



THE ROLE OF ULTRASOUND IN SCREENING FOR AND FOLLOW-UP OF PREECLAMPSIA

Journal:	<i>Ultrasound in Obstetrics and Gynecology</i>
Manuscript ID	UOG-2018-0346.R2
Wiley - Manuscript type:	Guideline
Date Submitted by the Author:	15-Jul-2018
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Manuscript Categories:	Obstetrics
Keywords:	pre-eclampsia, screening, guidelines

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GUIDELINES

THE ROLE OF ULTRASOUND IN SCREENING FOR AND FOLLOW-UP OF PREECLAMPSIA

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INTRODUCTION

Hypertensive disease of pregnancy affects up to 10% of pregnant women¹ and the pooled global incidence of preeclampsia is approximately 3%². Significant variations between developed and developing countries can be attributed to actual and methodological reasons. Preeclampsia and its complications are a major contributor to maternal and perinatal morbidity and mortality worldwide^{1,3}. Given that timely and effective care can improve the outcome of preeclampsia³, the development of effective prediction and prevention strategies has been a major objective of prenatal care and of research.

Preeclampsia is a multisystemic disease of multifactorial origin: it involves defective placentation, oxidative stress, autoimmunity, platelet and thrombin activation, intravascular inflammation, endothelial dysfunction, an imbalance in angiogenesis and maternal cardiac maladaptation^{4,5}. Defective placental invasion is strongly associated with most cases of early and severe preeclampsia⁴.

In contrast, defective placentation seems to be less important for the development of preeclampsia that manifests later in pregnancy, e.g. after 34 weeks. Placentas from pregnancies complicated with preeclampsia at or near term have a significantly lower

frequency of histological abnormalities compared to early-onset disease⁶ and maternal factors (e.g. metabolic syndrome or chronic hypertension) have a relatively greater significance⁴. Differences in early- and late-onset preeclampsia are also seen in risk factors⁷, maternal vascular responsiveness⁸, screening performance⁹ and prevention effectiveness¹⁰.

Increasing insight in these mechanisms has been reflected in the current screening strategies, which are based on four arms, i.e. maternal history, maternal demographics, uterine artery Doppler studies and biomarkers, including maternal blood pressure¹¹.

There are currently more than 10,000 PubMed-indexed articles related to preeclampsia screening, by any tests and modalities, illustrating the vast interest on this topic. Less than one-fifth of these refer to early screening, as this is a development of the last decade. The aim of this guideline is to review latest evidence and provide evidence-based recommendations, when possible, on the role of ultrasound in screening and follow-up of pre-eclampsia. The guideline intends to focus on the technical / clinical aspects of screening, without extending to health economics and policy issues, including the advisability and cost-effectiveness of screening. Moreover, this guideline was built under the assumption that the resources required for its implementation (equipment, examiners, expertise) are available. Therefore, the steps and procedures described in this Guideline are not intended to act as a legal standard for clinical service.

TERMINOLOGY: SCREENING vs. PREDICTION

Although the two terms are commonly used interchangeably, screening is in fact a wider process, beginning with invitation of a population to participate and ending with treatment for individuals identified at high risk¹². In this context, prediction, or the calculation of risk for disease, is an integral element of the screening process, but it is not equivalent with screening, as the latter also involves an intervention that is offered to individuals at high risk and aims to alter the natural history of the condition screened for, and ultimately to improve the outcome¹³. Screening in prenatal care has been commonly used for offering the option of timely termination of pregnancy to parents bearing fetuses with untreatable conditions, which is an extension to the WHO principles of screening. In the context of preeclampsia, *screening* will be the preferred term when identification of cases at risk may lead to prevention of its development, whereas *prediction* will be the preferred term when there is no evidence that identification of women at risk will eventually improve their outcome.

