

Wave

Sequential analysis of uterine artery Doppler **wave**forms in high risk population for placenta mediated disease undergoing prophylactic aspirin therapy controlled by levels of serum Thromboxane.

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Table of contents

Contents

Contacts.....	3
Summary	3
Background	4
Objective	6
Study design.....	6
Study population	7
Inclusion Criteria	7
Exclusion Criteria	7
Sample size	7
Recruitment strategy	8
Data collection	8
Investigations	8
Reliability and Validity of UAD measurements	9
Response to treatment assessment	9
Analysis.....	10
Data Protection.....	11
Ethical Issues	11
Project Management:	12
Funding	12
References.....	13

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Summary

Abnormal development of the placenta (afterbirth) can cause serious pregnancy complications such as abruption, preeclampsia, and small for gestational age (SGA) (complications also known as Placenta Mediated Disease [PMD]). PMD can lead to devastating pregnancy outcomes such as maternal and baby's death as well as affect mother's and baby's health later in life. Thus prediction and prevention of PMD remains a high priority for researchers and clinicians worldwide.

Currently all women deemed to be at increased risk for PMD are offered a low dose of Aspirin as a preventative measure. Unfortunately humans process aspirin differently the effectiveness of this preventative treatment varies with relative risk (RR) for preeclampsia 0.88, 95% CI 0.21-0.366, and for SGA RR 0.88, 95% CI 0.06—12.72(Odibo *et al.*, 2015).

A simple ultrasound assessment of the blood flow in the womb arteries performed at the time of 20 weeks scan has been shown to be a good predictor of poor pregnancy outcome. However the clinical importance of such assessment in women receiving aspirin therapy is unclear.

This study will explore the change (worsening or improvement) in the blood flow through the womb arteries from the start of aspirin therapy to the mid-point of pregnancy in those who respond to the treatment and those who do not. Women's response to aspirin will be checked by a blood test. The results of this study may allow a better understanding of aspirin's role in preventing PMD and also may allow clinicians to detect non-responders who are more likely to develop PMD and in whom alternative treatment could be offered.

Background

Abnormal placentation plays an important role in the pathogenesis of preeclampsia (PE), abruption and small for gestational age (SGA) fetus (Granger et al., 2001; Algeri et al., 2013). These conditions, often termed Placenta Mediated Disease (PMD), can lead to devastating perinatal outcomes, such as intrauterine death (IUD), premature delivery and short as well as long term poor outcomes due to fetal hypoxia. Therefore prediction and prevention of PMD remains a high priority for researchers and clinicians worldwide (Hogberg, 2005; Steegers et al., 2010).

Preeclampsia and eclampsia affects over four million women worldwide each year with 1.7% maternal fatality rate (Hogberg, 2005). The severity of PE ranges from mild late onset disease (>37 weeks gestation) to severe early onset disease progressing to eclampsia, HELLP syndrome and even maternal death. Currently the only cure for preeclampsia is delivery of the placenta. PE accounts for 6.3% of all stillbirths in England (Enquiries, 2009), substantially increases the risks of preterm delivery and SGA (NICE clinical guideline 107, Hypertension in pregnancy, 2011). Offspring are also at risk of developing long term morbidity (Vatten et al., 2003). Moreover, mothers affected by PE are more likely to develop cardiovascular disease later in life compared to unaffected mothers (Yinon et al., 2010).

Babies affected by SGA are at increased risk for perinatal morbidity even without associated PE (Bujold et al., 2010). According to the “in-utero programming” hypotheses, fetal growth impairment results in an increased risk of serious disease in adult life such as type 2 diabetes, hypertension and coronary heart disease (Godfrey and Barker, 2000).

Several meta-analyses and a systematic review have investigated preventative therapies for PE and found that low dose of aspirin (50-150mg/day), provided it is commenced prior to 16 weeks of gestation, reduces the incidence of PE (relative risk 0.47, 95% CI 0.36-0.62), SGA (relative risk 0.46, 95% CI 0.33- 0.64), pregnancy induced hypertension (relative risk 0.62, 95% CI 0.45- 0.840), preterm birth (relative risk 0.35, 95% CI 0.22-0.57) and perinatal death (RR = 0.41, 95% CI, 0.19-0.92). Aspirin started later in pregnancy (>16 weeks) is much less effective - the relative risk for PE is only 0.81 – 0.78 depending on the source (Bujold et al., 2010; Roberge et al., 2012; Roberge et al., 2013). Recent randomised controlled trial found no evidence that 81 mg/day aspirin started at 11+0 to 13+6 weeks pregnancy prevents preeclampsia (RR0.88, 95% CI 0.21-3.66)(Odibo et al., 2015). It remains unexplained why ASA still fails to prevent PMD in significant number of cases even when started early.

