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IS MID-GESTATIONAL UTERINE ARTERY DOPPLER STILL USEFUL IN A SETTING WITH ROUTINE FIRST TRIMESTER PREECLAMPSIA SCREENING? A COHORT STUDY

Short title: Uterine Doppler and FMF preeclampsia risk

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CONTRIBUTION

What are the novel findings of this work?

Routine uterine artery (UtAD) Doppler assessment in the second trimester may be used to further stratify the preeclampsia risk in women who have had first trimester preeclampsia screening using the Fetal Medicine Foundation (FMF) combined screening algorithm.

What are the clinical implications of this work?

Care should not be de-escalated in patients that were classified as at high preeclampsia risk in the first trimester by the FMF algorithm on the basis of low UtAD impedance. Conversely, escalation of care may be justified in low-risk women with high mid-gestational UtAD Doppler resistance.

ABSTRACT

Objective: To evaluate whether routine mid-gestational uterine artery Doppler (UtAD) modifies the risk for preterm preeclampsia after first trimester combined pre-eclampsia screening.

Design Retrospective cohort study

Setting London Tertiary Hospital

Population 7793 women with singleton pregnancies, first-trimester preeclampsia screening using the Fetal Medicine Foundation (FMF) algorithm and UtAD Pulsatility Index (PI) assessment at the mid-gestation ultrasound.

Methods: Pregnancies were divided into four groups: high risk in both trimesters (H^1H^2), high risk in first but not in second trimester (H^1L^2), low risk in first but high risk in second trimester (L^1H^2), and low risk in both trimesters (L^1L^2).

Main Outcome Measures: Small for gestational age (SGA), hypertensive disorders of pregnancy (HDP), stillbirth.

Results: 600 (7.7%) and 620 women (7.9%) were designated as high risk in the first and second trimesters respectively. Preterm preeclampsia was more prevalent in the H^1L^2 group (4.5%) than in low risk women in the first trimester (0.4%, $p<0.0001$). The prevalence of preterm preeclampsia in the L^1H^2 group (3.3%) was significantly lower than in women at high risk in the first trimester (7.0%, $p=0.0076$) and higher than the L^1L^2 group (0.2%, $p<0.0001$). Prevalence of SGA and term HDP followed similar trends.

Conclusions: Preeclampsia risk after first trimester FMF preeclampsia screening may be stratified through mid-gestational routine uterine artery Doppler (UtAD) assessment. Pregnancy care should not be de-escalated for low mid-gestational UtAD impedance in those classified as high risk in the first trimester. Escalation of care may be justified in low risk women with high mid-gestational UtAD resistance.

KEYWORDS: first trimester preeclampsia screening, Uterine artery Doppler, placenta-related adverse outcomes, Small for Gestational Age, Hypertensive Disorders of Pregnancy, Stillbirth

INTRODUCTION

Pre-eclampsia (PE) is associated with adverse perinatal outcomes such as fetal growth restriction, iatrogenic preterm birth and perinatal death[1]. In the United Kingdom, screening recommendations for pregnancies at high risk of placentally-mediated disorder from the National Institute for Health and Clinical Excellence (NICE) are based on a checklist-structured approach. This approach considers medical, social and obstetric characteristics as independent risk factors irrespective of their prevalence or strength of association with adverse pregnancy outcomes[2,3,4]. Despite widespread use of this approach in many countries, this method has limited screening performance, achieving a detection rate for term preeclampsia of 30.2% and 41.5% for preterm preeclampsia for a 10% screen positive rate[5,6]. As a consequence of this limitation, the Royal College of Obstetricians and Gynaecologists (RCOG) recommend re-evaluation of PE risk at the mid-gestation anatomy scan using uterine artery Doppler (UtAD) assessment in women considered to be at high-risk[7]. The rationale for this recommendation is based on robust data showing a strong association between increased mid-gestation UtAD vascular resistance and increased risk of hypertensive disorders of pregnancy (HDP), fetal growth restriction and stillbirth[,8,9,10,11].

Effective early pregnancy screening for PE using the Fetal Medicine Foundation (FMF) algorithm[12] with targeted interventions in the high risk group has been shown to reduce the incidence of preterm PE and associated pregnancy adverse outcomes[13,6,14,15,16] . However, there is a paucity of data on the clinical role for mid-gestation UtAD assessment in a population that has already undergone such early pregnancy screening. The aim of this study is to evaluate whether mid-gestational UtAD assessment significantly further modifies the risk of placentally-mediated adverse pregnancy outcomes in a population who has undergone the routine first trimester multi-parameter combined preeclampsia screening.

