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Lise-Marie Dorcier

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**Thèse pour l'obtention du DIPLÔME D'ÉTAT de DOCTEUR EN MEDECINE
DES GYNÉCOLOGIE-OBSTÉTRIQUE**

Présentée et soutenue publiquement le 3 juin 2019 par

DORCIER Lise-Marie

Née le 2 décembre 1990, à L'Isle-d'Espagnac (16)

Manual ROTation versus expectative in case of Persistent Occiput Posterior
position to decrease operative delivery

The MARO-POP multicenter single-blind randomized controlled trial

Rotation manuelle versus expectative en cas de variétés postérieures
persistantes pour diminuer les accouchements opératoires

Etude MARO-POP: étude multicentrique en simple aveugle randomisée
contrôlée

Élaboration et mise en place d'un protocole de recherche clinique

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| Monsieur le Docteur Frédéric COATLEVEN | Juge |
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CHU de Bordeaux

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List of abbreviations

OP: Occiput Posterior Position

POP: Persistent Occiput Posterior

OA: Occiput Anterior Position

CI: Confidence Interval

WG: Weeks of Gestation

OVD: Operative Vaginal Delivery

MR: Manual Rotation

SOGC: Society of Obstetricians and Gynecologists of Canada

OR: Odds-Ratio

CFEF: Collège Français d'Echographie Fœtale

CTG: Cardiotocogram

FHR: Fetal Heart Rate

CHU: Centre Hospitalier Universitaire

CRF: Case Report Form

MDMC: The Methodology and Data management

USMR: Unité de Soutien Méthodologique à la Recherche clinique

CPP: French ethic committee

ANSM: Agence Nationale de Sécurité des Médicaments

CNIL: National Commission for Informatics and Liberties

HAS : Haute Autorité de Santé

RR: Relative Risk

AE: Adverse Event

SAE: Serious Adverse Event

SUSAR: Suspected Unexpected Serious Adverse Reaction

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I. Introduction

GENERALITY

Occiput posterior position (OP) corresponds to occiput of the fetus towards the sacrum of the mother. Several articles suggest that OP would be a consequence of malrotation rather than malposition (1–5).

The frequency of fetuses in OP at the onset of labor is 15 to 32% most of these fetuses turn spontaneously to an occiput anterior position (OA) (6–8). In early second stage of labor, there are 10 to 20% fetuses still in OP, it is persistent occiput posterior (POP). Nonetheless, approximately 5-8% remain in OP at delivery. (1,2,9–12).

OP is more common in primiparas women and in controversial ways in patients with epidural anesthesia but the women with OP have more painful labors and request epidural analgesia more often (1,13–16). Fitzpatrick et al., in their prospective observational study found that the incidence of POP position was significantly greater among primiparas (2.4%) than multiparas (1.3%; $p < .001$; 95% confidence interval (CI) 1.4-2.4) and was significantly associated with higher incidences of prolonged pregnancy, induction of labor, oxytocin augmentation of labor, epidural use, and prolonged labor (14). To Ponkey et al., the POP delivery rate is higher in women with previous caesarean section (14.4% vs 21.9%, $p=0.02$) (13). There is no difference in body mass index and ethnic origin of women giving birth to OP compared with those delivery to OA (13). An anterior placentation location was seen significantly more often in the OP (17).

DIAGNOSIS OF FETAL POSITION

During labor, diagnosis of the fetal head position is done by digital examination, and palpation of sagittal suture and position of anterior and posterior fontanel (Figure 1 and 2). Sometimes, the clinical diagnosis of fetal head position is difficult, in case of large caput succedaneum who can mask fetal sutures and fontanel or with asynclitism who can lead to an asymmetric location of classical anatomical landmarks; in this

situation we can use palpation of bones of nose (16,18). Therefore digital examination is not always reliable, and depends on the experience of practitioner. It was suggested recently that ultrasound be performed in the labor ward to facilitate clinical fetal occiput assessment (19).

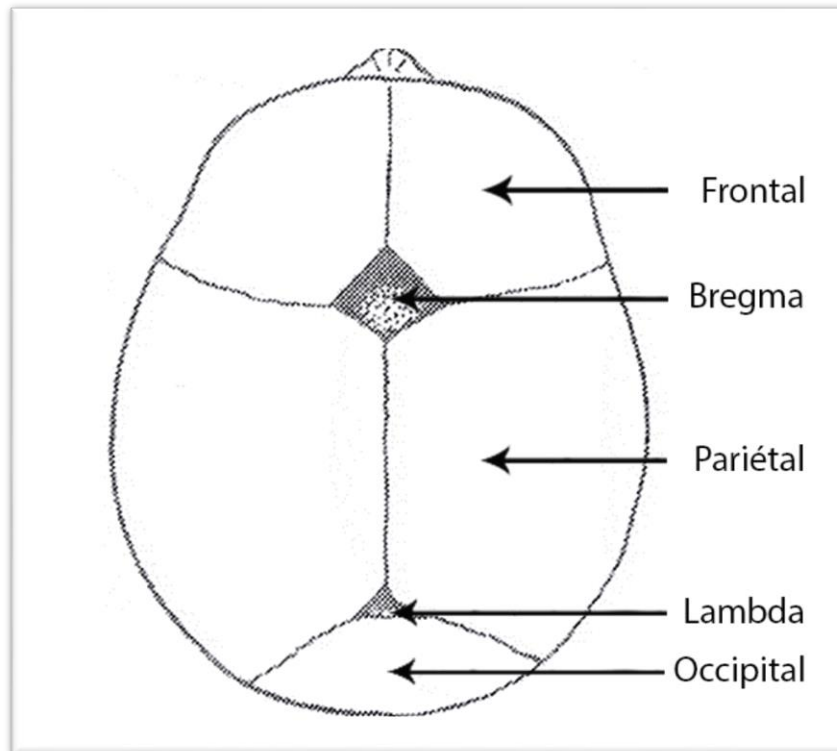


Figure 1 Anatomy of fetal skull.
Source Université virtuelle de maïeutique française

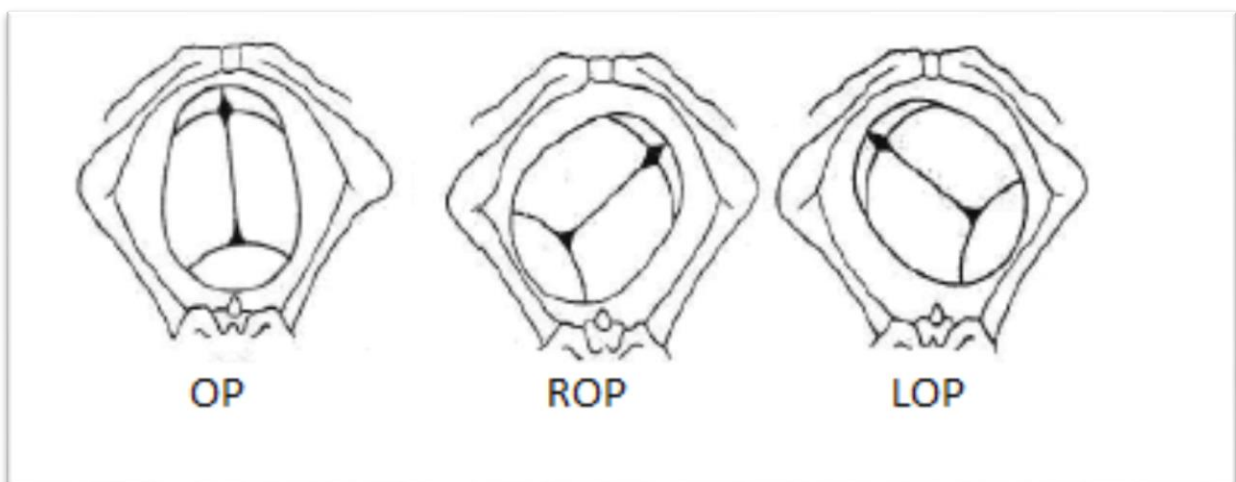


Figure 2 Occiput posterior position. OP: occiput posterior, ROP Right occiput posterior, LOP Left occiput posterior
Source <https://sites.google.com/site/olythie/home/obstetrique>

Ultrasound then holds all its place associated with digital examination, making it possible to provide a diagnosis of certainty (3,16,20). The use of ultrasound to determine fetal presentation is also an easy skill to acquire even for the less experienced (20). Landmarks can be used to determine the fetal occiput position via a transabdominal approach, the two fetal orbits for the occiput posterior, the midline cerebral echo for the occiput transverse, and the occiput itself (and cervical spine) for the occiput-anterior position (19) (Figure 3). This simple and reliable technique might improve recognition of OP.

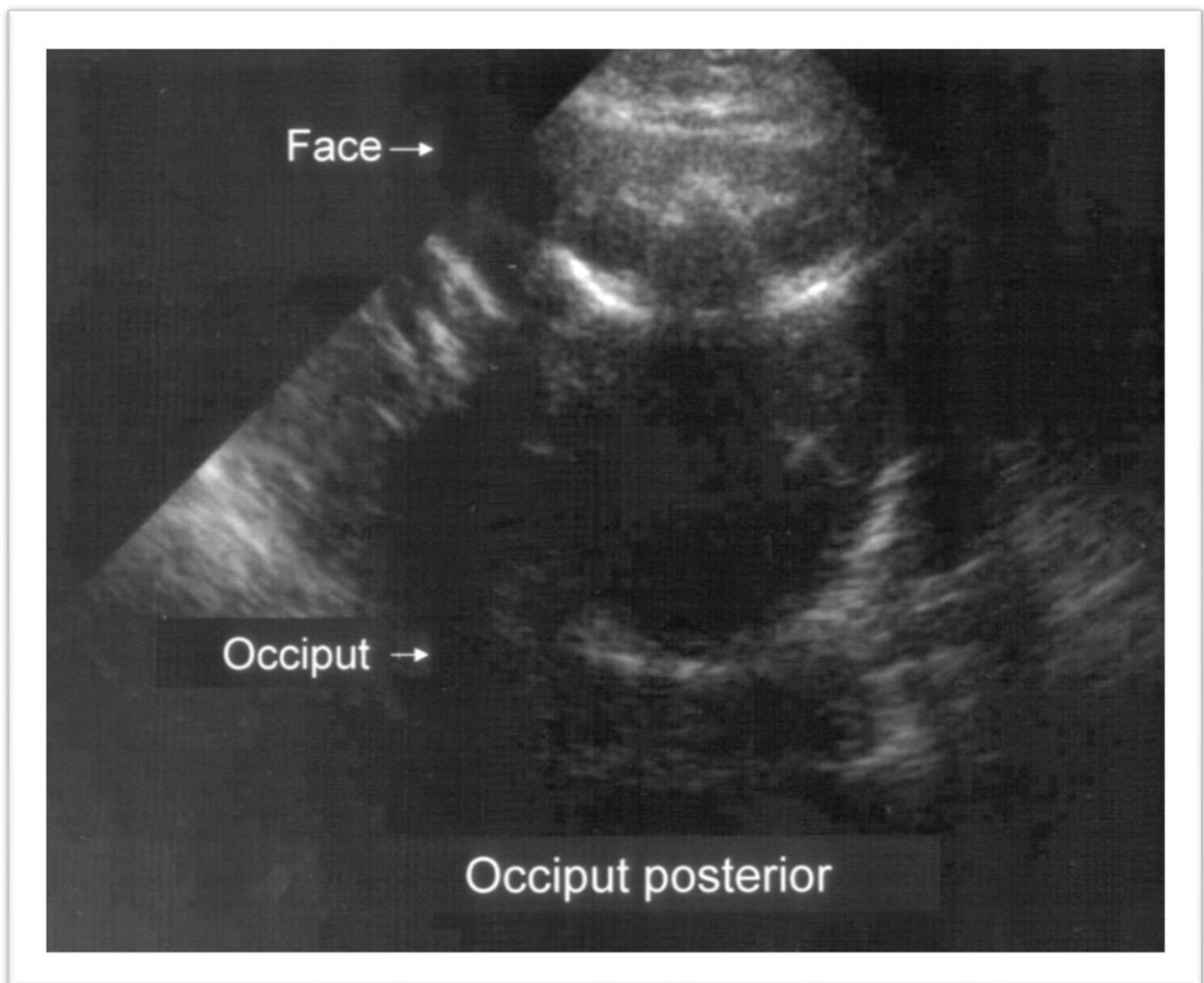


Figure 3 Occiput posterior identified by transabdominal ultrasound
Source Lieberman. *Fetal Position and Epidural Analgesia*. *Obstet Gynecol* 2005.

Ultrasound is an essential component of obstetric practice: junior and senior staff, as well as midwives, should all be trained in its use, especially in labor and emergency situations.

COMPLICATIONS OF OCCIPUT POSTERIOR

Several studies have studied the maternal morbidity of OP delivery. In the short term, OP delivery significantly increases the rate of (5,10,14–16,21,22) :

- third- and fourth-degree perineal tears (23) (8 % vs 2 % primiparas, $p < 0,001$ and 7 % vs 0,3 % multiparas, $p < 0,001$ according to Fitzpatrick et al. (14))
- operative vaginal delivery (OVD) (13,14,24–26)
- caesarean delivery (13,14,24,25)
- prolonged first and second stage of labor (13,14). Labor is significantly higher than 12 hours (18 % vs 4 % primiparas $p < 0,001$ and 5 % vs 0 % multiparas $p < 0,001$ according to Fitzpatrick et al. (14))
- a higher risk of postpartum hemorrhage (13)
- chorioamnionitis, wound infection and endometritis (13)

The use of epidural anesthesia is significantly more often in case of OP (74% vs 47%, $p < 0.001$) (14).

These complications are in part explained by the obstetrical mechanic of OP deliveries. Indeed, the fetuses in POP have a certain degree of deflexion and meet the pelvic floor with a large occipito frontal diameter 10.5-11.5 cm (in OA the diameter is 9.5cm) (5,21).

Adverse neonatal outcomes associated with the OP position include lower five-minute Apgar scores (<7), meconium-stained liquor, cord blood acidemia ($\text{pH} < 7$), birth trauma and admission to the neonatal intensive care unit (6,15,16). There is no more shoulder dystocia. However, several studies do not find any significant difference for five minute Apgar scores (13,14,24). Dahlqvist et al. moderate data and find a significant difference for five-minute Apgar scores but not for the others outcomes (25).

