). C: Molding of the cranium bones indicated with the arrow.

50x19mm (300 x 300 DPI)