TITLE:
OPHthalmic artEry DoppLer evaluation after 37 weeks of gestation and Intrapartum fetal Adverse outcomes (the OPHELIA Study)

ACRONYM: OPHELIA

Abstract

The ophthalmic artery Doppler has been recently proposed as a potential "soft marker" for placental insufficiency in retrospective and observational studies, with similar clinical significance with respect to Uterine Artery (UA) Doppler evaluation and it is currently being investigated as an adjunctive clinical instrument to predict pre-eclampsia (PE) occurrence.
Placental insufficiency strictly correlates with intrapartum fetal adverse outcomes and a concomitant induction of labor, alone, may further increase the hypoxic stress on the fetus during labor. This can be reflected by cardiotocographic alterations during labor, ultimately leading to emergency cesarean deliveries or instrumental vaginal deliveries.
Despite great advancements in understanding various maternal-fetal pathologies, we are still not able to properly detect fetuses that are at higher risk for intrapartum compromise among those receiving an induction of labor. Therefore, the aim of this prospective study is to investigate any potential association between altered ophthalmic artery Doppler PSV ratio measured before labor induction in at-term, pregnant patients with intra-partum fetal compromise. Furthermore, we aim to also measure an additional parameter that is the optic nerve sheath diameter (ONSD) – an indirect measure of intracranial pressure - before and after the second stage of labour, with the aim of studying its physiology during and after delivery.

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Introduction

Rationale

The ophthalmic artery (OA) Doppler has been recently proposed as a potential "soft marker" for placental insufficiency in retrospective and observational studies, with similar clinical significance with respect to Uterine Artery (UA) Doppler evaluation (1-9). It has been investigated in small-for-gestational-age (SGA) or fetal-growth-restricted (FGR) fetuses (5, 7), as well as in low-risk pregnancies and at various gestational ages during pregnancy (1, 2, 5, 8, 9), showing to be predictive of impaired placentation, and, consequently, of pre-eclampsia occurrence (1-4, 8, 9),
The OA is the first branch of the internal carotid artery and its Doppler velocity waveform has two systolic peaks. The first systolic wave (PSV1) is created by cardiac systole, with the opening of the aortic valve and ejection of blood into the aorta, whilst the second systolic wave (PSV2) is a reflective wave formed by the systolic pulse wave reaching smaller, higher resistance arterioles and being reflected back towards the heart. At the level of the aortic arch, a fraction is diverted cranially to the cerebral circulation as a forward wave to create PSV2. In this way, PSV2 is most influenced by peripheral arterial compliance and

resistance, whilst PSV1 is more affected by cardiac output. Therefore, an increase in the ratio of PSV2 to PSV1 (PSV ratio) could represent an increase in peripheral vascular resistance and/or a reduction in cardiac output, which are both indirect signs of placental dysfunction (10). The latter can be manifested during labor with well-established cardiotocographic patterns (11) and induction of labor, alone, may enhance the intrapartum hypoxic stress on the fetus (12).
Furthermore, another parameter that is currently understudy is the Optic Nerve Sheath Diameter (ONSD). Recent evidence suggests that ONSD increases in pre-eclamptic patients, possibly reflecting a transient increase in intracranial pressure (13, 14). However, evidence is scarce regarding its physiologic changes during and after labour.
In understanding the potential mechanisms behind intrapartum fetal compromise in gravid, at-term patients undergoing labor induction, our hypothesis is that placental dysfunction, albeit not necessarily clinically manifest earlier in pregnancy, may play a role in fetal compromise during labor, especially in pregnancies undergoing induction of labor. Hence, investigating potential associations between a "soft marker" of placental insufficiency as Ophthalmic artery Doppler PSV ratio alterations and intrapartum fetal compromise would be paramount.
Therefore the aim of this prospective interventional study is to investigate any association with altered OA PSV ratio and intrapartum fetal adverse outcomes in pregnant patients that reach term of pregnancy, undergoing induction of labor. In addition, we also aim to evaluate the ONSD before and after the second stage of labour in order to study its physiologic changes.