METHODS

Population

This was a single centre study conducted at St George's University Hospital NHS Trust. A retrospective analysis was performed on information routinely collected between May 2019 and January 2022. Data were extracted from the ultrasound databases (ViewPoint version 5.6.26.148, ViewPoint Bildverarbeitung GmbH, Wessling, Germany) and the maternity registry (EuroKing, Wellbeing Software, Mansfield, UK). These databases are subject to regular clinical governance review. The identifiable information of the patients was removed from the datasets. Details collected involved maternal demographics, pregnancy characteristics and previous medical history. Only women who had first and second trimester routine scans in our Unit and delivered in this Hospital were included. Patients having missing outcome data, multiple pregnancy, major fetal defects, or miscarriage <24 gestational weeks were excluded from the analysis. The local ethics committee advised that formal ethical approval was not required for this retrospective study.

Study variables and outcomes

At the first trimester routine ultrasound scan, the risk of developing preeclampsia was calculated for each woman as per the FMF algorithm[17], using maternal characteristics, mean arterial blood pressure (MAP), UtAD and pregnancy-associated plasma protein-A (PAPP-A). Maternal serum PAPP-A was used in the algorithm instead of Placental Growth Factor (PlGF) due to its routine utilisation in screening for fetal trisomies[18]. Women with a result of >1:50 were classified as high risk and prescribed prophylactic low-dose aspirin (150mg) according to the ASPRE study[19,20], serial growth scans at 28 and 36 gestational weeks and induction of labor at 40 weeks' gestation[6]. The suggested management of the patients with different screening results is schematised in (Figure 2).

All women underwent mid-gestation UtAD assessment at the time of the mid-gestational routine anomaly scan[21]. Women with a high mean UtAD PI (>1.25) corresponding to the 90th centile were classified as high risk[22]. Patients screened as high risk at the mid-gestation assessment were scheduled for additional fetal growth assessments at 28 and 36 weeks' gestation and induction of labor at 40 weeks of pregnancy. Women were divided in 4 distinct groups: patients at high risk in both

trimesters (H^1H^2), at high risk in the first but not the second trimester (H^1L^2), low risk in the first but high risk in the second trimester (L^1H^2), and low risk in both trimesters (L^1L^2). The primary maternal and neonatal outcomes were ascertained and defined as the rates of HDP, SGA and stillbirth delivering at term (≥37 weeks) or preterm (<37 weeks).

Statistical analysis

Descriptive data were presented in median and interquartile range for continuous variables and in numbers and percentages for categorical variables. Comparisons between groups were performed using the Chi-square test or Fisher's Exact test for categorical variables, with Yates' correction where appropriate. R software version 4.2.1 (2022-06-23) was used for data analyses.

RESULTS

Between May 2019 and January 2022, a total of 16,160 women booked for pregnancy care, and 7793 of these women had both screening assessments as well as birth outcomes, and constituted the study population. The maternal demographic and pregnancy characteristics are described in Table 1. Six hundred women (7.7%) were designated as high risk in the first trimester and 620 (7.9%) classified as high risk at mid-gestation (Figure 1). The risk groups were assigned as follows: 161 H^1H^2 (2.1%), 439 H^1L^2 (5.6%) ,459 L^1H^2 (5.9%) and 6734 L^1L^2 (86.4%).

The prevalence of preterm preeclampsia decreased consistently with risk groups from 13.7% in H^1H^2 group to 4.5% in H^1L^2, 3.3% in L^1H^2 and 0.2% in L^1L^2 groups (Table 2)(Figure 3). This was also the case for the other adverse pregnancy outcomes ascertained. The prevalence of preterm preeclampsia in high risk women with normal mid-gestational UtAD PI (H^1L^2, 4.5%) was significantly higher than in women classified as low risk in the first trimester (L^1H^2 + L^1L^2, 0.4%, $p<0.0001$, Table 3). Similarly, the prevalence of preterm preeclampsia in low risk women with high mid-gestational UtAD PI (L^1H^2, 3.3%) was significantly lower than in women classified as high risk in the first trimester (H^1H^2 + H^1L^2, 7.0%, $p=0.0076$). The prevalence for term HDP, SGA birth and stillbirth followed the same trends as for preterm preeclampsia (Table 3).