MANAGEMENT OF OCCIPUT POSTERIOR POSITION

During labor, 72-90% of OP have a spontaneous rotation and leads most teams to an expectative during this time (10,16). As a result, in many maternities there is no standardized management for POP position (15). Only 5-8% of women have an OP delivery but it significantly increase the maternal and neonatal morbidity (6,13,14,24). An active management of OP seems to be an option to study. Various strategies have

already been mentioned in the literature: maternal positioning, instrumental rotation (forceps, vacuum, spatulas) and of course manual rotation (MR). In our maternity, the practices are different according to the experience of the practitioner with realization of manual or instrumental rotation or expectancy.

Doctor De Gasquet in her writings referred to the active management of OP by maternal positioning. She describes a maternal position called "four legs arranged", that is to say, resting on the knees, the bust leaning forward and back stretching. Achieving this position for a minimum of 10 minutes during first stage of labor would let the rotation in OA almost immediately (16,27). Two strong trials were recently performed. EVADELA (28), multicenter randomized controlled trial, their conclusion is that lateral asymmetric decubitus position on the side opposite that of the fetal spine did not facilitate rotation of fetal head. And another one in Switzerland by Guittier et al. (29) could not demonstrate a benefit of the hands and knees position to correct the occiput posterior position of the fetus during the first stage of labor. Posturing during labor, nonetheless, should remain a woman's active choice (30).

The rotation by forceps has long been taught and used in France but considering the maternal and neonatal risks described, it's no longer performed in France (16,31,32). However in United Kingdom it's still up to date with recent publication since 2013. Stock et al. (33) published results of a Scottish retrospective cohort of 873 successful rotation forceps cases, performed between 2001 and 2008. They found 3.1% fetal wounds and 31.6% maternal complications. These rates of maternal and neonatal complications seem sufficiently important not to recommend the use of routine rotation forceps. Even if, the guidelines of Australia, New Zealand, America and Great Britain still proposes his utilization (34–36).

The vacuum rotation despite a success rate of 80-97%, is source of neonatal complications such as cephalhematoma or subgaleal hemorrhage (37–39). Spatula is an almost exclusively French instrument that explains poor data in literature. Vidal et al. compared maternal and neonatal outcomes in spontaneous OP deliveries, instrumental OP deliveries and instrumental delivery after rotation of the fetal head by Thierry's spatulas. The rates of complications were comparable in the 3 groups studied (40). Recently, Guerby et al. in their prospective observational cohort, found a significant decrease ($p < 0.002$) of the anal sphincter tears when rotated with

instrumental rotation to OVD in occiput posterior position with Thierry's spatulas, in the setting of failed manual rotation (41).

Only one study investigated morbidity of MR compared to an instrumental rotation : it is retrospective study of Shaffer et al. (42) comparing MR, vacuum rotations and forceps rotations. MR was associated with less maternal morbidity and neonatal birth trauma but a higher caesarean rate compared to rotation with forceps or vacuum (42). MR would therefore be less effective but significantly less traumatic for the mother and child than rotations using vacuum and forceps. Most recently, Bahl et al. compared in a prospective cohort of MR systematically followed by instrumental extraction, vacuum rotations and rotational forceps (43). Results were different from those of Shaffer with a lower caesarean rate in the MR group, but neonatal trauma rate was higher than the forceps rotations group. However, indication bias and variation between operators makes it difficult to interpret comparisons in these studies.

MANUAL ROTATION

Tarnier and Chantreuil already described MR in 1888 (44). Nevertheless it becomes more prevalent since the 2000s and entails the use of the operators hand or fingers to rotate the fetal head from the OP or occiput transverse position to the usual OA (16,21). The technique described by Tarnier and Chantreuil, is used in many studies because of its simplicity (12,45–48).

The patient must be placed in the lithotomy position with the legs in stirrups. Her bladder must be empty and membranes ruptured. The fetal head is rotated 180° if it is in an occipitosacral position, 135° for posterior positions, and 90° for transverse position. The hand used by the operator varies according to the position: the right hand holds onto the back of the fetus's right ear for the left position (left occiput transverse and left occiput posterior) and the left hand is behind the left ear for the right position (right occiput transverse and right occiput posterior). The operator then places his or her right hand behind the fetal ear and, during a contraction and a pushing effort, moves the fetal head in a rotating movement forward toward the pubic symphysis to move the occiput relative to the anterior arc of the mother's pelvis. The operator can be a midwife, a senior resident, or a senior obstetrician (12). This maneuver/movement must be carried out "firmly but without violence". MR can in some cases lead to

abnormalities of fetal heart rate, it must be performed under fetal monitoring (9,45,46). MR may take two or three contractions to be performed and the position is commonly held for two contractions while the woman bears down to reduce the risk of the fetus reverting to the OP (8,44).

The Society of Obstetricians and Gynecologists of Canada (SOGC) describes also a technique with an entire hand placed in the patient's vagina with the palm up; the fetal head is flexed and slightly dislodged. The occiput is rotated anteriorly by pronation or supination of the forearm (49).

None of these techniques has been shown to be superior (9), and they are both used in different trials (47,48). Digital rotation is also used, but we decided not to use it for the trial.

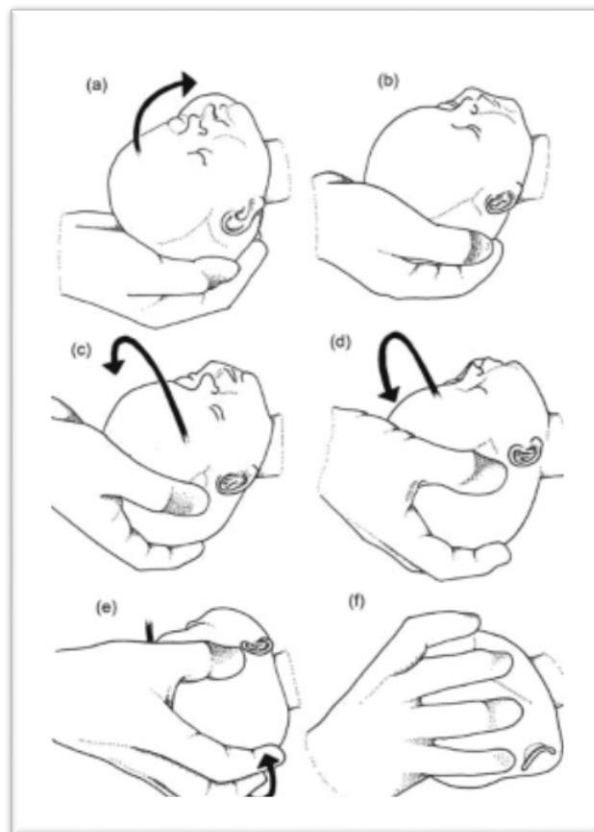


Figure 4 Manual rotation according SOGC

Source Argani CH, Satin A. Management of the fetus in occiput posterior position.

Le Ray et al. in a case control study found that attempted rotation before full dilatation tripled the risk of failure in comparison with rotation at full dilatation (adjusted odds ratio (OR) 3.4, 95% CI 1.3-8.6) and rotation for failure to progress quadrupled

that risk in comparison with prophylactic rotation (adjusted OR 3.3, 95% CI 1.2-8.5). Failure of MR was associated with a higher caesarean delivery rate than was success (58.8% compared with 3.8%, $p < .001$). The success or failure of attempted MR depends upon obstetric conditions, including the indication for rotation and cervical dilatation (46).

In their retrospective cohort, Shaffer et al. shown that multiparity (OR, 2.5; 95% CI, 1.5-3.8) and maternal age < 35 years (OR, 2.0; 95% CI, 1.1-3.4) were associated with successful MR of the fetal occiput (50). After successful rotation, the caesarean delivery rate was 2% versus 34% if the rotation failed ($p < 0.001$). Asian ethnicity, nulliparity, age > 35 years, labor induction, and epidural usage were associated with higher rates of caesarean delivery (50).

Bertholdt et al. suggested that factors associated with successful rotation were fetal engagement (adjusted OR 2.20, 95% CI 1.05-4.56), spontaneous labor (adjusted OR 1.85, 95% CI 1.01-3.43), and no failure to progress (adjusted OR 2.01, 95% CI 1.02-3.94) (51).

No neonatal variables were found to be significantly associated with RM success or failure (46,50).

The maternal complications of MR are a slightly risk of cervical laceration of 2-3% (45,52). According to Shaffer et al. this risk is multiply by two (adjusted OR 2.46; CI 1.1-5.4) (52). However, the duration of hospital stay is shorter with MR (10). There is also less cases of postpartum hemorrhage and chorioamnionitis with a MR (52).

There is also a 10-20% risk of developing a pathological cardiotocogram (CTG) or aggravating already present abnormalities (45,46). Le Ray et al. found that only one emergency caesarean section was required in the case of a pathological CTG (out of 64 manual rotations)(46). Outcomes of neonates born to women who had MR are similar to those who had expectative management, except for the rate of 5-min Apgar score < 7 who was lower in the rotation group (1.8%) compared to expectant management (3.7%, $p < 0.01$) according to Shaffer et al. (52). Although there were no differences in rates of neonatal acidemia, we also did not find a difference in the occurrence of shoulder dystocia or composite birth trauma.

There is one case report of umbilical cord prolapse, so it's important to do the MR during pushing and don't repulse the fetal heads (9,45).

PERSPECTIVE

The OP induced maternal and neonatal complications making it a public health issue. Actually, their management during labor is not codified and is not the subject of specific guidelines.

The MR seems to be an efficient and secure procedure. Furthermore, the success rate of MR is approximately 90% (12). Risks associated to MR are then lower than potential benefit associated to prevention of operative delivery. Manual rotation is also easily accessible to midwives, doctors and residents.

STUDY OBJECTIVE

The aim of our study is to conduct a large multicenter, interventional, randomized, prospective single blind controlled trial to properly assess the superiority on operative delivery of manual rotation in case of POP position at full dilatation over expectative management (standard care).

Our principal hypothesis is that a systematic manual rotation at second stage of labor (at full dilatation) in case of POP position will reduce the operative delivery rate.

Our main objective is to compare the efficacy of systematic manual rotation at full dilatation versus expectative (standard care alone), on the operative delivery rate for patients with POP.

So the primary outcome will be the operative delivery rate defined as proportion of vacuum, forceps, spatula and/or caesarean section deliveries. The secondary outcomes will be in a particular severe composite neonatal and maternal morbidity.

The objective of the thesis is to develop a randomized trial protocol comparing the effect of manual rotation with expectative management of POP during the second stage of labor.

II. Material and Methods

SUMMARY OF THE RESEARCH

(Appendix 1 French version)

| | |
|----------------------------------|--|
| SPONSOR | Centre Hospitalier Universitaire (CHU) de Bordeaux |
| COORDINATING INVESTIGATOR | Dr SARRAU Marie Department of Obstetrics and Gynecology Bordeaux University Hospital Place Amélie Raba Léon 33 000 Bordeaux Tel: +33 5 56 79 55 79 - Fax: +33 5 56 79 56 76 Email: marie.sarrau@chu-bordeaux.fr |
| TITLE | MANual ROTation vs expectative in Persistent Occiput Posterior position to decrease operative delivery. The MARO-POP multicenter single-blind randomized controlled trial |
| BACKGROUND | In second stage of labor, 15% of fetuses are in occiput posterior position (it is persistent occiput posterior position) and 5-8% at delivery. The OP increased the risk of operative delivery and associated with both maternal and neonatal complications. |
| OBJECTIVES | <p>Main objective</p> <p>To compare the efficacy of systematic manual rotation at full dilatation and expectative (standard care alone), on the operative delivery rate for patients with persistent occiput posterior position</p> <p>Secondary objectives</p> <p>To compare systematic manual rotation at full dilatation and expectative (standard care alone), for patients with persistent occiput posterior position, on the following outcomes:</p> <ul style="list-style-type: none"> - Severe maternal morbidity; - Severe neonatal morbidity; - Position of the fetal occiput at the delivery; - The incidence of postpartum hemorrhage (> 500 mL); - The incidence of episiotomy; - The incidence of operative vaginal delivery failure; - The incidence of shoulder dystocia; - The incidence of cord prolapse; - The duration of second stage of labor; |

| | |
|--------------------------------|---|
| | <ul style="list-style-type: none"> - Duration of maternal and neonatal hospital stay in days; - Satisfaction rating of mother at the end of hospital stay; |
| <p>OUTCOME MEASURES</p> | <p>Primary outcome</p> <p>The primary outcome of this study is the operative delivery rate (defined as the proportion of vacuum, forceps, spatula and/or caesarean section deliveries).</p> <p>Secondary outcomes</p> <p>Proportion of severe short-term maternal morbidity is a composite measure of severe short-term maternal morbidity, defined by fulfillment of at least one of the following criteria:</p> <ul style="list-style-type: none"> - Severe perineal tears (third and fourth degree); - Puerperal genital hematoma; - Cervical laceration; - An extended uterine incision for caesarean delivery; - Severe postpartum hemorrhage ($\geq 1,000$ mL); - Second-line therapies for postpartum hemorrhage; - Maternal infection during the hospital stay; - Thromboembolic events during the hospital stay; - Admission to the intensive care unit; - Maternal mortality during the hospital stay. <p>Proportion of severe neonatal morbidity is a composite measure of severe short-term neonatal morbidity, defined by fulfillment of at least one of the following criteria:</p> <ul style="list-style-type: none"> - 5-minute Apgar score less than 7; - Umbilical artery pH less than 7.00; - Need for resuscitation or intubation at birth; - Neonatal trauma; - Intraventricular hemorrhage above grade 2 during the hospital stay; - Intensive care unit stay for > 24 hours; - Neonatal sepsis, seizure and mortality during the hospital stay; <p>Proportion of occiput position at the delivery;</p> <p>Proportion of shoulder dystocia;</p> <p>Proportion of cord prolapse;</p> <p>Mean duration of the second stage of labor (period between full dilatation and delivery);</p> |

| | |
|-------------------------------|---|
| | <p>Proportion of operative vaginal delivery failure;</p> <p>Proportion of postpartum hemorrhage > 500 mL;</p> <p>Proportion of episiotomy;</p> <p>Mean duration of maternal hospital stay;</p> <p>Mean duration of neonatal hospital stay;</p> <p>Mean satisfaction of mother, assessed by a numeric rating scale at the end of the hospital stay;</p> |
| STUDY DESIGN | Multicenter superiority single (patient) blind randomized controlled trial, with two parallel groups. |
| INCLUSION CRITERIA | <ul style="list-style-type: none"> - Age ≥ 18 years; - Gestational age ≥ 37 weeks; - Singleton cephalic pregnancy; - Occiput posterior position confirmed by ultrasound; - Second stage of labor; - Planned vaginal birth; - Beneficiary or affiliated to health system; - Signed informed consent provided by the participant and the principal investigator or his (her) representative before any examination required by the research. |
| NON-INCLUSION CRITERIA | <ul style="list-style-type: none"> - Known fetal congenital anomaly or suspected fetal bleeding disorder; - In utero fetal death; - Brow or face presentation; - Pathological fetal heart rate with a risk of acidosis requiring corrective surgery and second-line examinations; - Chorioamnionitis; - Temperature above 38.5 °C during the first stage of labor; - Hemorrhage during the first stage of labor; - Poor understanding of the French language as evaluated by the principal investigator or his (her) representative; - Patient placed under judicial protection; - Patient participating in another research study that precludes their participation in other research; - Patient with severely compromised physical and/or psychological health that, in the opinion of the principal investigator or his (her) representative, could affect their compliance with the study, etc. |