RELEVANT INFORMATION AVAILABLE TO THE EXAMINER

Recommendation

- Examiners involved in screening for preeclampsia should have up-to-date knowledge regarding major risk factors for preeclampsia

GPP

Given that ultrasound screening for preeclampsia should not be isolated from the general concept of prenatal care, it is advisable that professionals who screen for preeclampsia have up-to-date knowledge about proven risk factors and engage at identifying them during screening. A global assessment of risk profile would encompass four broad areas, i.e. personal risk profile (including age, ethnicity, parity, smoking, medical and obstetric history and conception method), metabolic risk profile (including BMI and history of diabetes), cardiovascular risk profile (including existing cardiovascular conditions and measurement of mean arterial blood pressure) and placental risk profile (including uterine artery Doppler and maternal serum biomarkers) ¹¹.

SCREENING FOR PREECLAMPSIA USING ULTRASOUND

The use of ultrasound as a screening / prediction tool for preeclampsia is based on the fact that defective placentation results in incomplete transformation of the spiral arteries. The latter phenomenon is quantifiable through measurement of impedance (or resistance) to flow in the uterine arteries by Doppler assessment. Placental villous and vascular histopathological lesions are four-to-seven times more common in preeclamptic pregnancies ¹⁴ and are associated with increased resistance to uterine artery blood flow ¹⁵.

Which Doppler index to use

Recommendation

- The pulsatility index (PI) is the index that should be used for the examination of the uterine artery resistance in the context of preeclampsia screening

Grade: B

As described in the ISUOG Practice Guideline on the use of Doppler ultrasonography in obstetrics ¹⁶, systolic-diastolic (S/D) ratio, resistance index (RI) and pulsatility index (PI) are the three well-known indices to describe arterial flow velocity waveforms. The pulsatility index is the most commonly used index; its advantage over RI in the evaluation of the uterine artery Doppler waveform is that PI includes in the calculation the averaged value of all maximum velocities during the cardiac cycle

instead of only two moments in the cardiac cycle as it is in the resistance index.

Pulsatility index is more stable and it does not approach infinity when there are absent or reversed diastolic values¹⁶.

Uterine artery notching has also been used in screening for preeclampsia¹⁷, with the presence of bilateral notches being associated with indications of maternal endothelial dysfunction (lower flow-mediated dilatation of the brachial artery)¹⁸. Despite its theoretical plausibility, bilateral notching is anyway common (43%) in normal first-trimester pregnancies¹⁹, which reduces its specificity as a screening marker. Similarly, the presence of uterine artery notches in the second trimester has similar sensitivity to that of increased PI, but for a higher screen positive rate¹⁷, and there may be a degree of subjectivity in defining notching, which further limits the value of this finding as a screening marker.

A 2008 meta-analysis indicated that an increased pulsatility index, alone or combined with notching, is the most predictive Doppler index for preeclampsia²⁰. A considerable amount of evidence published since then indicates the superiority of mean uterine PI as the preferred Doppler index for preeclampsia screening, and this is the index tested for screening and prevention in the first trimester²¹⁻²³.

First trimester

Technical advice

- Doppler examination of the uterine arteries at 11⁺⁰ – 13⁺⁶ weeks can be performed either transabdominally or transvaginally, according to local conditions and resources
- Screening by first-trimester uterine artery PI above the 90th centile detects 48% of women who will develop early preeclampsia and 26% of any preeclampsia for a 10% screen positive rate

GPP

Level of evidence:
2++

Technique of first-trimester Doppler examination of the uterine arteries.

The most extensively studied period of Doppler examination of the uterine arteries is at 11⁺⁰ to 13⁺⁶ weeks. This is a common time for first trimester ultrasound in many countries and therefore practical in terms of logistics. Earlier assessment has not been sufficiently studied because trophoblast invasion is not yet advanced as to be assessable.

For the first-trimester assessment of uterine artery resistance, a transabdominal midsagittal section of the uterus and cervix is initially taken. Using color flow mapping, the transducer is gently tilted sideways, so that the uterine arteries are identified as a

high-velocity blood flow vessel along the side of the cervix and uterus. The sampling gate of pulsed wave (PW) Doppler is narrow (e.g. set at 2 mm) of either the ascending or descending branch of the uterine artery at the point closest to the internal cervical os, with an insonation angle of less than 30° ²⁴. The peak systolic velocity should be >60 cm/sec in order to verify that the uterine artery is examined. The PI is measured when 3 similar waveforms are obtained^{25,26}. The rationale for using this particular methodology is that it has been standardized, and underlies most of the first-trimester screening studies. Detailed methodology can be found in a practical advice paper published in the ISUOG's journal²⁷. Following this approach, uterine artery PI can be measured in more than 95% of the cases²⁵ (Figure 1).