DISCUSSION

The findings of this study suggest that routine uterine artery Doppler assessment in the second trimester may be used to further stratify the preeclampsia risk in women who have had first trimester combined preeclampsia screening using the FMF algorithm. When considering composite adverse perinatal outcomes, the level of care should not be de-escalated on the basis of low second trimester UtAD impedance in patients that were classified as at high preeclampsia risk in the first trimester. In contrast, escalation of care may be justified in women judged to be low-risk in the first trimester on the basis of high mid-gestational UtAD resistance.

Interpretation of study findings and comparison with published literature

HDP, SGA and stillbirth are a major cause of maternal and neonatal morbidity and mortality[23]. Previous work has highlighted the role of second trimester UtAD in an unscreened population for the identification of pregnancies at increased risk of both preterm preeclampsia and placentally-mediated complications[24]. Most studies looked at the use of UtAD in isolation, but others showed improved screening performance when combined with other biomarkers.[23] Combining UtAD, mean arterial blood pressure and PlGF together with the maternal demographic factors allowed 85% of preterm preeclampsia cases to be detected for a 10% false positive rate[25]. FMF first trimester screening identifies women at risk of preeclampsia and allows modification of disease course and outcomes through the offer of aspirin prophylaxis and additional monitoring and intervention[19,26]. Nevertheless, this screening test may not account for progressive maternal cardiovascular and uteroplacental system changes occurring later in pregnancy[27,28]. There is paucity of data on how the UtAD in the mid-trimester scan modifies the FMF preeclampsia risk. The findings of this study suggest that after first trimester FMF screening, mid-trimester UtAD assessment may have a role in further stratifying the risk of preeclampsia and other placentally mediated adverse outcomes.

Clinical and research implications

Women with a high first and a low second trimester risk for preeclampsia (H^1L^2) still had a significantly higher prevalence of preterm preeclampsia than the low-risk group from the first trimester (4.5% vs 0.4%, p<0.0001). Similarly, women with a low first and high second trimester risk (L^1H^2) still had a significantly lower prevalence of preterm preeclampsia than the first trimester high-risk group (3.3% vs 7.0%, p<0.0001). These findings indicate that for preterm preeclampsia, it would be inappropriate to de-escalate care in first trimester high-risk women after screening using second trimester UtAD assessment. However, women with a low first and high second trimester risk (L^1H^2) had a significantly lower but similar risk of preterm preeclampsia to women designated as high first and low second trimester (H^1L^2) risk

- 3.3% and 4.5%, respectively. This finding would support escalating care after mid-gestational UtAD assessment under these circumstances.

A strategy of escalating care in the low risk group by second trimester UtAD will require all women to have mid-gestational UtAD assessment and will result in a doubling of the high-risk group from 7.7% to 13.6%. For this increase in screen positive rate there will be only a modest improvement in the detection of adverse pregnancy outcomes. For example, the detection of all HDP would rise from 37.0% (162/438) to 47.7% (209/438). A notable finding in this study is that, overall, 53.8% of pregnancies from the first trimester high-risk group (H^1H^2+ H^1L^2) resulted in HDP, SGA and/or stillbirth. The high prevalence of adverse pregnancy outcomes justifies very close fetal and maternal monitoring in women assigned as high risk after first trimester FMF screening. Since aspirin use in the late second trimester has poor efficacy[29], escalation of care after mid-gestational UtAD would only involve serial fetal wellbeing and maternal blood pressure assessments[30].

Strengths and Limitations of the Study

This is a large pragmatic population-based study investigating how mid-gestational UtAD assessment influences the risk of placentally mediated adverse pregnancy outcomes in a population that has already been screened in the first trimester using the FMF combined screening algorithm for preeclampsia. Unfortunately, the study was underpowered to evaluate the impact on stillbirth prevention. There are inherent limitations to a single-centre retrospective study that lacks a control population and cannot account for the impact of intervention bias (treatment paradox). For example, the use of aspirin prophylaxis in the women at high-risk of preterm preeclampsia has been shown to have significantly reduced the prevalence of this disorder in the population[6]. Aspirin may have also had an effect on uterine artery, by decreasing the number of patients that would have been assigned to the H2 group. Furthermore, first trimester and mid-gestation risks were considered in a dichotomous way (high- versus low-risk), where the use of UtAD PI as a continuous variable may have led to improvements and personalisation of risk for the women – as with first trimester screening.