| | |
|-----------------------------|--|
| ARM AND INTERVENTION | <p>Experimental arm Prophylactic manual rotation at full dilatation</p> <p>Control arm Identical “sham” procedure but without rotation force (i.e. prolonged vaginal examination)</p> |
| STUDY SIZE | <p>According to the result of Le Ray et al.’s study in 2013 and to show a relative reduction of at least 30% in the incidence of the primary outcome from 40% to 28% or less in the experimental arm ($\alpha = 0.05$, $1-\beta = 0.90$, and a bilateral test) the study requires 326 women per group. We plan to include 674 patients in total to take into account the 3% of patients lost to follow-up.</p> |
| STUDY DURATION | <p>Duration of the recruitment period: 24 months Duration of participation of each participant: 15 days Total duration of the research: 24 months</p> |
| STATISTICAL ANALYSES | <p>Qualitative variables will be described with frequencies and proportions. For outcomes involving a qualitative variable, 95% two-sided confidence interval will be estimated with the exact binomial distribution. Quantitative variables will be described with frequencies, mean, standard deviation, median, minimum, maximum, 1st and 3rd quartiles. For outcomes involving a quantitative variable, 95% two-sided confidence interval will be estimated.</p> <p>Analyses will be conducted according to the intent to treat principle. This is a superiority trial (bilateral test). The operative delivery rate between the experimental group and the control group will be compared with a Chi² test or with Fisher's exact test, according to the size of the expected values under the hypothesis of independence. The 95% confidence intervals (exact binomial distribution) in each group will be calculated. Mixed effects logistic regression model will be used to adjust on stratification factor (random effect on centers and parity) and other major confounding factors listed in secondary outcomes. Assumption of the models (log-linearity of the associations) will be systematically checked.</p> |
| EXPECTED IMPACTS | <p>If manual rotation is effective in reducing operative delivery rates, its routine use should reduce the incidence of operative delivery and associated maternal and neonatal morbidity.</p> <p>If manual rotation proves unsatisfactory, this study will prevent the widespread use of an ineffective procedure associated with potential adverse effects in a routine practice.</p> |

STUDY DESIGN

The MARO-POP trial is a prospective, national, multicenter, single blind, with two parallel groups. The trial is designed to compare the impact on the operative delivery rate of standard care plus systematic manual rotation in case of POP position versus standard care alone (expectative).

STUDY OBJECTIVE

A. Hypothesis

Our principal hypothesis is that manual rotation at the second stage of labor in case of persistent occiput posterior position may reduce operative delivery (i.e. OVD and caesarian).

B. Main objective

To compare the efficacy of systematic manual rotation at full dilatation and expectative (standard care alone), on the operative delivery rate for POP position.

C. Secondary objectives

To compare systematic manual rotation at full dilatation and standard care alone, in POP position, on the following outcomes:

- Severe maternal morbidity (see below);
- Severe neonatal morbidity (see below);
- Position of the fetal occiput at the delivery;
- The incidence of OVD failure;
- The incidence of postpartum hemorrhage (> 500 mL) assessed with a collector bag;
- The incidence of episiotomy;
- The incidence of shoulder dystocia;
- The incidence of cord prolapse;

- The duration of second stage of labor;
- Duration of maternal and neonatal hospital stay;
- Satisfaction rating of mother at the end of hospital stay;

STUDY OUTCOMES

A. Primary outcomes

The primary outcome of this study is the operative delivery rate defined the proportion of as vacuum, forceps spatula and/or caesarean section deliveries among all deliveries.

B. Secondary outcomes

The secondary outcome measures are as follows:

- Proportion of severe short-term maternal morbidity is a composite measure of severe short-term maternal morbidity, defined by fulfillment of at least one of the following criteria:
 - Extensive perineal tearing involving the anal sphincter (third- or fourth-degree tears, defined by injury to the anal external sphincter or anal mucosa, respectively);
 - Puerperal genital hematoma;
 - Cervical laceration;
 - An extended uterine incision for caesarean delivery;
 - Severe postpartum hemorrhage (estimated blood loss \geq 1,000 mL)*;
 - Second-line therapies for postpartum hemorrhage (intrauterine balloon, uterine compression suture, uterine artery embolization, or peripartum hysterectomy for management of massive primary postpartum hemorrhage after failure of uterine massage and uterotonic agents to stop bleeding);
 - Maternal infection during the hospital stay(uterine infection requiring antibiotics), episiotomy infection (episiotomy scar suppuration or

- abscess) or wound infection (caesarean section scar suppuration or abscess) requiring surgery ;
 - Thromboembolic events during the hospital stay, defined as deep vein thrombosis diagnosed using bilateral leg Doppler ultrasound, or pulmonary embolism or cerebral embolism diagnosed using angiogram;
 - Admission to the intensive care unit;
 - Maternal mortality during the hospital stay.
- Proportion of severe neonatal morbidity is a composite measure of severe short-term neonatal morbidity, defined by fulfillment of at least one of the following criteria:
 - 5-minute Apgar score less than 7;
 - Umbilical artery pH less than 7.00 at delivery (umbilical artery blood gas values are routinely measured);
 - Need for resuscitation or intubation at birth;
 - Neonatal trauma, defined by fulfillment of at least one of the following criteria: fracture of the clavicle or a long bone, brachial plexus nerve injury, skull fracture, scalp hematoma, head laceration, facial nerve palsy and hematoma or intracranial bleed;
 - Intraventricular hemorrhage above grade 2 (Classification of Papile) assessed during its stay at hospital after delivery;
 - Intensive care unit stay for > 24 hours;
 - Neonatal sepsis assessed during its stay at hospital after delivery;
 - Neonatal seizure assessed during its stay at hospital after delivery;
 - Neonatal mortality assessed during its stay at hospital after delivery;
 - Proportion of occiput position at the delivery;
 - Mean duration of the second stage of labor (period between full dilatation and delivery);
 - Proportion of shoulder dystocia;
 - Proportion of cord prolapse;

- Proportion of episiotomy;
- Proportion of OVD failure;
- Proportion of postpartum hemorrhage > 500 mL*;
- Mean duration of maternal hospital stay in days ;
- Mean duration of neonatal hospital stay in days;
- Mean satisfaction of mother assessed by a numeric rating scale (0–10); at the end of the hospital stay;

*The method to estimate blood loss will be standardized after vaginal (collector bag) and caesarean deliveries (estimated gravimetrically based on suction volume and swab weight).

C. Data collection

Maternal, pregnancy, labor and delivery characteristics, will be assessed as follows:

- Maternal characteristics:
 - Maternal age (years);
 - Body mass index before pregnancy(kg/m²);
 - Parity;
 - Previous caesarean delivery;
 - Important element in medical history;
- Pregnancy characteristics:
 - Prenatal suspicion of small-for-gestational-age or macrosomia (defined, respectively, as less than the 10th and more than 90th percentile of gestational age based on Collège Français d'Echographie Foetale (CFEF) standards);
 - Gestational diabetes : yes/no;
 - Pre-eclampsia : yes/no;

- Labor characteristics:
 - Gestation at delivery (weeks of gestation);
 - Induced of labor : yes/no;
 - Epidural analgesia: yes/no;
 - Dose of oxytocin during labor (milli-international units);
 - Duration of the entire second stage of labor (complete dilatation to birth); and of the active second stage (from the beginning of expulsive efforts to birth [pushing time]) (hours and minutes);
- Manual rotation characteristics
 - Time from the manual rotation to the birth (hours and minutes);
 - Technique used:
 - Tarnier and Chantreuil;
 - SGOC;
 - Cord prolapse: yes/no;
 - Success: yes/non;
- Delivery characteristics:
 - Spontaneous delivery/OVD/caesarean section :
 - Sequential use of 2 instrument: yes/no;
 - Instrument type Spatula/forceps/ventouse;
 - Indication for OVD :
 - Nonreassuring fetal heart rate (FHR) only;
 - Arrested progress only;
 - Nonreassuring FHR and arrested progress;
 - Indication for caesarean
 - After failed OVD: yes/no;
 - Nonreassuring FHR only;
 - Arrested progress only;
 - Nonreassuring FHR and arrested progress;
 - Performance of a episiotomy or lack thereof: yes/no;

- Blood loss: estimation using a collector bag (mean);
- Need for an additional uterotonic agent;
- Second line therapies for postpartum hemorrhage;
- Shoulder dystocia: yes/no/reduction through surgery;
- Immediate postpartum data
 - Maternal data:
 - Perineal tears: third or fourth degree: yes/no;
 - Cervical lesions diagnosed by instrumental examination of the genital tract, requiring a suture;
 - Clinically diagnosed vaginal thrombosis: yes/no;
 - Surgical lesions: ureter (wound, section),intestinal (wound); bladder (wound with insertion of urinary catheter): yes/no;
 - Blood transfusion: yes (number of packed red cells)/no;
 - Postpartum endometritis: diagnosed based on the combination of fever, pelvic pain, and an infectious/biological disorder: yes/no;
 - Episiotomy wound healing disorder: yes/no;
 - Phlebitis/EP: diagnosed following Doppler ultrasound of the lower limbs or computed tomography angiography: yes/no;
 - Occlusion: yes/no;
 - Fistula: yes/no;
 - Transfer to the intensive care unit department: yes/no/reason;
 - Duration of hospital stay: in days, following delivery;
 - Maternal mortality during the hospital stay;
 - Neonatal data:
 - Child's sex: female/male;
 - Fetal occiput position at delivery;
 - Child's weight: grams;
 - 5-minute Apgar score;
 - Arterial umbilical cord pH and lactates levels at delivery;
 - Intubation, ventilation > 24 h: yes/no;

- Nasogastric tube feeding > 4 days: yes/no;
- Intensive care > 4 days: yes/no;
- Neonatal trauma;
 - Scalp laceration;
 - Scalp hematoma;
 - Fracture of a long bone;
 - Fracture of the clavicular;
 - Skull fracture ;
 - Facial nerve palsy
 - And hematoma or intracranial bleed
- Phototherapy in the case of hyperbilirubinemia: number of sessions;
- Clinically suspected fracture diagnosed using x-ray: yes/no;
- Intraventricular or cerebral hemorrhage diagnosed using cranial ultrasound: yes/no;
- Neonatal transfusion: number of packed red cells;
- Ischemic encephalopathy diagnosed using magnetic resonance imaging scan: yes/no;
- Department and duration of hospital stay in days;
- Perinatal death (i.e., up to 7 days following delivery);

Maternal and obstetric data will be collected from the medical records, and from the trial specific collection form filled in for each case for items not routinely entered in the medical files

Data collected will be those needed for:

- assessing the baseline comparability of the 2 groups
- assessing the management of delivery and third stage of labor, and its compliance with the trial's protocol
- assessing the trial's primary and secondary outcomes

ELIGIBILITY CRITERIA

A. Inclusion criteria

The following criteria must be met for a patient to be included in the trial:

- Age \geq 18 years;
- Gestational age \geq 37 weeks;
- Singleton cephalic pregnancy;
- Occiput posterior position confirmed by ultrasound;
- Second stage of labor;
- Planned vaginal birth;
- Beneficiary or affiliated to health system;
- Signed informed consent provided by the participant and the principal investigator or his (her) representative before any examination required by the research.

Transabdominal ultrasound performed at full dilation and the fetal orbits will be used to determine the presentation. The presentations will be classified into two groups: posterior position if a fetal orbit is visible and anterior position if no fetal orbit is visible.

B. Non-inclusion criteria

The patient will not be included in the trial if they fulfill one or more of the following criteria:

- Known fetal congenital anomaly or suspected fetal bleeding disorder;
- In utero fetal death;
- Brow or face presentation;
- Pathological fetal heart rate with a risk of acidosis requiring corrective surgery and second-line examinations;
- Chorioamnionitis;
- Temperature above 38.5 °C during the first stage of labor;

- Hemorrhage during the first stage of labor;
- Poor understanding of the French language as evaluated by the principal investigator or his (her) representative;
- Patient placed under judicial protection;
- Patient participating in another research study that precludes their participation in other research;
- Patient with severely compromised physical and/or psychological health that, in the opinion of the principal investigator or his (her) representative, could affect their compliance with the study, etc.

C. Eligibility criteria for study centers

Ability to provide a 24-hour on-call service with experienced operators to performing the intervention. Study centers should performed more than 1500 deliveries per year.

D. Feasibility and recruitment procedures

A midwife or obstetrician will provide eligible women with information about the study during a prenatal visit in the third trimester. This information will be discussed again when the participants arrive at the delivery room; they will then confirm their intention to participate and provide signed informed consent before delivery (Appendix 1 and 2).

Eligible women in delivery room will first be offered standard care, i.e. transvaginal digital examination. In case of suspicion of OP during labor or in the presence of caput succedaneum or asynclitism, a suprapubic transabdominal ultrasound will be performed, by the clinician caring for the woman, to determine a fetal occiput position at full dilatation. Fetal OP position will be established by obtaining a transverse view of the fetal orbits. After confirmation of the OP, a midwife or obstetrician will collect the patient's consent following an interview. Information about the study will be reiterated in this interview. At least two copies of the informed consent form will be signed by all parties.

At full dilatation, the clinician on-call will repeat the transabdominal ultrasound and if the OP position persists, will randomize the participant to either the control or intervention arm of the study.

Investigators assumed a 40% incidence of the primary composite outcome (operative delivery): based on Le Ray et al. 2013 prospective study's compared two French university hospital, one of which systematically realized a MR and another did not realize it. The operative delivery rate was significantly lower in the maternity performing MR (23.2% vs 38.7% for the other, OR adjusted 0.52, 95% CI 0.28–0.95). To show a relative reduction of at least 30% in the incidence of the primary outcome from 40% to 28% or less in the experimental arm ($\alpha = 0.05$, $1-\beta = 0.90$, and a bilateral test) the study requires 326 women per group (*calculation software: epiR package 0.9-96*). Given the expected proportion of women with withdrew consent and lost to follow-up (estimated at a maximum of 3%), the total number of randomized women will be greater in order to include the needed number of women: 337 women will be included in each group, for a total of 674 participant. Relative reduction of at least 30% in the incidence of the primary outcome seems clinically relevant to justify the realization of a systematic manual rotation in case of POP position.