The transvaginal measurement follows the same principles. The woman is placed in the lithotomy position, with her bladder empty, and a transvaginal probe is used to obtain a sagittal view of the cervix. The probe is then moved laterally until the paracervical vascular plexus is seen, and the uterine artery is identified at the level of the internal cervical os. Measurements are taken after it is ensured that the angle of insonation is $\leq 30^\circ$ ²⁸.

Technical advice

- A standard methodology, as described in the guideline, should be followed for the examination of the uterine artery Doppler indices

GPP

Adherence to a standard methodology is essential to ensure reproducible measurements. Studies evaluating the reproducibility of this technique have shown interobserver intraclass/concordance correlation coefficients of 0.80-0.85^{29,30}. However, the limits of agreement were found to be as high as $\pm 35\%$ for the transvaginal and $\pm 40\%$ for the transabdominal approach³⁰. Based on such results, the reproducibility of the method should be interpreted as being poor to moderate³¹. Besides differences caused by observers, Doppler indices may change over the span of an examination, owing to factors such as uterine contractions, different heart rate, etc. Although the effect of these latter factors cannot be prevented, adherence to the standard methodology of examination²⁷ is imperative to minimize the operator-dependent variability, as systematic error in the measurements can affect screen-positive rate³².

Technical advice

- The 95th centile for transabdominal uterine artery mean PI between 11+0 and 13+6 weeks is 2.35
- The resistance of the uterine arteries is higher in transvaginal compared to transabdominal measurement; the 95th centile of the measurable mean resistance (PI) values of the uterine arteries is approximately 3.10 for CRL up to 65 mm, gradually declining thereafter
- The uterine artery PI may also be affected by maternal factors, including ethnic origin, BMI and previous preeclampsia

Level of evidence: 2+

Level of evidence: 2+

Level of evidence: 2++

Recommendation

- Given that maternal factors can affect uterine artery PI, whenever feasible, inclusion of uterine artery PI in a multifactorial screening model should be preferred over its use as a standalone test with absolute cut-offs

Grade: B

The 95th centile of mean uterine artery PI with the transabdominal approach is about 2.35 for the period of 11+0 to 13+6 weeks²⁵, with no²⁵ or only a small trend to decrease³⁰ over this period. In two comparative studies, transvaginal approach gave significantly higher readings compared to the transabdominal one; the mean PIs in the two studies were 1.98 vs. 1.83³³, and 1.60 vs. 1.52³⁰. The reason for this may be that TVS ensures a closer proximity to the vessel and lower insonation angles³⁰. The 95th centile of the mean UtA PI for transvaginal measurements has been reported as approximately 3.10 for CRL up to 65 mm and progressively declines thereafter, reaching 2.36 at a CRL of 84 mm³³.

Maternal factors may affect uterine artery PI in women not developing preeclampsia, including ethnic origin (African is associated with increased PI), BMI (decreases with increasing BMI) and previous preeclampsia (associated with increased PI)²⁶. The association between decreasing PI and increasing BMI is not clear; the vasodilatory effect of increased levels of estrogens in these women on the uterine circulation has been postulated as a potential cause^{26,34}. Therefore, an absolute numerical cut-off for uterine artery PI may not accurately reflect uterine arteries resistance, and it has been suggested that first-trimester uterine artery PI should be expressed as multiples of the median (MoMs) rather than as absolute values³⁵

Recommendation

- The mean uterine artery PI should be the Doppler index used for screening in

the first trimester

Grade: B

In one of the earlier studies using the current standard methodology for the examination of uterine artery Doppler in the first trimester, a PI >95th centile had 27% sensitivity for preeclampsia and 60% sensitivity for preeclampsia requiring delivery before 32 weeks²⁵. Subsequent studies used lowest uterine artery PI (the PI of the side with the least resistance), as the point estimates for the area under the curve (AUC) were marginally better when the lowest rather than the mean PI was used in the regression model (0.91 vs. 0.90 for early preeclampsia)³⁶. However, the confidence intervals for the AUCs were overlapping, and the superiority of the lower PI was not confirmed by another large study (AUC 0.79 for mean and 0.76 for lowest PI for the outcome of early preeclampsia, with overlapping CIs)³⁷. Both techniques are acceptable, but the mean uterine artery PI is the most commonly used index for first- and second-trimester uterine artery Doppler examination, and the default reference values in most commercial software apply to this.