Uterine artery Doppler (UAD) has been shown to be an effective predictive test for PE; one meta-analysis showed that second trimester UAD was the most accurate test to predict early onset of PE and adverse pregnancy outcome related to PMD (Cnossen et al., 2008). Doppler flow velocity waveforms reflect the resistance of the blood flow in uterine arteries; high resistance is associated with poor trophoblastic invasion and an increased risk for adverse outcome.

In order to assess changes in UAD, sequential analysis of UAD flow velocity waveforms in first and second trimesters of pregnancy (i.e. during placentation) was performed by Gómez et al. (2006), Plasencia et al. (2008), Herraiz et al. (2012). Results of those studies were supportive of the value of sequential approach, showing a steeper decrease in uterine artery pulsatility index (PI) from first to second trimesters in the normal outcome group and relative worsening in PI in the group affected by early onset of PE. However, it was unclear from the published material, whether the subjects included in these studies were prescribed/taking aspirin. Only one study (Plasencia et al., 2008) accounts for aspirin intake with 3.4% of study population offered aspirin therapy. Therefore, results of these studies cannot be used to explain changes in UA blood flow in high risk for PMD group, where Aspirin is thought to play an important role.

The 'Hypertension in pregnancy' NICE clinical guideline (NICE clinical guideline 107, Hypertension in pregnancy, 2011) calls for more research to assess the clinical value of UAD assessment in the clinical management of women at risk of PE due to its ambiguous benefit in this cohort. Moreover "James Lind Alliance priority setting partnership" has identified Stillbirth (2015) and Preterm Birth (2014) in its top ten list of unanswered questions – specifically suggesting research into placental function during pregnancy and the effectiveness of preventative strategies for early onset of PE.

Aspirin acts by acetylation of platelet cyclooxygenase subsequently reducing levels of thromboxane A (TbxA). In the normal circulation thromboxane A acts as a platelet activator and contributes to vasoconstriction. Therefore the reduction in TbxA by aspirin inhibits platelet activity and reduces vasoconstriction. This mechanism is thought to contribute to the anti-inflammatory and anti-thrombotic properties of aspirin and contributes to improved trophoblastic invasion and placentation. Given the likely impact of aspirin on uterine haemodynamics it is reasonable to assume this may be detected by changes in uterine artery Doppler indices.

In a recently completed (but as yet unpublished) study ("ASPIRE") we found a high incidence of Aspirin non-response (~15%), as measured by persistently high TbxA, among high risk population undergoing ASA prophylaxis to prevent PMD. Individual response to Aspirin is highly variable presumed due to differences in metabolic rate, genetic characteristics, body size, rate of platelet turnover, age and compliance. Therefore there is an interest in monitoring response to Aspirin while assessing uterine artery haemodynamics with response being determined by serum and urinary inhibition of the Thromboxane.

Objective

To better understand the relationship between Uterine Artery Doppler (UAD) measurements and aspirin response.

The aim of the study is to compare sequential changes in UAD flow velocity waveforms in a population of women at high risk of PMD who have responded to aspirin (as determined by serum TbxA) and those who have not.

Research question

Is the change in uterine artery pulsatility index between first and second trimester influenced by response to aspirin therapy (as determined by serum Tbx inhibition) in women at high risk of placenta-mediated disease?

Outcomes:

- Serum Tbx inhibition (<10 ng/ml) in serum and Tbx and SUA in urine
 - Pregnancy outcome:
- 1) Diagnosis of preeclampsia made using following criteria:
Hypertension: Gestational hypertension (>140/90 after 20 weeks gestation) or pre-existent hypertension (>140/90 diagnosed prior or at booking) and proteinuria (300 mg /day, PCR 30).
Or in absence of proteinuria: new onset of hypertension with new onset of any of the following:
 - thrombocytopenia (platelet count <100 000)
 - renal insufficiency (creatinine >1.1mg/dL or a double the baseline)
 - impaired liver function (transaminases x 2 normal)
 - Pulmonary oedema
 - neurological symptoms
 - customised birth centile
 - 2) severe SGA (< 5 customised birthweight centile)
 - 3) normal outcome

Study design

This is a prospective cohort study.

Study population

Pregnant women at high risk for PE and SGA (as per current guidelines) attending Royal Victoria Infirmary, Newcastle and who have accepted aspirin prophylactic therapy.