Combined, the 13 participating maternity units perform 52200 deliveries per year. We approximately consider that 80% of parturient woman give birth without caesarean (caesarean rate in France 20.8% (53)). In this 80%, 15% of parturient would have an OP at the second stage of labor. So we estimate that 10% of parturient women visiting the participating centers, i.e. 5220/year, will be eligible for the trial. An inclusion period of 24 months should allow for recruitment of 1566 patients if we assume a participation rate of at least 15%. This participation rate seems realistic given the rates previously achieved in similar trials (54,55)).

Table 1 Expected recruitment in participating centers

| Center | Annual number of deliveries | Annual number of deliveries expected to be eligible for MARO-POP* | Expected recruitment per month (n, average) ** | Total expected recruitment by 24 months (n)** |
|--------------------------------------|-----------------------------|---|--|---|
| Bordeaux University Hospital | 5,200 | 520 | 6.5 | 156 |
| Jeanne de Flandres Hospital in Lille | 5,300 | 530 | 6.6 | 159 |
| Nantes University Hospital | 4,200 | 420 | 5.3 | 126 |
| Toulouse University Hospital | 5,000 | 500 | 6.3 | 150 |
| Strasbourg University Hospital | 3,200 | 320 | 4 | 96 |
| Women Mother Child Hospital, Bron | 4,100 | 410 | 5.1 | 123 |
| Rennes University Hospital | 3,500 | 350 | 4.4 | 105 |
| Robert Debré Hospital | 3600 | 360 | 4.5 | 108 |
| Bicêtre Hospital | 3,600 | 360 | 4.5 | 108 |
| Créteil Hospital | 3,500 | 350 | 4.4 | 105 |
| Clermont-Ferrand University Hospital | 3,600 | 360 | 4.5 | 108 |
| Caen University Hospital | 3,600 | 360 | 4.5 | 108 |
| Tours University Hospital | 3,800 | 380 | 4.8 | 114 |
| Total | 52200 | 5220 | 65.4 | 1566 |

* We estimate that 10% of parturient women will meet the criteria for study inclusion, excluding deliveries before gestational age ≥ 37 weeks and considering the other exclusion criteria. ** Assuming a participation rate of at least 15%.

STUDY INTERVENTION

A. Investigational strategy

In the case of randomized patients in the manual rotation group, manual rotation will be performed following randomization.

Women randomized to the manual rotation group, a manual rotation will be performed at full dilatation. The technique employed will be at the discretion of the operator performing the procedure.

Two methods are possible:

- Tarnier and Chantreuil's method: the right hand supports the back of the fetus' right ear in the case of left posterior positions, and the left hand supports the back of the fetus' left ear in the case of right posterior positions. The rotation movement is made towards the front, in the direction of the symphysis, during a thrust
- Method of the Society of Obstetricians and Gynecologists of Canada (SOGC): the entire hand is placed in the patient's vagina with the palm up; the fetal head is flexed and slightly dislodged. The occiput is rotated anteriorly by pronation or supination of the forearm

These two approaches are very similar with the only difference being the position of the hand on the fetus, and we assume the same efficiency for both.

In both cases, manual rotation should be attempted during a contraction with the membranes ruptured and the woman is asked to bear down. The operator will have the right to make only three attempts, because beyond this number, the chances of success are estimated to be null.

The examiner places the hand behind the fetal ear or the entire hand behind the occiput (depending on the chosen method) and applies constant flexion and rotation to the fetal head. The rotation movement is applied to the occiput for a rotation in anterior.

The operators should not make a digital rotation.

The fetal occiput will be then held in the OA position for a further one to two contractions. A repeat transabdominal ultrasound, will be used by the operator to confirm the final position of the fetal occiput and recorded. Manual rotation will be

considered to be successful if the fetal occiput was OA and within 45 degrees of the midline.

Only obstetricians or midwives who are experienced in performing a manual rotation and having declared to have performed at least 20 procedures will participate in the study. All operators will complete a declaration to claim to have done more than 20 manual rotation.

B. Comparative strategy

Women randomized to the 'sham rotation' group will have the same apparent vaginal examination as the intervention but with no rotational force applied. The woman will be asked to bear down. The operator will place fingers in the vagina over 5 contractions as if she were performing a manual rotation.

Only obstetricians or midwives who are experienced in performing a manual rotation and have performed at least 20 procedures will participate in the study.

C. Criteria for discontinuing or modifying the intervention

The intervention or sham will be discontinued if there is a clinical necessity or at the request of the participant.

This could occur if there is evidence of fetal compromise necessitating emergent delivery or if the participant is in significant discomfort.

Each operator will complete a data collection form at the time of the procedure or sham, which will describe in detail what was done.

All interventions and usual care provided by doctors and midwives looking after the participant will be allowed.

D. Blinding

The MARO-POP trial is single blinded, because it is difficult for maternities organization to perform a double blinded trial. Indeed, it would be necessary that the practitioner who realized the manual rotation, should not do the delivery.

The following groups will be masked:

- The participants
- The data collectors
- The statisticians who will perform the analysis

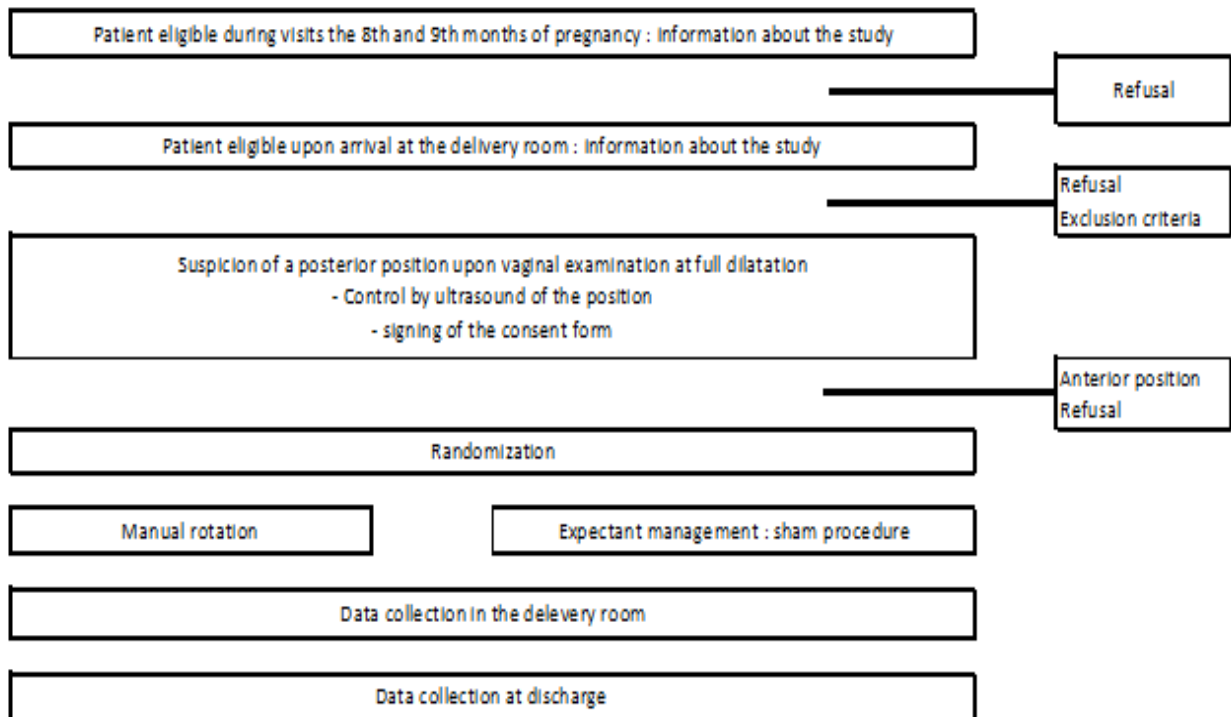
E. Random procedure

Randomization will take place after confirming the eligibility of all participants once they have completed the consent form on the day of delivery. Randomization will be performed centrally in a 1:1 ratio using an automated centralized Web-based electronic case report form (CRF) system, to ensure allocation concealment. The allocation will be stratified by center and parity. Randomization will take place on the day of delivery, after confirmation that the participant meets the eligibility criteria and completion of the participation form.

When an investigator wishes to apply the randomization/inclusion process after verifying the eligibility of the participant, he/she will connect to the website « Ennov Clinical ». The investigator will complete the "Randomization" Webpage having previously confirmed that the participant meets the eligibility criteria listed on the site. Then, the randomization/eligibility check can be carried out, and the site will immediately communicate the participant's unique research number to the investigator, the result of the randomization process/eligibility check and, in particular, the group allocation.

A document describing the preparation of the randomization list will be kept in a confidential and secure place in the Methodology and Data Management Centre (MDMC).

Figure 5 Participant timeline



ASSOCIATED TREATMENTS AND PROCEDURES

A. Authorized associated treatments and procedures

All the treatments and procedures recommended in current practice for standard care are authorized for use during the trial.

B. Prohibited associated treatments and procedures

No treatments or procedures are prohibited during the trial.

STUDY PROCEDURE

A. Study calendar

- Duration of the recruitment period: 24 months
- Duration of participation of each participant: 15 days
- Total duration of the research: 24 months

B. Table summarizing participant follow-up

Table 2 Summarizing participant follow-up

| | Screening M-2 to M0 | Inclusion M0 | Hospitalization stay |
|-----------------------------------|------------------------|-----------------|-------------------------|
| Information | ✓ | ✓ | |
| Signed informed | | ✓ | |
| Randomization | | ✓ | |
| Manual rotation * | | ✓ | |
| Clinical data | | ✓ | ✓ |
| Adverse events | | ✓ | ✓ |
| Thromboembolic | | | ✓ |
| Maternal infection | | | ✓ |
| Woman's satisfaction ¹ | | | ✓ |

M (Month); W (Week);

**Only for experimental arm*

¹Patient satisfaction: numerical rating scale (0–10).

[Screening visit M-2 to M0] A midwife or obstetrician will offer eligible woman information about the study during a prenatal visit in the third trimester.

[Inclusion visit M0] This information will be reiterated when the participant has arrived in the delivery room; each participant then will confirm their intention in participating by providing signed informed consent before delivery.

[Hospitalization stay from 3 to 15 days after delivery] Maternal infection, thromboembolic events and woman satisfaction will be assessed at the end of hospitalization stay.

C. Funding

To finance the trial, we will be respond to call for tender of Programme Hospitalier de Recherche Clinique National in 2020 (PHRC-N).

The estimate budget of the trial is 550 000 – 600 000 euros.

D. Screening/ inclusion visit

1. Signed informed consent

During the pre-inclusion/inclusion visit, the principal investigator or his (her) representatives will provide information to the participant and answer any questions regarding the purpose, nature of participant-related constraints, possible risks and expected benefits of the research. The investigator will also clarify the participant's rights and check that they fulfill the eligibility criteria.

Consent will occur at three possible time points

- Antenatally
- In the latent phase of labor
- In the active phase of the first stage of labor,
- In the beginning of the second stage of labor

A copy of the study information sheet and the consent form will then be given to the participant by the investigator (Appendix I and II). Subsequently, the participant will be granted time during which to reflect; if they still wish to participate, both the participant and the investigator will enter their forenames and surnames into the consent form, and then date and sign it. The form must be signed before any clinical or para-clinical examination is conducted.

2. Assessment visits

The pre-inclusion/inclusion visit will be supervised by the investigator and is scheduled to take place during the 2-month period preceding the inclusion visit. Prior to any research-related examination, the investigator will collect the participant's signed informed consent.

During these visits, no supplementary clinical examination or laboratory examination will be necessary, outside of those conducted in standard care.

E. Follow-up visits

There is no follow-up visits for the participant.

F. Participant-related constraint(s) and compensation

Patients included in the trial cannot participate in any other study until the last follow-up visit.

No financial compensation will be provided to the participants.

G. Biological sample collection

During the study, no biological sample collections will be necessary outside of those obtained in standard care.

MANAGEMENT OF ADVERSE EVENTS AND NEW INFORMATION

This section is described in Appendix 3.

ETHICAL AND REGULATORY CONSIDERATIONS

The sponsor and the investigator(s) undertake to ensure that this research is carried out in accordance with law no. 2012-300 of 5 March 2012 on research involving the human person, as well as in agreement with Good Clinical Practices (ICH version 4 of 9 November 2016 and the decision of 24 November 2006) and the Declaration of Helsinki (which can be found in full at <http://www.wma.net>).

The research will be conducted in accordance with this protocol. Except in emergency situations that require the implementation of specific therapeutic acts, the investigator(s) undertake(s) to respect the protocol in all points especially with regard to the collection of consent and notification and follow-up of serious adverse events.

Before initiating the study, the sponsor should authorizations from French:

- Ethic committee (CPP),
- Regulatory authority (ANSM),
- National Commission for Informatics and Liberties (CNIL).

In accordance with the provisions of the Public Health Code the CHU of Bordeaux, sponsor of this research, will take out a civil liability insurance contract with HDI Global SE for the entire duration of the research, guaranteeing its own civil liability as well as that of all participants (physicians or others involved in the research) (L. No°2004-806, Art L.1121-10 of the Public Health Code).

The data recorded during this research are the subject of computerized processing at Clinical Epidemiology Unit – Methodology Research Centre (Unité de Soutien Méthodologique à la Recherche Clinique et Epidémiologique du CHU de Bordeaux: USMR) - Bordeaux University Hospital in accordance with

- regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) and

- law n ° 78-17 known as "Informatique et Liberté" of January 6, 1978 relating to data processing, files and freedoms and the law n ° 2018-493 of June 20, 2018 relating to the protection of the personal data, modifying Law No. 78-17 of 6 January 1978 and Law No. 2004-801 of 6 August 2004 on the protection of individuals with regard to the processing of personal data.

This research will be registered in the European database EudraCT under number registration number and on the site <http://clinicaltrials.gov/>

After the research, the conservation of the collection of biological samples will be declared to the Minister in charge of research and to the director of the French Regional Health Agency (and submitted to the CPP for an opinion if there was a change of research purpose).

Changes to the protocol

Any substantial change, i.e. any change which is likely to have a significant impact on the safety of the subjects, the validity and results of the research, the quality and safety of the products tested, the interpretation of scientific documents that support the conduct of the research, or the way in which the research is conducted, will be submitted to the sponsor as a written amendment. The sponsor must then obtain, prior to implementation of the study, a favorable opinion from the CPP and, where applicable, authorization from the ANSM.