Conclusions

Routine uterine artery Doppler (UtAD) assessment in the second trimester may be used to further stratify the preeclampsia risk in women who have had first trimester preeclampsia screening using the Fetal Medicine Foundation (FMF) combined screening algorithm. Care should not be de-escalated in patients that were classified as at high preeclampsia risk in the first trimester by the FMF algorithm on the basis of low UtAD impedance. In contrast, escalation of care may be justified in low-risk women with high mid-gestational UtAD Doppler resistance.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

CONTRIBUTION TO AUTORSHIP

Conceptualisation: BT, AF

Methodology: BT

Data collection: AM, BL, MM, MM, RE

Statistical analysis: AM, RE

Data interpretation: AM, BT

Manuscript draft: AM, BT

Manuscript review and editing: AM, MM, MM, BL, AF, BT

DETAILS OF ETHICAL APPROVAL

This retrospective study of routinely collected clinical data was collated from an ongoing continuous audit and was deemed not to require ethics approval or signed patient consent as per the Health Regional Authority (HRA) decision tool.

FUNDING

None.

TABLE LEGENDS

Table 1: Maternal and pregnancy characteristics of the study population of 7793 women. Data showed as median (interquartile range) or number (%).

Table 2: Prevalence of the various placentally-mediated adverse outcomes in the study population. Women were divided in 4 distinct groups: patients at high risk in both trimesters (H^1H^2), at high risk in the first but not the second trimester (H^1L^2), low risk in the first but high risk in the second trimester (L^1H^2), and low risk in both trimesters (L^1L^2). The outcomes include hypertensive disorders of pregnancy (HDP) and small for gestational age (SGA).

Table 3: Statistical analysis of the prevalence of placentally-mediated adverse outcomes in the study population. Comparisons are shown for H^1L^2 versus either H^1H^2 or all women designated high risk (H^1H^2 + H^1L^2) and also for L^1H^2 versus L^1L^2 and all low risk women (L^1L^2 + L^1H^2).

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Table 1: Maternal and pregnancy characteristics of the study population of 7793 women. Data showed as median (interquartile range) or number (%).

	Total population (n=7793)
Weight [kg]	66.4 (59.0-76.2)
Height [cm]	164 (160-169)
Age [years]	32.0 (29.0-35.0)
Nulliparous	4016 (51.5%)
Ethnicity	
White	4928 (63.2%)
Black	944 (12.1%)
South Asian	1414 (18.1%)
East Asian	238 (3.1%)
Mixed	269 (3.5%)
Smoker	318 (4.1%)
Previous pre-eclampsia	221 (2.8%)
ART (IVF/ICSI/other)	330 (4.2%)
Renal disease	9 (0.1%)
Autoimmune disease (SLE/APLS)	95 (1.2%)
Pre-pregnancy diabetes	88 (1.1%)
Chronic hypertension	68 (0.9%)
Gestation at birth	39.6 (39.0-40.6)
Birthweight [g]	3300 (3035-3700)
Preterm births	412 (5.3%)

Table 2: Prevalence of the various placentally-mediated adverse outcomes in the study population. Women were divided in 4 distinct groups: patients at high risk in both trimesters (H^1H^2), at high risk in the first but not the second trimester (H^1L^2), low risk in the first but high risk in the second trimester (L^1H^2), and low risk in both trimesters (L^1L^2). The outcomes include hypertensive disorders of pregnancy (HDP) and small for gestational age (SGA).