Inclusion Criteria

- Risk factors for PE as per NICE (NICE clinical guideline 107, Hypertension in pregnancy: The management of hypertensive disorders during pregnancy, 2011); specifically women with either 2 moderate or one high risk factor:

Moderate risk factors for pre-eclampsia

- first pregnancy
- age 40 years or older
- pregnancy interval more than 10 years
- BMI 35 kg/m² or more at first visit
- family history of pre-eclampsia
- multiple pregnancy.

High risk factors for pre-eclampsia

- hypertensive disease during previous pregnancy
- chronic kidney disease
- autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome
- type 1 or type 2 diabetes
- chronic hypertension

Exclusion Criteria

- Unable to give informed consent
- <16 years old

Sample size

A total of 334 participants (which we predict will include 50 non-responders to aspirin) needed to detect 0.5 SD in change in uterine artery PI between 11-14 and 18-20 weeks of pregnancy with 80% power. This estimate is based on “Aspire” none response rate of 15 per cent at 20 weeks gestation and our local prior observations in 120 high risk women taking aspirin (mean change in PI of -0.315 with SD 2.7). Once 39 cases available from pilot data from “Aspire” are subtracted, the sample size for this study reduces to 295 with 41 non-responders.

An extra 10 percent (30 participants) will be added to accommodate established attrition rate. In addition 16 participants will be replaced as were recruited under previous small for gestation criteria and subsequently were withdrawn from the analysis due to a change in local aspirin prescription policy. Therefore to achieve the

sample size of 295 participants we need to increase the recruitment target by 46 participants resulting in a total of 341.

With the established recruitment rate of 4 participants a week we will be able to achieve this target by 18th of March 2019 and end the trial on 14.10.2019.

Recruitment strategy

An appropriate member of a clinical research team (nurse, midwife, AHP or clinical trial associate) will review all antenatal booking proformas received in the antenatal clinic at the Royal Victoria Infirmary daily. Women at increased risk of developing preeclampsia and SGA (according to NICE guidelines) will be sent an approved patient information sheet and an invitation letter. These women will then be approached in the antenatal clinic and invited to participate in the study.

Alternatively women who are only identified as eligible at the time of the 11-14 weeks scan still will be offered a patient information sheet about the study and will be given a minimum of 48 hours to decide whether or not to participate in study.

Data collection

Demographic data, maternal biometric characteristics, medical history, gestation, UAD pulsatility index and serum TbxA results will be collected. Doppler measurements of right and left uterine arteries will be performed by a qualified research sonographer during the dating scan (11 – 14 weeks) and repeated during the routine fetal anomaly survey scan (18+0 to 20+6 weeks). All scans will be performed using GE E8 ultrasound equipment.

A single urine sample will be collected at the time of 20 weeks visit.

Please see appendix 1 – CRF.

Duration of participation

Participants will attend two study visits at the time of their routine scans or clinic visits.

End of study definition

The study will close once the data collection for 295 study participants including serum Thromboxane and pregnancy outcomes will be complete and analysed.

Investigations

Doppler

During the first trimester transabdominal scan, following viability confirmation, the crown-rump-length (CRL) will be measured for the purposes of dating. In addition, an early anatomy survey will be performed to confirm normal development. Right and left uterine arteries will be visualised using a transabdominal approach using colour

Doppler facility. UAD waveforms will be recorded from both uterine arteries using a parasagittal approach at the level of the cervix as described by Prefumo et al. (2004). In the second trimester, UAD waveforms will be obtained following a full anatomy survey and confirmation of absence of structural fetal abnormalities. Right and left uterine arteries will be examined medially at the crossover with internal iliac arteries as described previously (Arduini et al., 1990).

Pulsatility Index (PI) was chosen to delineate blood flow pattern:

$$PI = (PSV - EDV) / TAV,$$

PI – pulsatility index,

PSV – pick systolic velocity,

EDV – pick end diastolic velocity

TAV – time averaged velocity.

Both UAD measurements will be available to clinicians as part of current clinical practice in high risk population.

Reliability and Validity of UAD measurements

Uterine artery Doppler (UAD) measurements will be performed by qualified research sonographers during the dating scan (11 – 14weeks) and again during the fetal anomaly scan (18 +0 to 20+6 weeks).

Pulsatility index (PI) will be calculated using GE system automatic wave tracking facility under operator's inspection and optimisation. Two measurements will be performed over a minimum of 5 cardiac cycles on each side and an average PI recorded to minimise intra-observer variability. Images of Uterine Artery Doppler will be recorded for audit purposes.

In addition, intra-observer and inter-observer agreement of change in uterine artery PI will be performed to evaluate limits of agreement (Bland and Altman, 1986). The repeatability of the change in PI will be assessed on 10 study participants at the time of first and second UAD examinations. UAD PI will be measured twice by a blinded operator at the first instance and once again by a different operator.