Non-substantial changes, i.e. those which have no significant impact on any aspect of the research, will be communicated to the CPP.

All changes will be validated by the sponsor and all stakeholders before submission to the CPP and, where applicable, the ANSM. This process may require a meeting between all committees formed for the purpose of the study.

All changes to the protocol must be made known to the investigators participating in the study.

Any modification to participant care, or to the associated benefits, risks and constraints of the research, will be detailed in a new study note. The information notice and consent form will also be revised accordingly, following the procedure detailed above.

III. Results and Analyze

STUDY SIZE

Efficacy of systematic MR is compared to standard care on the operative delivery rate for POP position. This proportion in standard group is estimated to 40%. We assume that the new strategy is relevant if it decreases this proportion by 1/3 to 28%. With a two-sided type I error rate of 5% and power of 90%, sample size is estimated to 652 patients. Taking into account 3% of potential missing data on operative delivery mode, even if very unlikely, the total sample size is increased to a total of 674 patients.

STATISTICAL ANALYSIS

A. Analyses strategy

The study data will be analyzed by a biostatistician at the MDMC (USMR, Bordeaux University Hospital).

An intention-to-treat analysis will be performed as the principal analysis, i.e. all randomized patients will be included in the analysis in the group in which they first were randomized and all their data will be used, regardless of any changes in treatment over the study duration, using the “missing = failure” strategy to replace missing data for primary criteria.

Then an “under treatment analysis” will be performed, in which participants will be included in the correct group based on the treatment they received.

Descriptive analyses will always be overall and by group.

Comparative analyses between groups will be performed systematically with adjustment for stratification factors of randomization (center).

All comparisons will be performed with a type I error of 5%.

B. Missing data

For each variable, the number of missing data will be described. The reason for being missing will be documented as much as possible in order to interpret the results.

For dates, a missing day will be imputed by the 15th, which corresponds to the middle of a month. A missing month will be imputed by 7 (July). Imputation of dates will permit to calculate time to event data. However, the consistency of an imputed date will have to be verified before the calculation of time to events.

Missing data for the primary criterion will be replaced by a failure of the diagnostic strategy (missing=failure analysis). Analyses of missing data's sensitivity will be analyzed (extreme case analyses, only on the available data, multiple imputation, etc.).

C. Descriptive statistical methods

Qualitative variables will be described by numbers and percentages.

Quantitative variables will be described by numbers, mean, standard deviation, 95% confidence interval of the mean, median, range, and interquartile range. We will attempt as far as possible to provide a graphic representation of the analyses.

Between groups differences will be described through relatives' risks and absolute differences, and their 95% confidence interval.

D. Calculation rules in the statistical analyses

Qualitative variables will be compared using the Chi-square test, the corrected Chi-square test, or the exact Fisher test according to the expected values under the hypothesis of independence. The conditions of validity of these models will be checked (log-linearity).

Quantitative variables will be compared using Student's t-test if the conditions of validity are respected (normal distribution, homogeneous variances). If the variances differ between the two groups, Student's t-test for unequal variances will be used. In the event of non-normal distribution, the Mann-Whitney-Wilcoxon test will be used. The

conditions of validity of this model will be checked (normality and homoscedasticity of residuals).

P value $<.05$ will be considered to be significant.

E. Software

Statistical analyses will be performed using SAS® software (version 9.4 or higher).

F. Analysis plan

A detailed analysis plan will be defined and validated by the scientific committee of the study.

1. Description of the inclusions and follow up

- Database assessment: number of captured forms in each table
- Number of included participants
- Number of participants included in the analyses and reasons of exclusion if needed
- Protocol deviations

Flow chart according CONSORT recommendations will be drawn.

2. Patients included in the analysis

Only patients presenting at least one of the following conditions can be excluded from the analysis:

- patients wrongly included because of unsigned consent;
- patients wrongly included because of major invalidity of eligibility criteria;
- patients who withdrew their informed consent.

The scientific committee will make the decision of exclusion after documentation of observations by the MDMC, blinded to the strategy group and to the patient's evolution after inclusion.

Except for these exclusions, patients who die are lost to follow-up or leave the study will all be included in the analysis.

3. Baseline characteristics

The participants will be described at baseline and during the follow-up according to the following variables:

- Demographics
- Maternal characteristics
- Pregnancy characteristics
- Labor characteristics
- Delivery characteristics
- Severe maternal morbidity
- Severe neonatal morbidity
- Deviations
- Deaths

4. Analysis of primary endpoints

The operative delivery rate between the experimental group and the control group will be compared with a Chi² test or with Fisher's exact test, according to the size of the expected values under the hypothesis of independence. The 95% confidence intervals (exact binomial distribution) in each group will be calculated. This is a superiority trial (bilateral test).

Logistic regression model will be used to adjust on stratification factor and other major confounding factors. Assumption of the models (log-linearity of the associations) will be systematically checked.

5. Analysis of secondary endpoints

The analysis of secondary endpoints will use the descriptive and comparative methods described in paragraph III.C.

The analysis plan does not include any intermediate statistical analysis.

A detailed analysis plan will be defined before data being locked and will have to be validated by the scientific committee of the study.

RIGHT OF ACCESS TO DATA AND SOURCE DOCUMENTS

A. Access to data

Agreeing to participate in this study implies that permission has been granted to the investigators to make documents and personal data available as necessary for monitoring, quality control and auditing, in accordance with the laws and regulations currently in force.

B. Source data

Source data refers to information contained in original documents, or in authenticated copies of such documents, relating to clinical examinations, observations or other activities conducted as part of the study that are necessary for reconstitution and evaluation of the research. Documents in which the source data are saved are the source documents.

Maternal and obstetric data will be collected prospectively every day and recorded in patients' medical files.

C. Data confidentiality

In accordance with legislative provisions currently in force, persons having direct access to source data will take all necessary precautions to ensure the confidentiality of information relating to investigational medicinal products, research, and participants,

especially in regard to identity and the results obtained. These persons as the investigators, are subject to the principles of professional secrecy.

During or at the end of the research, data collected and sent to the sponsor by the investigators (or any other specialized contributor) will be anonymized. The study data will never explicitly mention the names of the persons concerned or their addresses and will be fully anonymized, with each patient identified by (i) the first letter of her last name, (ii) the first letter of her first name, and (iii) an alphanumeric code. This identification indicator will appear on the patient's electronic record.

The sponsor will ensure that each participant has granted his/her written agreement for their data to be accessed, as necessary for quality control of the research.

DATA MANAGEMENT

This section is described in Appendix 4.

QUALITY CONTROL, DATA AND SAFETY MONITORING

A. Guidelines for collecting data

All informations required for the study must be recorded in an electronic CRF and an explanation must be provided for any missing data. The data must be collected as and when they are obtained and transcribed in a clear and legible way.

B. Quality control

A clinical researcher appointed by the sponsor will regularly visit the lead investigator of each center during implementation of the research, once or more during the research according to the recruitment progress, and again at the end of the study. During these visits, and in accordance with a risk-based monitoring plan (covering participants, logistics, research impact, and resources), the following aspects will be reviewed:

- informed consent process,

- compliance with the research protocol and the procedures defined therein,
- quality of the data collected in the CRF, in terms of accuracy, missing data, consistency of the data with the source documents (medical records, appointment books, originals copies of laboratory results, etc.).

All visits will be subject to a written monitoring report.

C. Audits and inspections

Individuals appointed by the sponsor, independent of those conducting the study, may carry out audits at any time to ensure the safety of the participants, and that their rights are being upheld, and to confirm compliance with applicable regulations and data reliability.

An inspection may also be undertaken by a competent authority (the ANSM in France and the EMA for a European study, for example).

An audit or inspection may occur at any stage of the research, from protocol development to the publication of results, and concern how the data are classified, used or produced as part of the project.

The investigators will comply with the sponsor's requirements regarding the audit and any inspections by the competent authority.

DATA HANDLING AND RECORD KEEPING

The following documents related to this research will be archived by the investigator in accordance with Good Clinical Practice guidelines

- For a period of 15 years following the end of the research
 - The protocol and any modifications thereof
 - CRF (copies)
 - Source records of participants who have signed a consent form
 - All other documents and correspondence related to the research

- For a period of 30 years following the end of the research
 - Original copies of the signed informed consent

All of the above-listed documents are the responsibility of the investigator during the archiving period.

No documents may be destroyed or removed without the agreement of the sponsor. At the end of the archiving period, the sponsor will be consulted regarding the destruction of certain documents. All data, documents and reports may be subject to audit or inspection.

FINAL REPORT

Within one year after the end of the study, a final report will be prepared and signed by the sponsor and the investigator. This report will remain at the disposal of the competent authority; the sponsor will transmit it to the CPP and, where applicable, the results of the research will be submitted to the ANSM in the form of a summary of the final report, again within one year after the end of the research.

RULES FOR PUBLICATION AND DISSEMINATION

A. Scientific communication

The data analysis conducted by the investigating centers will be carried out by USMR. The analysis will eventually inform a written report to be submitted to the sponsor, who will then forward it to the CPP and competent authority.

Prior consent of the coordinating investigator and, where appropriate, all committees that were established for the purposes of the study, will be obtained before written or oral communication of the results of the research.

The coordinating and principal investigators will make negative, inconclusive and positive research results available to the public.

The publication of the main study results must mention the name of the sponsor, all persons who helped with participant recruitment and follow-up, all methodologists, biostatisticians and data managers who contributed to the project, medical personnel

who facilitated participant safety analysis and members of the committee(s) constituted for the purposes of the study. International rules governing the writing and publication of research will be adhered to (the Uniform Requirements for Manuscripts Submitted to Biomedical Journals of the International Committee Of Medical Journal Editors, April 2010).

B. Communication of results to participants

In accordance with law no. 2002-303 dated 4th March, 2002, the participants will be informed on request of the overall results of the study.

C. Transfer of data

Data management will be conducted by Clinical Epidemiology Unit – Methodology Research Centre (USMR du CHU de Bordeaux :) - Bordeaux University Hospital. The conditions for transfer of all or part of the study database will be determined by the sponsor and subject to a written contract.

IV. Discussion

OCCIPUT POSTERIOR AND LITTERATURE

The OP is source of many complications, compared to the OA, in particular maternal and neonatal complications. Especially, OP delivery significantly increases the rate of operative delivery i.e. OVD and caesarean delivery, only 40% of women with OP had a spontaneous delivery (10,13,14,24,25).

Indeed, risk of OVD for primiparas patients with POP almost doubles according to Sizer et al. (24) : 24.4% vs 43.7% ($p < 0.001$), and Yancey et al. (26) : 24.9% vs 50.9% (Relative Risk (RR) at 2.0, CI 95% [1.5-2.7]). Fitzpatrick et al. found also significantly more OVD in woman with POP (29 % vs 7 % primiparas, $p < 0,001$ and 21 % vs 1 % multiparas, $p < 0,001$) (14). Furthermore, Fitzpatrick et al. found 26% of caesarean delivery in case of POP vs 9% in primiparas ($p < 0.001$), and 17% vs 4% in multiparas ($p < 0.001$) (14). Ponkey et al. found 37.7% of caesarean delivery in case of POP vs 6.6% in case of OA ($p < 0.001$) (13). The main indication of operative delivery was failure to advance after active pushing and dystocia (4,14).

Otherwise, operative delivery is associated with significant maternal and neonatal morbidity compared to spontaneous delivery (56). Several studies have compared the morbidity of OVD and spontaneous vaginal delivery. In the short term, OVD significantly increases the rate of third- and fourth-degree perineal tears (57–60), and seems to be associated with a higher risk of postpartum hemorrhage (61–63) and urinary retention (64).

Because of this association between POP and operative delivery with maternal and neonatal complications, operative delivery was selected as the primary outcome. Decrease the rate of operative delivery seems to be a public health issue. Maternal and neonatal morbidities will be reported as secondary outcomes. The feeling of MR by the patients has not been studied so far, in our study it will be assessed by a numeric rating scale at the end of the hospital stay.

Actually there is not specific recommendations by scholarly societies for management of the OP for lack of studies of high level of evidence. The review of the literature that we have done, shows different proposals for management of POP. However, the MR seems to be the more efficient and secure procedure. The MR is mentioned by to reduce a fail OVD in guidelines of French, American, British and Canadian societies (34,36,65–67).

Several preliminary studies have shown that MR could be an efficient procedure in management of the OP. Furthermore all studies show a significant decrease of the caesarean rate in case of success of RM or in the MR group (Table 3) (10,12,45,46,50,52).

Le Ray et al. (12) 2013 compared two French university hospitals, the operative delivery rate was significantly lower in the maternity performing systematic MR vs no MR (23.2% vs 38.7% for the other, adjusted OR 0.52, 95% CI 0.28–0.95). However, selection bias and residual confounding cannot be ruled out in this observational setting.

In a retrospective study involving 731 manual rotation attempts and 2527 expectant management and covering a period from 1976 to 2001, Shaffer et al. found a decrease in the use of caesarean section in the manual rotation group (adjusted OR 0.12 [0.09, 0.16]) persisting after adjustment to parity (52). The possible relationship between the age of the data and the use of manual rotation is not discussed in the article, so it is impossible to isolate the impact of the management changes of recent decades (antibiotic prophylaxis, prevention of postpartum hemorrhage, improvement of fetal surveillance) in improving obstetric outcomes.

Finally, in a prospective study including two consecutive groups of 30 and 31 patients, Reichman et al. evaluated the effect of digital rotation on prior variety placement and spontaneous delivery rate. The intervention increased the rate of spontaneous delivery by more than 50% (26.4% versus 77.4%, $p = 0.0001$)(10).

The 2017 French guidelines about normal delivery, says that OP expose to perineal complications and a higher OVD rate. The MR could reduce the OVD rate but there is no arguments to do it systematically. No more oxytocin and no extra ultra sound are recommended to manage OP (68). The 2018 French guidelines to perineal prevention and protection says that manual rotation of cephalic posterior positions to

the anterior during the second stage of labor may make it possible to reduce the risk of OVD, although no reduction in the risk of perineal injuries or obstetrical anal sphincter injury has been clearly demonstrated (30). To finish, the Canadian guidelines for OVD says manual rotation may be used alone or in conjunction with instrumental birth with little or no increased risk neither to the pregnant woman or to the fetus (49)

This potential efficacy of manual rotation has not been proved with a high level of evidence and is, therefore, rarely performed by obstetric gynecologists.