Although bilateral notching has been associated with 22-fold increased risk for preeclampsia and almost 9-fold increased risk for small-for-gestational age neonate³⁸, it can be found in more than 50% of women at 11+0 to 13+6 weeks^{25,39}. Therefore, this marker has a very low specificity for preeclampsia.

A recent meta-analysis reported that first-trimester Doppler examination of the uterine arteries can predict 47.8% of early preeclampsia (7.9% false positive rate), 39.2% of early fetal growth restriction (6.7% false positive rate) and 26.4% of any preeclampsia (6.6% false positive rate), when using the 90th centile of PI or RI as cut-off⁴⁰.

However, combined screening (maternal factors, maternal mean arterial blood pressure, uterine arteries Doppler, P/GF measurement) has superior predictive performance (please see at the relevant section) and should be preferred over Doppler-based screening, if available.

Second trimester

Technical advice

- Doppler examination of the uterine arteries can be performed either transabdominally or transvaginally, according to the local conditions and resources

GPP

Uterine artery flow resistance can be assessed either transabdominally or transvaginally.

The transabdominal technique is similar to that of the first trimester, the main difference being that right and left uterine arteries are identified at the apparent crossover with the external iliac arteries rather than paracervically. After the arteries are identified, pulsed-wave Doppler is used to obtain the waveforms. When three similar consecutive waveforms are obtained, the pulsatility index (PI) is measured, and the presence or absence of early diastolic notch is recorded ⁴¹.

In the transvaginal technique, the woman is asked to empty her bladder and is placed in the dorsal lithotomy position. The ultrasound probe is inserted into the anterior fornix, and the cervix is identified in the midsagittal plane. Subsequently, the probe is moved into the lateral fornix and the uterine artery is identified using color Doppler at the level of the internal cervical os on either side. Pulsed wave Doppler is used to obtain three similar consecutive waveforms. The pulsatility and resistance index can then be measured and the presence or absence of early diastolic notch can be recorded ¹⁷. The examination of uterine artery Doppler waveform following this approach is feasible in 99% of women ⁴².

As in the first trimester, using either transabdominal or transvaginal approach, care should be taken to maintain the angle of insonation $<30^\circ$ and the peak systolic velocity >60 cm/sec to ensure that the uterine artery rather than the arcuate artery is being examined ²⁴.

Technical advice

- As in the first trimester, uterine artery PI in the second trimester is higher when measured transvaginally
- The 95th centile for mean uterine artery PI is 1.44 for the transabdominal approach and 1.58 for the transvaginal approach at 23 weeks.
- The 95th centile for the mean uterine artery PI decreases by about 20% between 20 and 24 weeks, and it does not change significantly between 22-24 weeks

Level of evidence: 2++

Level of evidence: 2+

Level of evidence: 2++

Recommendation

- The mean uterine artery PI may be used for prediction of preeclampsia. In case of a unilateral placenta, a unilaterally increased PI does not appear to increase the risk for preeclampsia if the mean PI is within normal limits.

Grade: B

Similarly to first trimester, when the uterine arteries are examined transvaginally, the PI readings are higher compared to the transabdominal approach. In a comparative series

of 96 women between 20 and 26 weeks, the mean UtA PI was 1.07 with the transvaginal vs. 0.96 with the transabdominal approach. The median angle of insonation was lower using TVS (10.0° vs. 17.5°); however, PI being a ratio, the most likely reason for the differences between transabdominal and transvaginal differences is the different anatomical location of the examination. Both techniques have similar reproducibility (interobserver concordance coefficient 0.86 vs. 0.81, limits of agreement $\pm 35\%$)³⁰.