Objective:

Primary objective:

- to investigate any association between altered Ophthalmic Artery Doppler and in-labor cesarean delivery rate for fetal hypoxic stress ;

Secondary objectives:

to investigate any association between altered Ophthalmic Artery Doppler and:

- instrumental vaginal delivery for fetal hypoxic stress;
- in-labor cesarean delivery for any indications;
- cesarean delivery for subclinical/clinical chorioamnionitis;
- arterial umbilical cord pH < 7.0;
- Apgar score <7 at 5 minutes;
- admission to Neonatal Intensive Care Unit (NICU);

To investigate differences in Optic Nerve Sheath Diameter (ONSD) before and after the second stage of labour;

METHODS

Study design:

single-center, Interventional prospective study

Setting and duration:

The study will last 24 months. Enrollment will last for 18 months and will be performed at the "UOC di Ostetricia e Patologia Ostetrica" of the Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome (RM), Italy, Largo A. Gemelli 1, 00168

Participants:

We will enroll 1477 pregnant patients that reach term of pregnancy (e.g. > 37 weeks of gestation) undergoing induction of labor at Fondazione Policlinico Universitario A. Gemelli IRCCS of Rome, Italy. We will collect both maternal and perinatal clinical data.

Inclusion Criteria:

- Age > 18 years;
- Pregnant patients that reach term (e.g. > 37 weeks of gestation) undergoing induction of labor
- Ability to provide written informed consent

Exclusion Criteria:

- Age < 18 years
- known fetal malformations
- known fetal genetic syndromes
- multiple pregnancies
- known maculopathies
- patients who do not wish to sign written informed consent

Variables and procedures

We will collect both maternal and perinatal clinical data.
As for the mother, we will collect the following data: age, BMI, parity, mode of conception, cardioaspirin use, reason for induction, method of induction used, gestational age at index measurement and at birth, use of oxytocin, type of birth (i.e. spontaneous vaginal, instrumental vaginal, cesarean delivery), episiotomy, Peak Systolic Velocity (PSV) of Ophthalmic artery, optic nerve sheath diameter (ONSD).
Concerning the fetus/newborn, we will collect: pulsatility index (PI) of umbilical artery, middle cerebral artery, birthweight, Neonatal Intensive Care Unit (NICU) admission, Apgar score, umbilical artery pH, need for respiratory assistance at birth.

Right before labour induction, once the patient is already admitted into the inpatient ward – as an elective admission for scheduled labour induction - we will perform an ultrasound by gently applying the probe onto the eyelid of the patient, using sterile gel. We will then measure both the Doppler velocity of the Ophthalmic Artery as well as the Optic Nerve Sheath Diameter (ONSD).
The ONSD will then be measured again right after delivery following the exact same procedure.

Ophthalmic artery doppler measurement
To measure the ophthalmic artery doppler, the patient needs to be in the supine position where a 6–15-MHz linear transducer is placed transversely and gently over her closed upper eyelid after application of conduction gel. Color flow is used to identify the ophthalmic artery, which is found superior and medial to the hypoechoic band representing the optic nerve. Pulsed-wave Doppler will then be used to record three to five similar waveforms; the angle of insonation is kept at <20◦, the sample gate is 2 mm, the depth is 3.0–4.5 cm, the high-pass filter is 50 Hz, and the pulse repetition frequency is set at 125 kHz.
The first peak of systolic velocity is obtained automatically by the machine and the second peak of systolic velocity is measured manually, because it is not given automatically. One measurement for each eye will be taken. For each recording, the PSV ratio is calculated. A mean measurement from both eyes will be obtained.
This procedure can be easily performed by both expert attendings in obstetric ultrasound as well as residents in training.

Optic Nerve Sheath Diameter (ONSD) measurement
OSND measurement will be conducted in transverse plane. High-frequency linear probe of 7–12 MHz will be used, while patients are in supine position. Using two-dimensional mode, depth of the optic nerve will be localized and marked at 3 mm behind the retinal and optic nerve junction with the help of machine caliper. At this point, transverse diameter of optic nerve will be calculated. Scanning begins from lateral side of eye in coronal section and then in oblique sagittal plane measuring OSND in both the axes. Minimal pressure will be insured on the eyeball, and ample amount of sterile-conducting medium will be used. This measurement will be undertaken simultaneously with that of the Ophthalmic Artery (OA) Doppler.