Currently, three randomized trials are ongoing (clinicaltrials.gov) (NCT02695238, NCT03009435). The POP-OUT trial in Australia which have the same primary outcome (operative delivery rate) but we must note differences in clinical practices between Australia (caesarean rate of 34%) and France that will prevent the generalization of the results to the French setting (47,53). Two monocentric trials are currently ongoing in France (RMOS in Angers, and PROPOP in Marseille) with limited potential for generalization (48).

We therefore propose to conduct a multicenter single (patient) blind randomized controlled trial with two parallel groups, to test the superiority of systematic MR over expectative management to decrease operative delivery rate of POP presentation.

Table 3 Studies about manual rotation (MR) and their impact on the caesarean rate [modified from Le Ray et al. 2011(9)]

| Author | Year/Country | Methods | Compare | Caesarean rate in case of success of MR or in MR group | Caesarean rate in case of failure of RM or in expectative |
|---------------|--------------------|---------------------------------|--------------------------|--|---|
| Haddad (45) | 1995/France | Retrospective cohort | Success vs failure of MR | 18.6 % | 87.5 % |
| Shaffer (50) | 2006/United States | Retrospective cohort | Success vs failure of MR | 2.1 % | 34.3 % |
| Le Ray (46) | 2007/France | Retrospective case-control | Success vs failure of MR | 3.8 % | 58.8 % |
| Reichman (10) | 2008/Israel | Prospective before-after | MR vs expectative | 0 % | 23.3 % |
| Shaffer (52) | 2010/United States | Retrospective cohort | MR vs expectative | 8.6 % | 41.4 % |
| Le Ray (12) | 2013/France | Prospective exposed-non exposed | MR vs expectative | 8.2% | 9.9% |

Source : Le Ray C, Goffinet F. Manual rotation of occiput posterior presentation. *Gynécol Obstét Fertil.* 2011;39(10):575–578. doi: 10.1016/j.gyobfe.2011.08.03

STRENGTHS AND LIMITATIONS

Our study has a number of strengths. Randomized Controlled Trials are less susceptible to selection bias than other cohort designs. It uses a multicenter design because it requires a large number of participants to ensure high external validity of the results. All of the centers in the trial have shown the ability to recruit large cohorts over several months, having recently participated in various randomized controlled trials regarding perinatal issues and to recruit large sample size cohorts during several months: DAME (69), TRACOR (55), INDAO (70), SAFE21 (71) as well as TRAAP1 (54) and ongoing TRAAP2 both for which the main investigator is the current head of the Obstetrics Department of the study sponsor (CHU Bordeaux). All these trials have been published in very high-ranking journal such as New England Journal of Medicine (TRAAP1), JAMA (INDAO and SAFE21), and Lancet (DAME).

Secondly, as the primary outcome is the mode of delivery which occurs within a few hours of randomization, there is almost no opportunity for bias due to loss of following-up or measurement error for the primary outcome. We choose 3% of potential missing data on operative delivery mode, even if very unlikely.

To improve our recruitment and avoid a MR on an OA, we decided that every woman with suspicion of OP during labor or in the presence of caput succedaneum or asynclitism, will have a suprapubic transabdominal ultrasound. Studies have documented rates of inaccurate diagnosis for vaginal examinations performed in the fetal occiput position of 12–39%, when ultrasound was used as standard (3,7,18,72,73). Chou et al. (74) are the only authors to compare ultrasound and vaginal examination accuracy rates based on the actual occiput position (92.0% vs. 71.6%, respectively $p < 0.02$). In their study, clinical evaluations proved inaccurate in cases with an occiput posterior or transverse position, in the presence of caput succedaneum or asynclitism, and when medical intervention was likely to be required. Ultrasound is a useful tool to assess occiput position, in addition to a vaginal examination, especially in the presence of a caput succedaneum or asynclitism (3,7,18,72,73). However, to not increase our research budget, only maternities with more than 1,500 deliveries could participate. In France, according to Haute Autorité de Santé (HAS) recommendations (and a decree dated 25th April 2000), maternities wards with > 1,500 deliveries/year must have an ultrasound scanner in their labor wards (75).

Individual randomization requires a smaller cohort than does cluster randomization, and has clearly shown feasibility in other obstetrics studies assessing treatments or medical strategies in emergency situations [TRAAP (54,76), TRAAP2 (77) and TUB trial (78)]; in particular, computers are present in labor rooms. The allocation will be stratified by center and parity to avoid selection bias. OP is more significantly more common in primiparas women (1,13–16). Furthermore, the operative delivery rate is significantly lower for multiparas women (79).

In order to reduce the risk of randomizing an ineligible participant, randomization will occur immediately before the intervention or sham procedure is to be performed. An example of a participant becoming ineligible would be if the fetus rotated from the occiput posterior to occiput transverse position.

Blinding may be difficult in the case of procedural interventions. In our trial, MR could be considered like an invasive intervention for patients. To do a double blind, we need that another practitioner, who does not follow the labor, perform the MR and does not do delivery. In this period of obstetric violence, it does not seem ethical to propose that. Furthermore, it will be difficult mostly during night to find a different practitioner, who will not take part of patient care. Therefore, we propose a single (patient) blinded. A sham procedure was chosen as a comparator to reduce the risk of performance bias. However, the woman will do not have the possibility to know if a manual rotation is performed before the delivery, because if they are in the control arm they have the same apparent vaginal examination as the intervention arm but no rotational force will be applied.

The efficacy of procedural interventions may depend on the experience and training of individual operators. To limit this bias, we have decided operators will declare they have done 20 manual rotations. We have also decided operators will do not use digital rotation, and will choose between SOGCs method and Tarniers method. Several attempts can be made if necessary, but it seems that a maximum of three MR can be attempted. Indeed, beyond this number, the chances of success would be zero (46). According to Tarnier and Chantreuil, MR can be attempted as soon as 7 cm of dilatation in case of stagnation or abnormal fetal heart rate in order to accelerate the duration of the work. Le Ray et al. in a case control study found that attempted rotation

before full dilatation tripled the risk of failure in comparison with rotation at full dilatation (adjusted odds ratio (OR) 3.4, 95% CI 1.3-8.6)(46). We decided that the procedure will be do at full dilation, it seems more effective at full dilatation and more secure (46).

We have limited the duration of study for patients at 15 days, even if the World Health Organization defines the maternal morbidity like the events until 42 days after delivery. This to limit budget overruns that entails a long follow up.

Finally, due to the ethics of consent in labor, consent will be sometimes obtained when it is unknown if the fetus will be in the occiput posterior position in the second stage of labor, which is an eligibility criterion.

However, with this large multicenter randomized trial, we will be able to realize a high level of evidence trial.

EXPECTED IMPACT

If our study proves that the manual rotation is significantly effective in reducing operative delivery rates, its routine use should reduce the incidence of operative delivery and associated maternal and neonatal morbidity. Our conclusion will be with a high level of evidence. Manual rotation is a simple, secure and effective method with a success rate of almost 90%. Its will be accessible to all practitioners and even in developing country.

If our study proves that the manual rotation is unsatisfactory to reduce OVD, this study will prevented the widespread use of an ineffective procedure associated with potential adverse effects in a routine practice.

V. Conclusion

In early second stage of labor, there are 10 to 20% fetuses still in OP, it is persistent occiput posterior. Nonetheless, approximately 5-8% remain in OP at delivery. The POP is associated to an increase of maternal and neonatal complications especially higher rate of operative delivery and its associated complications.

The management of POP lack of specific recommendations by scholarly societies, because of the absence of studies with a high level of evidence.

Many procedure have been study, especially maternal posturing and instrumental rotation. However, the review of literature shows that the manual rotation, described since 1888, is a secure and a potential effective procedure. According to studies, risks associated to manual rotation are thus lower than potential benefit associated to prevention of operative delivery.

Numerous studies (retrospective and observational) have shown that using systematic manual rotation versus expectant in case of POP is associated with a significantly decrease of operative delivery rates. However, there are currently no complete studies with strong methodology whose conclusions are applicable in France.

It is in this context that we decided to write this protocol. This protocol is the first step to conduct a large multicenter single blinded controlled trial. The main objective is to compare the efficacy of systematic manual rotation at full dilatation and standard care alone, on the operative delivery rate for patients with persistent occiput posterior position.

The project will be respond to call for tender of Programme Hospitalier de Recherche Clinique National in 2020 (PHRC-N).

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Appendices

Appendix 1 Summary Research (From English to French)

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|---------------------------------------|--|
| PROMOTEUR | Centre Hospitalier Universitaire (CHU) de Bordeaux |
| INVESTIGATEUR COORDINATEUR | Dr SARRAU Marie Service de Gynécologie Obstétrique CHU de Bordeaux Place Amélie Raba Léon 33 000 Bordeaux Tel: +33 5 56 79 55 79 - Fax: +33 5 56 79 56 76 Email: marie.sarrau@chu-bordeaux.fr |
| TITRE | Rotation manuelle versus expectative en cas de variétés postérieures persistantes pour diminuer les accouchements opératoires. Etude MARO-POP: étude multicentrique en simple aveugle randomisée contrôlée |
| RATIONNEL | A la seconde phase du travail, 15% des fœtus sont en variétés postérieures cela correspond à la variété postérieure persistante, et 5-8% seront en VP à l'expulsion. Les VP augmentent les risques d'accouchement opératoire et donc des complications maternelles et néonatales qui y sont associés. |
| OBJECTIFS | <p>Objectif principal</p> <p>Comparer l'efficacité d'une rotation manuelle en systématique à dilatation complète versus l'expectative (soins standards seuls), sur le taux d'accouchement opératoire des patientes avec une variété postérieure persistante</p> <p>Objectifs secondaires</p> <p>Comparer l'efficacité d'une rotation manuelle en systématique à dilatation complète versus l'expectative (soins standards seuls), des patientes avec une variété postérieure persistante sur les paramètres suivant:</p> <ul style="list-style-type: none"> - Morbidité maternelle sévère ; - Morbidité néonatale sévère; - Position de l'occiput fœtal à l'expulsion; - Incidence de l'hémorragie de postpartum (> 500 ml); - Incidence de l'épisiotomie; - Incidence de l'échec d'extractions instrumentales; - Incidence de la dystocie des épaules; - Incidence de la procidence du cordon; - Durée de la seconde phase du travail; - Durée maternelle et néonatale des séjours hospitaliers; |

| | |
|------------------------------------|--|
| | <ul style="list-style-type: none"> - Satisfaction maternelle à la fin du séjour; |
| <p>CRITERES DE JUGEMENT</p> | <p><i>Critères de jugement principal</i></p> <p>Le critère de jugement principal de cette étude est le taux d'accouchement opératoire (défini comme la proportion d'extraction instrumentale par ventouse, forceps et spatules, et/ou la proportion de césarienne).</p> <p><i>Critères de jugement secondaires</i></p> <p>La proportion de morbidité maternelle à court terme, mesurée par un critère composite défini par la présence d'au moins un des critères suivant:</p> <ul style="list-style-type: none"> - Lésions sévères du périnée (Troisième ou quatrième degré) - Thrombus vaginal puerpéral; - Lésions cervicales; - Une incision utérine étendue lors d'une césarienne; - Une hémorragie sévère du post-partum ($\geq 1,000$ ml); - L'utilisation de thérapie de seconde ligne lors d'une hémorragie du post-partum; - Une infection maternelle durant le séjour hospitalier; - Un événement thromboembolique durant le séjour hospitalier; - Une admission en unité de soins intensifs; - Un décès maternel durant le séjour hospitalier. <p>La proportion de morbidité néonatale à court terme, mesurée par un critère composite défini par la présence d'au moins un des critères suivant:</p> <ul style="list-style-type: none"> - Un score Apgar à 5 minutes inférieur à 7; - Un pH artériel ombilical inférieur à 7; - La nécessité d'une réanimation ou d'une intubation à la naissance; - Un traumatisme néonatal; - Une hémorragie intraventriculaire au-dessus du grade 2 durant le séjour hospitalier ; - Un séjour en néonatalogie supérieur à 24 heures - Un sepsis néonatale, une épilepsie, un décès durant le séjour hospitalier; <p>La proportion des variétés de présentation à l'expulsion;</p> <p>La proportion de dystocie des épaules;</p> <p>La proportion de procidence du cordon;</p> <p>La durée moyenne de la seconde phase du travail (entre la dilatation complète et l'expulsion);</p> |

| | |
|----------------------------------|---|
| | <p>La proportion d'échec d'extraction instrumentale;</p> <p>La proportion d'hémorragie du post-partum > 500 ml;</p> <p>La proportion d'épisiotomie;</p> <p>La durée moyenne du séjour maternel;</p> <p>La durée moyenne du séjour du nouveau-né;</p> <p>La satisfaction moyenne des mères, obtenue grâce à une échelle numérique à la fin du séjour hospitalier;</p> |
| DESIGN DE L'ETUDE | Etude multicentrique de supériorité, en simple aveugle (patient) randomisé en deux groupes parallèles dont un contrôle. |
| CRITERES D'INCLUSION | <ul style="list-style-type: none"> - Age ≥ 18 ans; - ≥ 37 semaines d'aménorrhée; - Grossesse singleton; - Variétés postérieures confirmées à l'échographie; - Seconde phase du travail; - Accouchement par voie basse prévue; - Patiente bénéficiaire ou affilié au système de santé; - Consentement signé par le participant et l'investigateur principal ou son représentant avant toute intervention prévu pour la recherche. |
| CRITERES DE NON INCLUSION | <ul style="list-style-type: none"> - Pathologie fœtale congénitale connu ou suspicion d'anomalies de la coagulation fœtale; - Mort fœtale in utéro; - Présentation de la face ou du front ; - Anomalies du rythme cardiaque fœtal avec risque d'acidose nécessitant une césarienne ou des examens de seconde ligne; - Chorioamniotite; - Température supérieure à 38.5 °C durant la première phase du travail; - Hémorragie génitale durant la première phase du travail; - Mauvaise compréhension de la langue française selon l'investigateur principal ou son représentant; - Patiente placé sous tutelle ou curatelle; - Patiente participante à une autre étude excluant la participation à une autre étude; |