The 95th centile of the mean UtA PI with the transabdominal approach has been reported as 1.44⁴¹ whereas the corresponding value for the transvaginal approach was 1.58⁴³ at 23 weeks. The 95th centile of the mean uterine artery PI decreases by about 15% between 20 and 24 weeks, and by $<10\%$ between 22-24 weeks⁴⁴.

In case of a unilaterally localized placenta, the resistance to the uterine flow opposite to the placenta is commonly increased. A unilaterally increased PI does not appear to be associated with a higher risk for preeclampsia, if the mean PI is within normal limits⁴⁵.

Performance of second-trimester prediction of preeclampsia

The predictive performance of uterine artery Doppler is preferentially higher for early-onset preeclampsia; a study of more than 32,000 women indicated that, for a false positive rate of 10%, UtA PI alone can predict 85% of the cases of early-onset preeclampsia, vs. 48% of late-onset preeclampsia when combined with maternal factors⁴⁶. Furthermore, the risk for early preeclampsia appears to increase with increasing UtA resistance; a mean PI of 1.6 was associated with a LR of 3.07, vs. LR 8.00 for a mean PI of 1.8 and LR 27.08 for mean PI 2.2 (transvaginal measurements). In general, the UtA Doppler velocimetry tends to predict better more severe and complicated cases. For example, mean $PI > 1.65$ (TVS) was found to predict 41% of all preeclampsia cases, but when subgroups were examined, this rate was 69% for preeclampsia with fetal growth restriction vs. 24% for preeclampsia with normal fetal growth¹⁷. This finding can be explained by the fact that high impedance in the uterine arteries reflects defective placentation, with its concomitant deleterious effect on fetal growth.

Bilateral diastolic notches in the UtA Doppler waveform are also associated with increased risk for preeclampsia^{17 41 42 46 47}. However, for the same false positive rate, UtA PI is associated with better sensitivity than notches⁴², making their addition to screening not recommendable, although not all studies agree on the latter⁴⁷.

In terms of maternal health, a study of 491 women undergoing transthoracic echocardiography at the time of second-trimester screening for preeclampsia, showed

that women with a mean UtA PI >90th centile (1.25 for this study), had a higher prevalence of previously undiagnosed, functionally significant, cardiac defects (4.4%) as compared to women with normal mean UtA PI (0.3%). This risk was particularly higher among migrant women ⁴⁸.

Third trimester

Technical advice

- Although uterine artery velocimetry can also be transvaginally examined, the commonest method of examination of the uterine arteries Doppler in the third trimester is transabdominal
- The 95th centile of mean uterine artery PI is 1.17 for transabdominal scan at 30-34 weeks

Level of evidence: 4

Level of evidence: 2+

Recommendation

- There are currently no randomized trials on the impact of third-trimester screening for preeclampsia on maternal fetal and neonatal outcomes; consequently, its implementation into routine practice cannot be recommended at present.
- The mean uterine artery PI should be used for prediction for preeclampsia, if this is offered in the third trimester

GPP

Grade: B

The standard method for Doppler examination of the uterine arteries Doppler in the third trimester is by transabdominal approach, similarly as for the second trimester ^{24 41}.

In a large, multicenter study from the UK, the 90th and 95th centile for mean uterine arteries PI between 30⁺⁰ and 34⁺⁶ weeks was 1.03 and 1.17, respectively ⁴⁹. Mean uterine artery PI >95th centile (5% false-positive rate) alone could predict 54% of preeclampsia before 37 weeks and 14% of preeclampsia ≥37 weeks. The corresponding rates for mean PI >90th centile (10% false-positive rate) were 68% and 14%, respectively, highlighting the poor performance of Doppler studies alone in predicting term preeclampsia ⁴⁹. The same group assessed the effectiveness of screening at 35-37 weeks; uterine artery Doppler alone was a poor predictor for preeclampsia; even when combined with maternal factors, the detection rate was 26% for 5% false positive rate,

and 37% for 10% false positive rate⁵⁰.

Reversed diastolic flow has been sporadically reported in the third trimester and was associated with adverse outcome in cases with placental insufficiency, e.g. progress to eclampsia, or intrauterine demise^{51 52}.