PREVALENCE	SGA<10th centile	SGA<5th centile	Stillbirth	All HDP	Preterm HDP
H^1H^2 (n=161)	68 (42.2%)	52 (32.3%)	5 (3.1%)	53 (32.9%)	22 (13.7%)
H^1L^2 (n=439)	87 (19.8%)	51 (11.6%)	1 (0.2%)	109 (24.8%)	20 (4.5%)
L^1H^2 (n=459)	146 (31.8%)	101 (22.0%)	4 (0.9%)	47 (10.2%)	15 (3.3%)
L^1L^2 (n=6734)	833 (12.4%)	472 (7.0%)	21 (0.3%)	229 (3.4%)	11 (0.2%)
Total (n=7793)	1134 (14.6%)	676 (8.7%)	31 (0.4%)	438 (5.6%)	68 (0.9%)

Table 3: Statistical analysis of the prevalence of placentally-mediated adverse outcomes in the study population. Comparisons are shown for H^1L^2 versus either H^1H^2 or all women designated high risk (H^1H^2 + H^1L^2) and also for L^1H^2 versus L^1L^2 and all low risk women (L^1L^2 + L^1H^2).

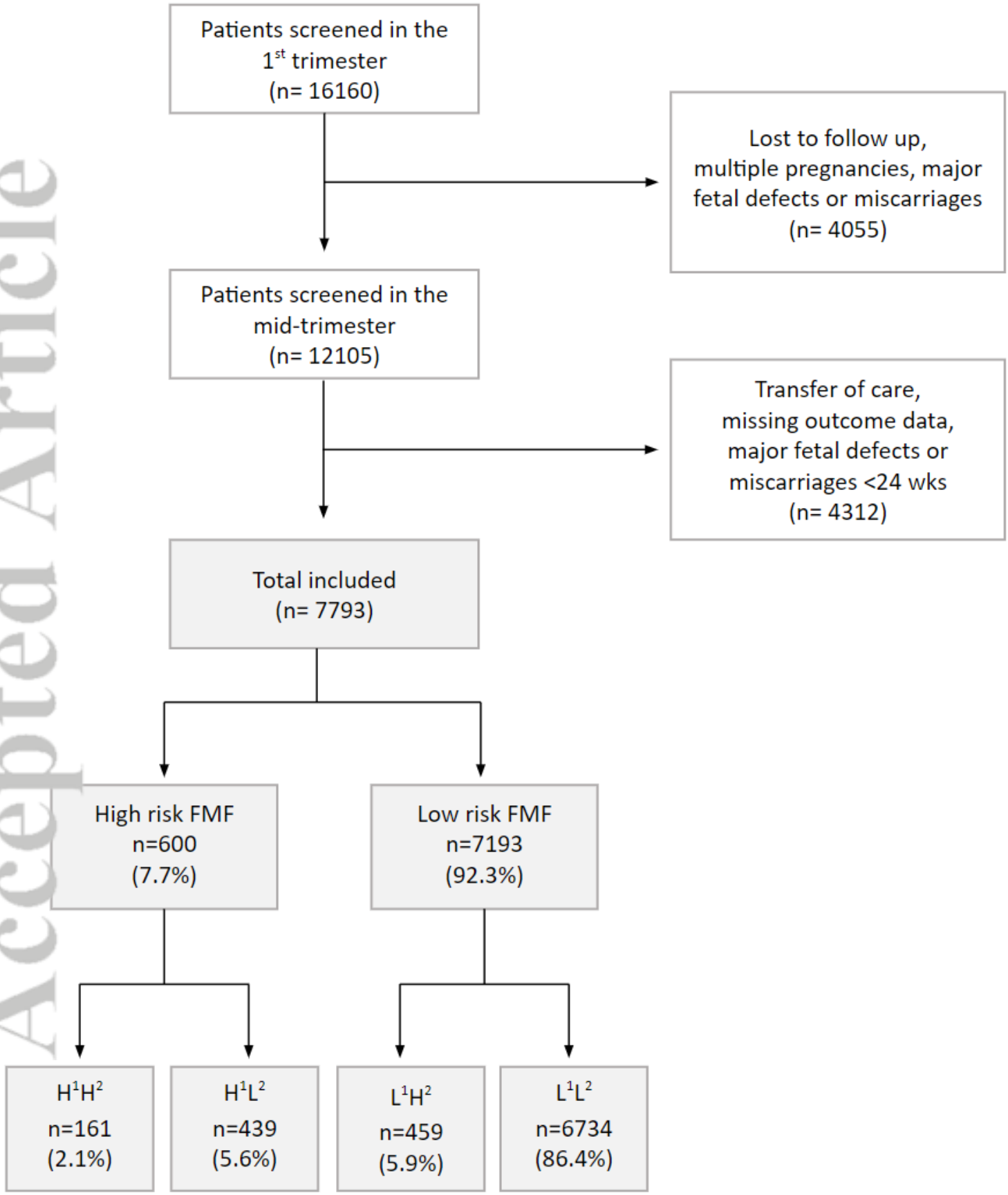
PREVALENCE	SGA<10th centile	SGA<5th centile	Stillbirth	All HDP	Preterm HDP
H^1L^2 vs H^1H^2	**< 0.0001**	**< 0.0001**	**0.0062**	**0.0479**	**0.0001**
H^1L^2 vs [L^1H^2+L^1L^2]	**0.0003**	**0.0067**	1	**< 0.0001**	**< 0.0001**
L^1H^2 vs L^1L^2	**< 0.0001**	**<0.0001**	0.0714	**< 0.0001**	**<0.0001**
L^1H^2 vs [H^1H^2 + H^1L^2]	**0.0326**	**0.0479**	1	**< 0.0001**	**0.0076**