| | |
|--------------------------------------|--|
| | <ul style="list-style-type: none"> - Patiente avec un état physique ou psychologique pouvant compromettre la compliance à l'étude selon l'investigateur principal ou son représentant. |
| INTERVENTION ET BRAS CONTROLE | <p>Bras interventionnel Rotation manuelle à dilatation complète</p> <p>Bras contrôle Procédure « placebo » identique mais sans application d'une force rotationnel (c'est-à-dire un examen vaginal prolongé)</p> |
| TAILLE DE L'ETUDE | <p>Selon les résultats de l'étude Le Ray et al. en 2013, et pour montrer une réduction relative d'au moins 30% de l'incidence du critère de jugement principal, de 40 à 25 % ou moins dans le bras expérimental ($\alpha = 0.05$, $1-\beta = 0.90$, et un test bilatéral), l'étude requière 326 patientes par groupe. Nous prévoyons d'inclure au moins 674 patientes en prenant en compte un taux de 3% de perdu de vue.</p> |
| DUREE DE L'ETUDE | <p>Durée de la période de recrutement: 24 mois Durée de participation de chaque participant: 15 jours Durée totale de la recherche: 24 mois</p> |
| ANALYSES STATISTIQUES | <p>Les variables qualitatives seront décrites avec des fréquences et des proportions. Pour les résultats impliquant une variable qualitative, un intervalle de confiance bilatéral à 95% sera estimé avec la distribution binomiale exacte. Les variables quantitatives seront décrites avec les fréquences, la moyenne, l'écart type, la médiane, le minimum, le maximum, les 1er et 3ème quartiles. Pour les résultats impliquant une variable quantitative, un intervalle de confiance bilatéral à 95% sera estimé.</p> <p>Les analyses seront effectuées selon le principe de l'intention de traiter. Ceci est un essai de supériorité (test bilatéral). Le taux d'accouchement opératoire entre le groupe expérimental et le groupe témoin sera comparé à un test de Chi² ou au test exact de Fisher, en fonction de la taille des valeurs attendues dans l'hypothèse de l'indépendance. Les intervalles de confiance à 95% (distribution binomiale exacte) de chaque groupe seront calculés. Le modèle de régression logistique à effets mixtes sera utilisé pour ajuster le facteur de stratification (effet aléatoire sur les centres et la parité) et les autres facteurs de confusion principaux énumérés dans les critères de jugement secondaires. L'hypothèse des modèles (log-linéarité des associations) sera systématiquement vérifiée.</p> |
| IMPACTS ATTENDUS | <p>Si la rotation manuelle est efficace pour réduire les taux d'accouchement opératoire, son utilisation systématique devrait réduire l'incidence de l'accouchement opératoire et de la morbidité maternelle et néonatale associée.</p> <p>Si la rotation manuelle s'avère non efficace, cette étude empêchera la généralisation d'une procédure inefficace associée à des effets indésirables potentiels dans une pratique courante.</p> |

Appendix 2 Information notice and consent form (French)

NOTICE D'INFORMATION

Rotation manuelle à dilatation complète des variétés postérieures persistantes :

Étude MARO-POP multicentrique simple aveugle contrôlée randomisée

Promoteur de la recherche : **CHU de Bordeaux – code promoteur CHUBX 20XX/XX**

Investigateur coordonnateur : **Docteur Marie SARRAU**

Madame,

Ce document est destiné à vous fournir des informations sur l'étude à laquelle nous vous proposons de participer. Avant de donner votre accord, il est important que vous le lisiez attentivement. Le médecin qui vous recevra est à votre disposition pour répondre à toutes vos questions.

Pourquoi cette recherche ?

Il est prévu que vous accouchiez par les voies naturelles. Cependant, dans 10-15% des cas environ à dilatation complète, la position de la tête de votre enfant est en variété postérieure soit « les yeux tournés vers le ciel ». Cette position expose à un risque de césarienne et d'extractions instrumentales plus importantes, ainsi que les complications maternelles et fœtales qui en découlent, notamment des lésions périnéales sévères. Actuellement, la prise en charge des variétés postérieures n'est pas codifiée.

Quel est l'objectif de cette recherche ?

Le but de l'étude à laquelle nous vous proposons de participer est de déterminer si la rotation manuelle permettrait de diminuer le taux d'accouchement opérationnel, c'est-à-dire soit une césarienne soit un accouchement voie basse avec l'aide d'instruments, et ainsi diminuer les complications liées à la variété postérieure. La rotation manuelle est décrite depuis 1888, et est réalisée de façon commune dans de nombreuses maternités depuis plusieurs années. C'est une manœuvre réalisée à la main par un opérateur expérimenté, qui consiste à tourner la tête de votre enfant pour que « les yeux soient tournés vers le sol ». Les risques pour vous de cette manœuvre sont principalement les lésions cervicales (2-3% contre 1% sans rotation manuelle). Des anomalies du rythme cardiaque fœtal peuvent apparaître ou être aggravées durant la rotation dans 10-20% des cas, mais sans conséquence sur l'état néonatal.

Comment va se dérouler cette recherche ?

674 patientes sont attendues dans l'étude MARO-POP. Si vous acceptez d'y participer, votre participation durera le temps de votre hospitalisation.

L'étude MARO-POP est un essai randomisé, c'est-à-dire que la prise en charge que vous recevrez résultera d'un tirage au sort. Deux groupes de femmes seront évalués en fonction du tirage au sort : soit la rotation manuelle en complément de la prise en charge habituelle, soit la prise en charge habituelle avec une fausse rotation manuelle. Vous ne saurez pas dans quel groupe vous avez été tiré.

La prise en charge de votre accouchement, à l'exception de la rotation manuelle, ne sera en rien modifiée par votre participation à cette étude. Lorsque vous aurez lu cette note d'information et obtenu les réponses aux questions que vous vous posez en interrogeant le médecin, il vous sera proposé, si vous en êtes d'accord, de donner votre consentement écrit en signant le formulaire préparé à cet effet.

Que vous demandera-t-on ?

Si vous êtes d'accord pour participer à cette étude, après vérification à l'échographie de la position de la tête de votre enfant, une randomisation sera effectuée (cf. supra). Vous ne saurez pas le résultat de la randomisation, donc vous ne serez pas informé si la rotation manuelle sera faite. Dans tous les cas, vous serez installée en position gynécologique et un toucher vaginal sera réalisé. Il vous sera demandé de réaliser quelques efforts de poussée. Les informations concernant votre accouchement seront alors collectées en salle de naissance. Enfin, à la fin de votre séjour, votre satisfaction sera évaluée sur une échelle de 1 à 10.

Quels sont vos droits ?

Votre médecin doit vous fournir toutes les explications nécessaires concernant cette recherche. Si vous souhaitez vous en retirer à quelque moment que ce soit, et quel que soit le motif, vous continuerez à bénéficier du suivi médical et cela n'affectera en rien votre surveillance future.

Dans le cadre de la recherche à laquelle le CHU de Bordeaux vous propose de participer, un traitement informatique de vos données personnelles va être mis en œuvre pour permettre d'analyser les résultats de la recherche au regard de l'objectif de cette dernière qui vous a été présenté. A cette fin, les données médicales vous concernant seront transmises au promoteur de la recherche ou aux personnes ou sociétés agissant pour son compte, en France ou à l'étranger. Ces données seront identifiées par un code et/ou vos initiales. Ces données

pourront également, dans des conditions assurant leur confidentialité, être transmises aux autorités de santé françaises ou étrangères et à d'autres entités du CHU de Bordeaux. Vous avez le droit de vous y opposer.

Conformément aux dispositions de la loi relative à l'informatique, aux fichiers et aux libertés et au Règlement Européens sur la Protection des Données (RGPS), vous disposez à tout moment d'un droit d'accès et de rectification des données informatisées vous concernant. Vous disposez également d'un droit d'opposition à la transmission des données couvertes par le secret professionnel susceptibles d'être utilisées dans le cadre de cette recherche et d'être traitées. Vous pouvez également accéder directement ou par l'intermédiaire du médecin de votre choix à l'ensemble de vos données médicales en application des dispositions de l'article L1111-7 du code de la santé publique. Ces droits s'exercent auprès de l'investigateur qui vous suit dans le cadre de la recherche et qui connaît votre identité.

Conformément à la loi n°2012-300 du 5 mars 2012 relative aux recherches impliquant la personne humaine :

- cette recherche a obtenu un avis favorable d'un Comité de Protection des Personnes, l'autorisation de l'Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM) et l'autorisation de la CNIL,
- le promoteur de cette recherche, CHU de Bordeaux (12, rue Dubernat – 33404 Talence Cedex), a souscrit une assurance de responsabilité civile auprès de xxx
- les personnes ayant subi un préjudice après participation à une recherche clinique peuvent faire valoir leurs droits auprès des commissions régionales de conciliation et d'indemnisation des accidents médicaux,
- lorsque cette recherche sera terminée, vous serez tenu(e) informé(e) personnellement des résultats globaux par votre investigateur dès que ceux-ci seront disponibles, si vous le souhaitez

Après avoir lu cette note d'information, n'hésitez pas à poser à votre médecin toutes les questions que vous désirez. Après un délai de réflexion, si vous acceptez de participer à cette recherche, vous devez compléter et signer le formulaire de consentement de participation. Un exemplaire du document complet vous sera remis.

Nous vous remercions de votre participation.

FORMULAIRE DE CONSENTEMENT ECLAIRE

Rotation manuelle versus expectative en cas des variétés postérieures persistantes à dilatation complète:

Étude MARO-POP multicentrique simple aveugle contrôlée randomisée

Promoteur de la recherche : **CHU de Bordeaux – code promoteur CHUBX 20XX/XX**

Investigateur coordonnateur : **Docteur Marie SARRAU**

Je soussignée (*Nom, prénom*) certifie avoir lu et compris la note d'information qui m'a été remise.

J'ai eu la possibilité de poser toutes les questions que je souhaitais au Pr/Dr (*Nom, prénom*) qui m'a expliqué la nature, les objectifs, les risques potentiels et les contraintes liées à ma participation à cette recherche.

Je connais la possibilité qui m'est réservée d'interrompre ma participation à cette recherche à tout moment sans avoir à justifier ma décision et je ferai mon possible pour en informer le médecin qui me suit dans la recherche. Cela ne remettra naturellement pas en cause la qualité des soins ultérieurs.

J'ai eu l'assurance que les décisions qui s'imposent pour ma santé seront prises à tout moment, conformément à l'état actuel des connaissances médicales.

J'ai pris connaissance que cette recherche a reçu l'avis favorable du Comité de Protection des Personnes, l'autorisation de l'ANSM et l'autorisation de la Commission Nationale Informatique et Libertés (CNIL).

Le promoteur de la recherche (CHU de Bordeaux, 12 rue Dubernat 33404 Talence Cedex) a souscrit une assurance de responsabilité civile en cas de préjudice auprès de la société xxxx.

J'accepte que les personnes qui collaborent à cette recherche ou qui sont mandatées par le promoteur, ainsi qu'éventuellement le représentant des Autorités de Santé, aient accès à l'information dans le respect le plus strict de la confidentialité.

J'accepte que les données enregistrées à l'occasion de cette recherche, puissent faire l'objet d'un traitement informatisé sous la responsabilité du promoteur.

J'ai bien noté que, conformément aux dispositions de la loi relative à l'informatique, aux fichiers et aux libertés, je dispose d'un droit d'accès et de rectification. Je dispose également d'un droit d'opposition à la transmission des données couvertes par le secret professionnel susceptibles d'être utilisées dans le cadre de cette recherche et d'être traitées. Ces droits s'exercent auprès du médecin qui me suit dans le cadre de cette recherche et qui connaît mon identité.

Mon consentement ne décharge en rien l'investigateur et le promoteur de la recherche de leurs responsabilités à mon égard. Je conserve tous les droits garantis par la loi.

Les résultats globaux de la recherche me seront communiqués directement, si je le souhaite, conformément à la loi du 4 mars 2002 relative aux droits des malades et à la qualité du système de santé.

Ayant disposé d'un temps de réflexion suffisant avant de prendre ma décision, j'accepte librement et volontairement de participer à la recherche MARO-POP.

Je pourrai à tout moment demander des informations complémentaires au médecin qui m'a proposé de participer à cette recherche, n° Téléphone :

Fait à

Le

Signature de la participante :

Fait à

le

Signature de l'investigateur :

Appendix 3 Information notice and consent form (translated in English from French)

Letter of Information for an adult participating in the clinical trial entitled

**MANual ROTation vs expectative in Persistent Occiput Posterior position:
The MARO-POP multicenter open-label randomized controlled trial**

Sponsor: **Bordeaux University Hospital**

Madam,

This document will give you with all the informations you need about the study we are carrying out and you could participate/join in. Before giving your consent, it is important that you read it carefully. The midwife or doctor you will see is available to answer all your questions.

It is expected that you will give birth vaginally. However, in 10-15% of the cases at full dilatation, your fetus will be in persistent occiput posterior position. This position decrease the risk of operative delivery and associated maternal and neonatal complication especially perineal tears.

Actually, there is no specific management of persistent occiput posterior position.

STUDY OBJECTIVE

The aim of the study that we are asking you to participate is to determine if a systematic manual rotation in case of persistent occiput posterior may decrease operative delivery rate. Manual rotation is describe since 1888, and it is realized in many maternities. Manual rotation will be realized by an experimented operator, it consist with operator hands to turn fetus in occiput anterior. The risk of manual rotation are cervical laceration (2-3% versus 1% without manual rotation). There is also a risk of developing a pathological cardiotocogram or aggravating already present abnormalities about 10-20%, but without consequences on neonatal state.

STUDY PROCEDURES

MARO-POP study will last for 24 months. If you agree to participate, your own participation will be our hospital stay.

The MARO-POP study is a randomized trial, that is to say, the management you receive for this situation will depend in a random drawing (like flipping a coin, but more complicated). Two groups of women will be studied, one is managed with manual rotation in addition to standard care or a standard care alone with a sham procedure.

The management of your delivery, except for this one procedure, will not be modified by your participation in this study.

You will be given information about this study at your appointment at the maternity ward at the end of pregnancy and when you come into the delivery room before delivery. Following this consultation and on reflection, if you want to participate in this research, you will be asked to sign the consent form and give it to the doctor or midwife who will be following you for this study.

If you agree to participate in this study and if your fetus is an occiput posterior position, a manual rotation will be realized only according to the randomization (see above) and information about your delivery will be collected while you are in the delivery room.

Finally, at the end of your hospital stay we will be asking your satisfaction rate with a numeric scale.

WHAT ARE YOUR RIGHTS?

Your doctor must provide you with all the necessary explanations concerning this research. If you wish to withdraw from it at any time, and for whatever reason, you will continue to benefit from medical follow-up and this will not affect your future monitoring.

As part of the research that the CHU de Bordeaux invites you to participate, a computer processing of your personal data will be implemented to allow analysis of the results of the research with regard to the objective of the latter which you have been presented. For this purpose, the medical data concerning you will be transmitted to the sponsor of the research or to the persons or companies acting on his behalf, in France or abroad. These data will be identified by a code and / or your initials. These data may also, under conditions ensure their confidentiality, be transmitted to French or foreign health authorities and other entities of the Bordeaux University Hospital. You have the right to object.