Longitudinal changes in Doppler indices

Technical advice

- Persistently increased uterine artery resistance from first- to second trimester may identify women at highest risk for preeclampsia

Level of evidence:
2++

Recommendation

- Given that preventive strategies (e.g. low-dose aspirin) for reducing the risk of preeclampsia are effective if started in the first trimester, delaying their commencement to assess the evolution of Doppler in the second trimester should be avoided

GPP

Apart from cross-sectional measurements of Doppler indices, their longitudinal changes have also been studied in the prediction of preeclampsia.

A study sequentially examining uterine artery Doppler at 11-14 and 19-22 weeks (N=870) reported that 73% of cases with increased PI at the first trimester normalized at the second. Women with persistently increased PI at the first and second trimester were at highest risk (37.5%) for adverse pregnancy outcome, i.e. growth restriction or hypertensive disorders. In contrast, women with normal PI at the first trimester had a 95% chance of normal measurements at the second trimester as well, and this was the group with the lowest incidence of adverse outcome (5.3%)⁵³.

Another index that has been tested is the difference between second-trimester PI and first-trimester PI, both expressed in MoMs for the corresponding gestational ages. An increasing gap between first- and second-trimester PI MoMs, reflecting defective spiral artery transformation, appeared to be the most accurate predictor for early (area under the curve, AUC 0.85) and preterm (AUC 0.79) preeclampsia⁵⁴. Another study on 104 women with increased uterine artery PI at 20-22 weeks reported that the abnormal findings persisted at 26-28 weeks in 59.6% of cases; women with persistently increased PI had a greater risk for preeclampsia (16% vs. 1%), SGA (32% vs. 1%) and admission to a neonatal intensive care unit (26% vs. 4%), compared to women with normalization of

the PI⁵⁵.

A problem with sequential assessment of Doppler is that the window of opportunity for preventative interventions (i.e. gestational age <16 weeks) is missed, waiting for possible changes in a subsequent scan.

Placental volume

Recommendation

- Although placental volume and vascularization indices have been tested as predictors for preeclampsia, their limited reproducibility and the fact that their measurement requires special equipment and is time-consuming limit their use for screening

GPP

Shortly after the introduction of three-dimensional ultrasound, first-trimester placental volume was tested as a potential predictor of preeclampsia. In one of the initial studies, placental volume at 12 weeks was compared to uterine artery Doppler examination at 22 weeks; the predictive performances of these two methods were 20% and 28%, respectively for preeclampsia without SGA; 31% and 46%, respectively for preeclampsia with SGA; and 50% and 50%, respectively for early preeclampsia⁵⁶. Similarly, placental volume had comparable predictive performance with first-trimester uterine artery mean pulsatility index for preeclampsia (56% vs 50%) and preeclampsia requiring delivery before 32 weeks (67% vs. 67%)⁵⁷. However, these findings have not been confirmed by all studies⁵⁸⁻⁵⁹. Three-dimensional placental vascularization indices have also been evaluated⁵⁸⁻⁶²; however, they can be affected by attenuation due to depth and tissue interfaces, the use of different ultrasound settings and the lack of a robust reproducibility (intra- and interobserver intraclass correlation coefficients <0.48 and <0.66, respectively)⁶³, which all limit their clinical applicability.

Although a good reproducibility is reported for placental volume calculation⁶⁴⁻⁶⁵, still its normal variation is very wide, limiting its clinical applicability; published values for first-trimester mean placental volume range from 45 to 74 mm³⁵⁹⁻⁶¹⁻⁶⁴⁻⁶⁶. Moreover, placental volume calculation is currently a non-automated measurement subjected to operators variations, and can be time-consuming, depending on the number of frames used for volume analysis⁶⁷.