The figure captions are in the manuscript PDF file. See below:

Figure 1: Flowchart summarizing the process of patient selection and the final distribution of the patients in the four study groups. A total of 7793 patients were included and then divided on the basis of the first trimester FMF preeclampsia screening and on the Uterine arteries impedance (UtAD PI) at the midgestational
scan. H1H2: patients at high risk in both trimesters; H1L2: patients at high risk in the first but not the second trimester; L1H2: patients at low risk in the first but high risk in the second trimester; L1L2: patients at low risk in both trimesters.

Figure 2: Suggested management of the patients with different screening results. Women with a result of >1:50 at the first trimester FMF preeclampsia screening are classified as high risk and prescribed prophylactic low-dose aspirin. Mid-gestational Uterine artery PI is then measured and recorded. Serial growth scans at 28 and 36 gestational weeks are scheduled, with intermediate scans when deemed necessary.
Women classified as low risk at the first trimester FMF screening do not receive any prophylaxis. Uterine arteries are sampled at the routine 20-22 weeks scan: depending on the mean UtAd PI, fetal growth and Dopplers are checked at 36 weeks or anticipated at 28 weeks, when the mean UtAd PI is (>1.25). UtAd: Uterine Artery Doppler.

Figure 3: Distributions and proportions of patients with preterm Hypertensive Disorders of Pregnancy (HDP) for the 4 groups of risk. H1H2: High risk first trimester screening and High UtAD PI at the mid-gestational scan; H1L2: High risk first trimester screening and Low UtAD PI at the mid-gestational scan; L1H2: Low risk first trimester screening and High UtAD PI at the mid-gestational scan; L1L2: Low risk first trimester screening and Low UtAD PI at the mid-gestational scan.



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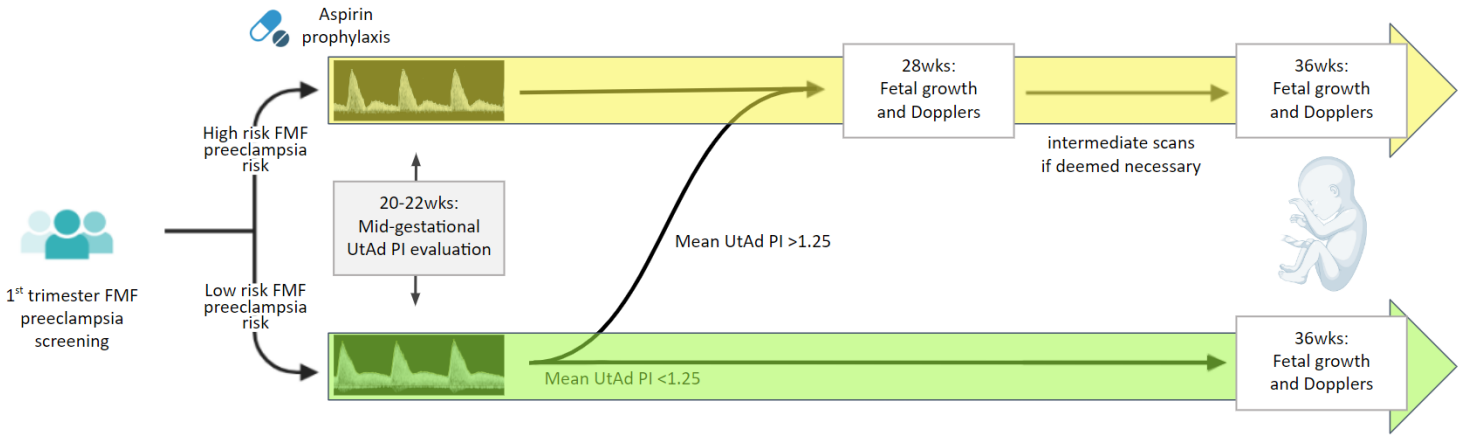