In accordance with the provisions of the European Data Protection Act, the European Data Protection Act (RGPS) and the Data Protection Act, you have the right to access and rectify data concerning you at any time. You also have the right to oppose the transmission of data covered by professional secrecy that may be used in the context of this research and to be processed. You can also access directly or through the doctor of your choice to all of your medical data in application of the provisions of Article L1111-7 of the Public Health Code.

These rights are exercised with the investigator who follows you as part of the research and who knows your identity.

In accordance with the law n ° 2012-300 of March 5th, 2012 relating to research involving the human person:

- this research has obtained a favorable opinion from a Committee for the Protection of Persons, the authorization of the National Agency for the Safety of Medicines and Health Products (ANSM) and the authorization of the CNIL,
- the sponsor of this research, Bordeaux University Hospital (12, rue Dubernat - 33404 Talence Cedex), has taken out civil liability insurance with HDI Global SE,
- people who have suffered harm after participating in a clinical research can assert their rights with the regional commissions for conciliation and compensation of medical accidents,
- When this research is completed, you will be personally informed of the overall results by your investigator as soon as they are available, if you wish

If you wish, you will be informed of the overall results of this study by the doctor or the midwife.

Your participation in this research is your own free decision. Moreover, you may exercise your right to withdraw from this study at any moment. When you have read this information form and your questions answered by the doctor or midwife, you will be asked, if you agree, to give your written consent by signing the form.

You can talk to Dr. (name of the principal investigator at the center). (Tel)
for any further information.

INFORMED CONSENT FORM (translated from French)

I, the undersigned

Ms., Mrs., Miss (*cross out the inapplicable titles*) (*last name, first name*)..... freely and voluntarily agree to participate in the research study named

Manual Rotation vs expectative in Persistent Occiput Posterior position:

The MARO-POP multicenter open-label randomized controlled trial

which Bordeaux University Hospital is sponsoring, and which was proposed to me by (last name, first name, telephone number),
midwife OR physician (*cross out the inapplicable term*).

I agree that:

- The midwife or doctor informed me and answered all my questions told me. My participation is voluntary and I may exercise my right to withdraw at any time,
- Before participating in this research, I received a medical examination, the results of which were communicated to me,
- I can communicate through the doctor during or after the end of this study about information he has about my health,
- I understand from the information form given to me that in order to participate in this research I must be covered by or eligible for social security health insurance. I confirm that I am so covered,
- My consent does not discharge the physician or Sponsor from any of their responsibility or liability and I keep all my rights guaranteed by law.

In accordance with the CNIL (law relating to data, files, and privacy) and GPDR, I have a right of access to my files and a right to have them corrected. I also have the right to object to the transmission of data covered by professional privilege that might be used and treated as part of this study.

Bordeaux University Hospital, which is organizing this research as its Sponsor, has taken out insurance in accordance with the law, to guarantee its own liability and that of anyone involved in this study, with the HDI Global SE company (number XXXX), an insurance broker.

I will receive a copy of the letter of Information and the consent form after I sign it.

| | |
|-----------|-----------|
| Signed in | |
| Date: | Signature |

| | |
|---|-----------|
| Signature of the midwife or physician who attests that (s)he had fully explained to the signer the aim, the procedures as well as the potential risks of this research. | |
| Date: | Signature |

Appendix 4 Management of adverse events and new information

A. Definitions

- **Adverse Event** (AE) (Article R1123-46 of the Public Health Code)

Any harmful event experienced by a human participant in a research study, whether or not the event is related to the research or product to which the research pertains.

- **Adverse reaction** (AR) (Article R1123-46 of the Public Health Code)

Any AE experienced by a human participant in a research study that is related to the research or product to which the research pertains.

- **Serious adverse reaction or event** (SAE) (Article R1123-46 of the Public Health Code and guideline ICH-E2B)

Any adverse reaction or event that:

- results in death,
- endangers the life of the participant,
- requires hospitalization or prolongation of hospitalization,
- causes injury or significant or long-term disability,
- results in an abnormality or congenital malformation,
- can be considered medically serious,
- and with respect to a drug, occurs regardless of the dose administered.

The expression "life-threatening" is reserved for an immediate threat to life at the time of the AE.

- **Unexpected adverse reaction** (Article R1123-46 of the Public Health Code)

An unexpected adverse reaction is any adverse reaction that, in nature, severity, or development, is inconsistent with the information regarding the products, procedures, and methods used in the research.

- **New fact** (Article R1123-46 of the Public Health Code)

Any new data that may lead to reassessment of the benefit-risk ratio of the research or product being researched, changes in the use of the product, the conduct of the

research or the documents relating to it, or data that may lead to the suspension, discontinuation or modification of the research protocol or similar research.

B. Description of expected serious adverse events

The serious maternal AE anticipated during this study are:

- Third or fourth-degree perineal laceration
- Postpartum hemorrhage or second-line therapy: uterine compression suture, uterine artery embolization, and peripartum hysterectomy for management of massive primary postpartum hemorrhage after failure of uterine massage and uterotonic agents to stop bleeding
- Uterine rupture
- Infection: endometritis, episiotomy infection, or wound infection requiring surgery
- Thromboembolic events
- Amniotic fluid embolism
- Maternal death

The serious neonatal AE expected within the framework of the protocol are:

- Poor adaptation to the extra-uterine life (5-min Apgar score less than 7)
- Acidosis (arterial pH \leq 7.00)
- Meconium inhalation syndrome
- Scalp hematoma
- Neonatal trauma: fracture of the clavicle, fracture of a long bone, brachial plexus injury, cephalohematoma, skull fracture, head laceration, facial nerve palsy and hematoma or intracranial bleed
- Intraventricular hemorrhage
- Sepsis
- Seizure

- Neonatal death

Any SAE that is not on the list of expected events, or in the latest version of the Registration Document, is considered unexpected.

C. Conduct to be maintained by the investigator in the event of an adverse event, or new information

1. Collection of adverse event data

Upon signing the consent form, the investigator becomes responsible for collecting all AE data. He/she will report all SAE and non-SAE (biological and clinical) that occur between the signing of the consent form and the end of the patient's participation, or the end of the AE data collection period, in the CRF.

AE will be assessed at each visit during the study by questionnaire, and during clinical examination of the patient.

2. Notification of serious adverse events, adverse events of interest and new facts

The investigator will evaluate each AE in terms of its seriousness.

The investigator will notify the sponsor without delay, on the day on which he/she becomes aware, of any SAE or AE of interest, if it occurs:

- after the consent form is signed, or
- during the planned follow-up period

If an investigator becomes aware of an SAE, that he/she suspects is causally related to the research, occurring after the end of the clinical trial in a participant he/she has treated, he/she will inform the sponsor without delay.

Any exception to notification without delay must be justified.

The investigator should document the event as thoroughly as possible, and provide a medical diagnosis as appropriate. The investigator must ensure that all relevant follow-up information is communicated to the sponsor immediately.

The investigator must submit, in addition to the SAE notification form, copies of laboratory results or reports of examinations or hospitalizations relating to the SAE, including any relevant adverse findings and with full anonymization of all documentation, and enter the patient's research number and code.

The investigator must follow-up with any patient who presented with an SAE until its resolution, stabilization to a level deemed medically acceptable, or return to the previous state, even if the patient has discontinued their participation. Further information regarding the evolution of the event will be sent to the sponsor by the investigator if not mentioned in the first report.

The investigator and sponsor should independently evaluate the causal relationship between the SAE and the study.

All events for which the investigator or sponsor believes a causal relationship can be reasonably inferred will be considered suspected SAE.

The investigator must notify the sponsor of any new and relevant information that he/she becomes aware of.

3. Summary of the notification process by event type

Table 4 Summary of the notification process by event type

| Type of event | Method of notification | Deadline for notification to the sponsor |
|--|--|---|
| Non-serious adverse event | Case report form | No requirement for notification without delay |
| Serious adverse event or event of interest | Initial SAR declaration form + follow-up if necessary + documentation in the case report form | Notification of sponsor without delay |
| New and medically relevant information | Written report | Notification of sponsor without delay |

SAR, serious adverse reaction

Contact details for the vigilance unit of the sponsor

Clinical Research Safety and Vigilance Unit - CHU de Bordeaux

Tel.: 05 57 82 16 26

Fax: 05 57 82 12 62

Email: vigilance.essais-cliniques@chu-bordeaux.fr

D. Declaration by the sponsor regarding unexpected serious adverse reactions, new information or other events

The sponsor will assess whether any serious adverse reaction is expected or unexpected, based on the list of expected SAE.

The sponsor/vigilance unit will report safety information to the competent authorities and the Committee for the Protection of Persons (CPP) in accordance with the applicable deadlines and regulatory requirements specific to the trial.

The safety and vigilance unit will report to the competent authorities any suspected unexpected serious adverse reaction (SUSAR) occurred in France or outside the national territory within the following deadlines:

- 1) In the case of a SUSAR leading to death or life-threatening, without delay from the day in which the sponsor becomes aware of it,
- 2) In the case of other SUSARs, no later than 15 days from the day the sponsor becomes aware of them.

Without delay, the sponsor/vigilance unit will declare any new and relevant information that has arisen during the research to:

- the *Agence Nationale de Sécurité des Médicaments et des produits de santé* (ANSM),
- the Committee for the Protection of Persons (ethics committee)

The sponsor and investigator will take the appropriate measures, and the sponsor will inform the competent authority and the Ethical committee

E. Annual safety report

(Article R1123-61 of the Public Health Code)

Within 60 days of randomization of the first participant, the sponsor will write a safety report including:

- a list of serious adverse reaction that may be related to the experimental treatment(s) applied during the research, including expected and unexpected serious reactions occurring during the reporting period,
- a concise and critical analysis of the safety of the study for the participants.
- summary tables of all serious adverse reaction that have occurred since commencement of the study.

This report will be sent to the ANSM and CPP within 60 days of randomization of the first participant.

Appendix 5 Data Management

A. Data management software

1. Software use

The software to be used for data management is Ennov-Clinical, from the Ennov company, version 7.0 or any later version.

2. Data hosting

The Ennov clinical company will be in charge of data hosting and database maintenance, according to the procedures and technical specifications of Bordeaux University Hospital Centre. The server is hosted in a data center in Roubaix, France.

3. Data security

A backup of the server of Bordeaux University Hospital Centre will be hosted at a different site in Roubaix, France, and a second backup will be hosted at a distant site in Gravelines, France. Management of the rights to the Ennov Clinical software is the responsibility of the Ennov Clinical Administrator of Bordeaux University Hospital Centre, and management of the rights of access to the electronic CRF data, for the investigating physicians and their collaborators, is the responsibility of the data manager of the study.

The forms for the study were created in Word software (Microsoft Corp., Redmond, WA, USA) by the clinical research coordinator. Validation of the final version of the CRF will be done by the data manager. This process is described in the standard CRF. After validation, the data manager will complete the form.

B. Data entry

Data entry into the electronic CRF is the responsibility of the investigator at each center. Any person other than the investigator must be trained and authorized by the investigator before entering data. The electronic CRF was developed using the Clinsight software by the data manager.

C. Access rights

Only the data managers, Data Methodology and Management Centre project team and auditors have direct access to the database.

D. Roles

The study team is responsible for any modifications to the data; the MDMC project team members cannot assume this responsibility. Event and treatment coding are also the responsibility of the investigators. The data manager is responsible for queries, which must be disseminated regularly.

E. Data coding

The prescribed treatments and clinical events will be coded in the electronic CRF to allow data testing and analysis.

The following dictionaries will be used for the coding of medical terms:

- MedDRA (current version) France/USA
- ATC

F. Data testing

Controls are in place for checking the consistency and completeness of the data entered into the electronic CRF. The controls were defined jointly by the coordinating investigator and the MDMC within the data validation plan.

Amendment requests will be handled by the data manager; after being sent to an investigator via the electronic CRF, the investigator will make the necessary corrections.

G. Reviewing information in the database on adverse events and serious adverse events

Information in the study database on AE and SAE will be reviewed as necessary.

H. Closure of the of database

The database will be closed prior to the final analysis in accordance with the procedures of the MDMC.

I. Data transfer

Data transfers (sending, receiving) will be carried out in accordance with the current procedure in operation at the MDMC. The data transfer arrangements are to be defined in the Data Management Plan. For security reasons, data files will be anonymized and then transferred via a secure platform (Cirrus Logic, Inc., Austin, TX, USA).

J. Archiving of the database

The archiving of the database will be the responsibility of the study sponsor. The data will be stored in the server of Ennov Clinical and a physical copy (i.e. a CD-ROM) will be retained by the sponsor.

K. Quality management

The activities of the MDMC project team are integrated within the management quality system. Non-compliance is managed by the MDMC via audits and inspections.

Abstract

Background. The frequency of persistent occiput posterior (POP) presentations is 10 to 20%. These POP presentations are associated with higher rates of operative delivery and associated maternal and neonatal complications. Actually, there is no standardized management for POP. Numerous observational studies have shown that using systematic manual rotation (MR) versus expectant in case of POP is associated with a decrease in operative delivery rates. However, selection bias and residual confounding cannot be ruled out in this observational setting. Risks associated to MR are thus lower than potential benefit associated to prevention of operative delivery. We therefore propose to conduct a multicenter randomized controlled trial to test the superiority of systematic MR over expectative management to decrease operative delivery rate of POP.

Methods. Eligible participants with a suspicion of POP will have a transabdominal ultrasound to confirm position. After confirming a POP, participants with written consent will be randomized into an experimental group (MR) or a control group (sham procedure). Based on a background risk of operative delivery of 40%, then for a reduction to 30% ($\alpha = 0.05$, $1-\beta = 0.90$, and a bilateral test) the study requires 326 women per group. The primary outcome will be operative delivery. Secondary outcomes will be in particular maternal and neonatal morbidities. Analysis will be by intention-to-treat. Primary and secondary outcomes will be compared using a chi-squared test. A logistic regression for the primary outcome will be undertaken to account for potential confounders.

Discussion. Given that the efficacy of MR has not been proven with a high level of evidence, the practice of this technique is not systematically recommended by scholarly societies and is, therefore, rarely performed by obstetric gynecologists. If our hypothesis regarding the superiority of MR is confirmed, our study will help change delivery practices in cases of POP.

Keywords: Occiput posterior, manual rotation, operative delivery, fetal malposition, maternal complications, neonatal complications, transabdominal ultrasound.

Serment d'Hippocrate

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer leurs consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera.

Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me sont confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses : que je sois déshonoré(e) et méprisé(e) si j'y manque