Combined screening strategies

Recommendation

- A combination of maternal factors, maternal arterial blood pressure, uterine artery Doppler and placental growth factor (PIGF) at 11-13 weeks appears to be the most efficient screening model for identification of women at risk of preeclampsia. **Grade: B**
- Given the superiority of combined screening, the use of Doppler cut-offs as a standalone screening modality should be avoided if combined screening is available. **Grade: B**
- The transabdominal approach should be preferred for calculating first-trimester individual patient risk, as most screening algorithms were calculated using transabdominal ultrasound. **GPP**

Maternal (history, demographics, cardiovascular and metabolic profile) and placental (including uterine artery resistance and biomarkers) risk factors have been identified for the development of preeclampsia. Therefore, the current trend in screening involves combining the presence or absence of multiple risk factors in order to calculate a personalized risk and then act on consequence, in way similar to the screening for chromosomal abnormalities¹¹. On a population basis, combined screening aims at improving the sensitivity of single marker screening and, at the same time, reducing its false positive rate.

Combined screening has been the topic of approximately 400 PubMed articles as of April 2018. Multiple studies have shown that women who will develop preeclampsia have, on average higher mean arterial pressure⁶⁸, higher concentrations of maternal serum soluble fms-like tyrosine kinase-1 (sFlt-1)^{69 70} and alpha-fetoprotein (AFP)⁷¹, and lower concentrations of pregnancy associated plasma protein-A (PAPP-A)⁷², placental growth factor (PIGF)^{70 73}, along with higher resistance in the uterine arteries⁷⁴, compared to women who did not. For all these predictors, the predictive performance was greater for early than for late preeclampsia^{9 70}, and was also greater later in pregnancy than at 11-13 weeks, i.e. closer to the development of preeclampsia^{68-71 73-75}.

Data from almost 36000 prospectively followed singleton pregnancies showed that, at a false-positive rate of 10%, maternal factors alone (including age, weight, ethnic origin, reproductive and medical history, smoking) could predict 49% of preeclampsia <37 weeks. The addition of PIGF increased this rate to 60%, and combined screening with maternal characteristics, uterine artery mean pulsatility index, mean arterial pressure and PIGF at 11-13 weeks predicted 75% of preeclampsia <37 weeks and 47% of

preeclampsia >37 weeks,⁹. The same protocol was used in the context of the ASPRE trial; in this trial combined screening was followed by randomization to aspirin versus placebo in those at high risk. This algorithm combining maternal factors, mean arterial pressure, mean uterine artery PI and PIGF achieved 100% detection rate for preeclampsia developing <32 weeks, 75% for preeclampsia developing <37 weeks and 43% for preeclampsia developing ≥37 weeks, for 10% FPR^{21 76}. The fetal fraction of cell-free DNA in the maternal circulation is also significantly associated with maternal and fetal factors for preeclampsia, and there is a significant relationship between low fraction and increased risk for preeclampsia⁷⁷; however, its impact on first-trimester screening has not been evaluated in prospective studies.

Similar to the first trimester, a second-trimester model using uterine artery PI, maternal factors including BMI, ethnic origin, previous obstetric history, smoking status, type of conception, medical history) and mean arterial blood pressure may detect as much as 100% of women who will develop early preeclampsia for a false positive rate of 10%; the sensitivity for late preeclampsia and gestational hypertension is 56.4% and 54.1% respectively⁷⁸.

In the third trimester, a combination of maternal factors and sFlt-1 measurement may predict 83% and 38% of preeclampsia before and after 37 weeks, respectively, for a false positive rate of 5%. The corresponding figures for 10% false positive rate are 94% and 51%, respectively⁴⁹. Prior screening in the first and second trimester does not further improve prediction accuracy over that of third-trimester alone⁷⁹. Ethnic origin affects the sensitivity and false positive rate of third-trimester prediction, with both being higher in women of Afro-Caribbean origin⁸⁰. Maternal and biochemical markers become more important for the prediction of preeclampsia in late pregnancy. Thus, among several potential factors, mean arterial pressure, PIGF and sFlt-1 were the ones associated with the prediction of preeclampsia between 30-34⁸¹ and 35-37⁸² weeks. In contrast, the addition of uterine artery PI and maternal cardiovascular parameters (total peripheral resistance, cardiac output) did not improve the prediction of preeclampsia after 35-36 weeks⁸³. The sFlt-1/PIGF ratio as a standalone marker can predict more than 75% of the cases who will develop preeclampsia within 4 weeks, but its sensitivity is significantly higher at 31-34 than at 35-37 weeks (false positive rates 1.7% vs. 9.6%, respectively)⁸⁴.