Response to treatment assessment

A single sample of 10 ml of blood and urine will be obtained at 20 weeks to measure levels of Tbx. Quantitation of urinary Tbx offers an advantage over serum Tbx because measurements are not subject to interference from in vitro platelet activation, which commonly occurs as a result of variables such as local vein

trauma during phlebotomy. While offering an advantage of non-activation of platelets during blood collection and handling urinary Thromboxane levels could be affected by rate of the excretion. Therefore there is a benefit in collection and analysis of urinary Thromboxane alongside with serum Thromboxane.

Based on results of serum and urinary Tbx participants will be allocated to response and non-response groups using a cut –off of 10 ng/ml (Frelinger *et al.*, 2006; Good *et al.*, 2015); Reilly *et al.*, 2016).

Serum and urine Tbx will be analysed by Newcastle upon Tyne NHS Foundation Trust lab. Any remaining sample will be frozen for the purposed of further testing if such is needed.

Analysis

Mean PI will be recorded for each Doppler examination and then converted into multiples of median (MoM) to account for gestational variability of the measurement.

$$MoM = \frac{Patient\ PI}{Population\ median\ PI}$$

MoM will be calculated based on data reported by Gómez *et al.* (2008).

$$MoM = \frac{PI}{Exp(1.39 - 0.012\ GA + 0.0000198\ GA^2)^*}$$

*GA- gestational age measured in days

This process will result in four variables: PI1 – pulsatory index in first trimester, PI2 - pulsatory index in second trimester, MoMPI1 and MoMPI2 are MoMs of pulsatory index in the first and second trimesters, respectively.

In order to describe dynamics of a change in the blood flow, an additional variable will be calculated: the difference between second and first trimester UAD PI MoM, defined as

$$\Delta MoM = MoMPI2 - MoMPI1.$$

Variables described above will be analysed in two groups by result of serum Tbx:

- Responders (inhibition of Tbx)
- Non-responders

Descriptive statistics will be used to describe the study population, Doppler values and their derivatives. Independent t test was used to assess differences in Doppler variables.

IBM SPSS version 21 statistical software will be used to analyse the data with support from Newcastle University statistician.

Data Protection

Caldicott approval will be obtained prior to commencement of the study. Personal data will be stored only for the purposes of obtaining informed consent and arranging follow up appointments. Contact details will only be linked to the research data by designated research personnel. Personal contact details will be held securely on a shared server accessible only by the study team on a password protected database.

The research team and local R&D monitors may require access to the participant's clinical notes; participants will be informed of this in the participant information sheet, and permission to do so form part of the consent form. Research data generated by the study will be stored for 10 years. After the end of the study, data will be stored securely at a restricted access secure storage facility used by the Newcastle Hospitals NHS Foundation Trust. Electronic research data will be stored on a University secure server. All personal identifying information will be removed when presenting the data generated from the study.

Ethical Issues

Ethical opinion will be sought from a REC. An experienced member of a research team will conduct the research process. Full, written consent will be obtained. At all stages, potential participants will be reminded that they are under no obligation to take part and that their decision will have no impact on any future care they may receive. It will be ensured that participants have the capacity to give consent, have a full understanding of the purpose of the research, the involvement required and the risks and benefits involved.

Every effort will be made to minimise potential discomfort or distress. There is a possibility that participants will experience some discomfort from the venepuncture, however, they will be offered the option of a local anaesthetic, and the researcher is experienced in undertaking venepuncture. It is not anticipated that any unusual discomfort will be experienced.

All UAD measurements will be recorded in patients' clinical records and available for the managing clinician as is currently the case. Change of the care will be at the discretion of a senior medical staff and will not be influenced by participation in this study.

Neither patients nor clinicians will be given the Tbx results, as there is no evidence this is a predictor of outcome. Reporting Tbx results could unnecessarily increase patient anxiety.

Project Management:

The study will be conducted in accordance with the Research Governance Framework for Health and Social Care. The research team (Professor S Robson, R Vinogradov, Dr VJ Snaith) will meet every 4 weeks to review progress, but there will be opportunity to meet more frequently should issues or unforeseen concerns.

Funding

College of Radiographers Industry Partnership Scheme Research Grants £5044.

Impact

This study has got potential to improve patient care and outcomes and assist clinicians with decision making in a course of high risk pregnancy. It could aid with timely identification of women who remain at high risk for PMD despite prophylactic therapy who may benefit from an increased dose and/or alternate medication such as heparin as well as increased ultrasound surveillance of the pregnancy.

The project has the potential to be generalised to other fields of medicine where aspirin is used as prophylactic medication such as in area of cardiovascular disease.

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