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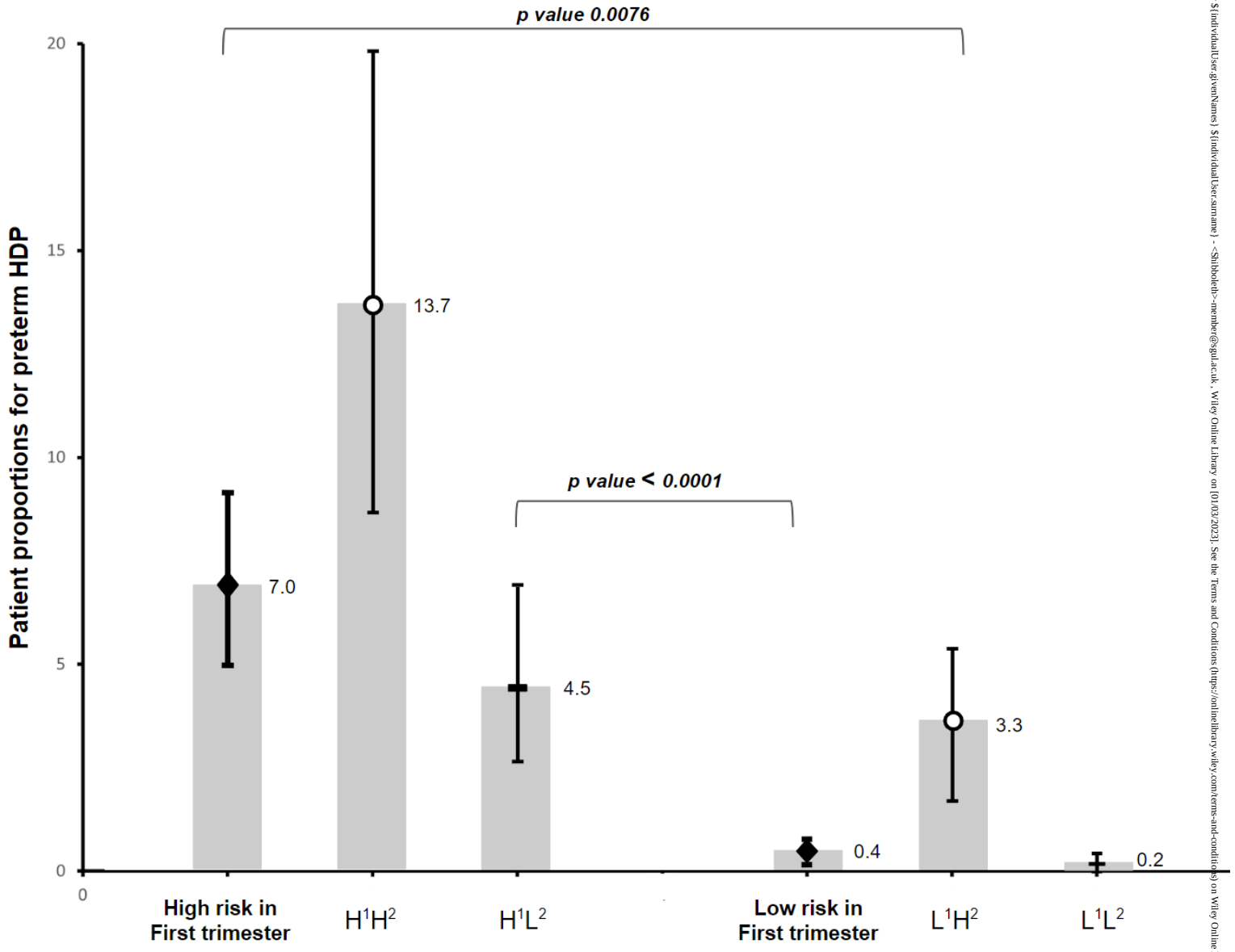

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