Primary Endpoint:

- Any potential association between altered Ophthalmic Artery Doppler and in-labor cesarean delivery rate for fetal hypoxic stress;

Secondary Endpoints:

Any potential association between altered Ophthalmic Artery Doppler and:

- instrumental vaginal delivery for fetal hypoxic stress ;
- cesarean delivery rates for any indications;
- cesarean delivery rates for subclinical and clinical chorioamnionitis;
- arterial umbilical cord pH < 7.0 at delivery;
- Apgar score <7 at 5 minutes
- admission to Neonatal Intensive Care Unit (NICU)

To investigate differences in Optic Nerve Sheath Diameter (ONSD) before and after the second stage of labour;

Sample Size

The primary endpoint of this study is the incidence of in-labor cesarean delivery rate for cardiotocographic alterations and its association with the ophthalmic artery (OA) Doppler indices. The association will be primarily investigated with the logistic model. A logistic regression of a binary response variable (Y=in-labor caesarean delivery for cardiotocographic alterations) on a continuous variable (X=OA Doppler indices) with a sample size of 1477 observations achieves 80% power at a 0.05 significance level to detect an odds ratio of 1.8 when the proportion of Y in the population is 0.017. This odds ratio is the ratio of the odds that Y = 1 when X is one standard deviation above its mean to the odds that Y = 1 when X is equal to its mean.

Statistical analysis

The demographic and clinical characteristics will be summarized by applying a descriptive statistical analysis.

Quantitative variables with Gaussian distribution will be presented as mean and standard deviation (SD) while those which differ from normal distribution, assumption that will be verified by the Kolmogorov-Smirnov test, will be reported as a median and interquartile range (IQR). The qualitative variables will be reported as absolute and relative frequencies (percentages) and graphically with histograms.

Associations between the OA Doppler indices and the incidence of primary and secondary endpoints will be mainly performed using the logistic regression. The AUCs will be also calculated and different cut-offs tested in order to describe diagnostic performances of the OA Doppler indices in terms of sensitivity, specificity and accuracy. The main results will be reported with their 95% confidence intervals.

Optic Nerve Sheath Diameter (ONSD) before and after the second stage of labour will be analyzed using the paired Student t-test or the Wilcoxon test, once tested the normality of the before-after difference distribution.

All analyses will be performed using IBM SPSS Statistics for Windows, Version 29. Armonk (NY): IBM Corp.; 2023.

Population

Pregnant patients admitted to our ward after 37 weeks of gestation undergoing induction of labor.

Clinical and research implications

In understanding the potential mechanisms behind intrapartum fetal compromise in gravid, at-term patients undergoing labor induction, our hypothesis is that placental dysfunction, albeit not necessarily clinically manifest earlier in pregnancy, may play a role in fetal compromise during labor, especially in pregnancies undergoing induction of labor. Hence, investigating potential associations between a “soft marker” of placental insufficiency as Ophthalmic artery Doppler PSV ratio alterations and intrapartum fetal compromise would be paramount. This could potentially allow us to precociously identify which patients (among those undergoing an induction of labor) might benefit from an earlier labor induction and/or might need special surveillance during labor, hence paving the way for larger studies, possibly with a RCT design. Additionally, understanding the physiologic changes of the ONSD during and after labour

will allow us to pave the way for future studies aimed at investigating possible changes of maternal intracranial pressure during labour.

Funding

No funding will be needed for this study.

Ethical aspects

This study will be conducted in accordance with GCP, with ethical principles derived from the Declaration of Helsinki and with the current normative with regards to interventional studies. This project will be conducted after Fondazione Policlinico Universitario "Agostino Gemelli" (FPG) IRCCS Ethical Committee's approval.

Informed consent

Each patient will be given the opportunity and sufficient time to read the information sheet and to request any necessary clarification. If the patient agrees to participate, the patient's signed consent form will be obtained.

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