A common concern with combined screening models is that they may perform differently when prospectively applied in populations different than the ones they were derived from⁸⁵. To this end, the performance of the combined screening model used for the ASPRE trial (maternal factors, mean arterial pressure, mean uterine artery PI, placental growth

factor) was practically identical to the dataset used for development of the model^{9 76}. In fact, this strategy was found to be considerably more efficient for the prediction of early preeclampsia than the history-based screening policies recommended by both the American College of Obstetricians and Gynecologists and the UK National Institute for Health and Care Excellence^{22 86}.

ASSESSMENT OF MATERNAL HEMODYNAMICS

Recommendation

- Despite the fact that maternal hemodynamic assessment may be of value in prediction of preeclampsia, there are still few data to support their routine implementation in clinical practice as standalone tests.

GPP

Cardiovascular adaptation plays a critical role in the hemodynamic changes observed in normal pregnancy. Failure of this adaptation, or possibly subclinical pre-pregnancy cardiovascular dysfunction, have been associated with the risk of developing preeclampsia⁸⁷⁻⁸⁹. Women who develop preeclampsia have pre-pregnancy cardiovascular risk factors, demonstrate increased arterial stiffness and impaired cardiac function at the time of the clinical diagnosis, as well as several weeks before the clinical onset of the pathology and several months after the incident pregnancy⁹⁰⁻¹⁰¹. The cardiovascular implications of pre-eclampsia appear to continue in the long-term, as shown by both by increased frequency of prolonged subclinical impairment of systolic biventricular¹⁰² and endothelial function¹⁰³, and by the increased risk of cardiovascular morbidity later in life¹⁰⁴⁻¹⁰⁶. The hazard ratio for developing cardiovascular disease later in life is as high as 5.4 in women who had severe pre-eclampsia/eclampsia¹⁰⁵. Moreover, compared to women with no recurrent disease, women who develop recurrent preeclampsia in a subsequent pregnancy tend to have altered cardiovascular parameters between pregnancies, which may hinder their normal adaptation in the next pregnancy¹⁰⁷.

The simplest hemodynamic parameter with established value in the context of combined screening is maternal mean arterial pressure^{9 76 78 108}. Additionally, arterial stiffness can be estimated by ultrasound and this parameter has been found to differ significantly in women with preeclampsia from women with normal pregnancies. In a systematic review of 23 studies evaluating arterial stiffness in association with hypertensive disease of pregnancy, women with preeclampsia had elevated arterial stiffness both during and

after pregnancy, and to a greater extent than in gestational hypertension (GH)⁹⁰. Interestingly, more severe preeclampsia is associated with greater arterial stiffness⁹⁰. Both pulse wave analysis and the augmentation index have also been observed to be higher in the sub-clinical stage (as early as 11 weeks) in women who will develop preeclampsia^{91 92}. Cross-sectional and longitudinal studies have demonstrated that arterial stiffness indices could be used as a screening test, as early as 11 weeks' gestation, to predict subsequent development of early and late-onset pre-eclampsia, especially when combined with other maternal variables such as central systolic blood pressure^{91 92}. Lower flow-mediated dilatation has been reported in the first and second trimesters among high-risk women who subsequently developed preeclampsia^{109 110}.

Cardiac output was significantly higher at 11-13 weeks in women who later developed preeclampsia or gestational hypertension, compared to uncomplicated pregnancies⁹⁴. When combined with maternal variables, for a 10% false-positive rate, the detection rates were 43.4% for all types preeclampsia, 52% for preeclampsia without a small for gestational age foetus, and 23.3% for gestational hypertension⁹⁴. Women who subsequently develop preeclampsia have evidence of left ventricular concentric remodelling at mid-gestation⁹⁷.

Despite the fact that maternal hemodynamics are promising screening markers of preeclampsia, a combined approach taking into account maternal characteristics and biochemical markers is required to reach a clinically useful prediction model. Meanwhile, as assessment of maternal hemodynamics is increasingly being performed in preeclampsia studies, it is imperative that relevant devices and techniques are appropriately used in pregnant populations¹¹¹.

WHAT TO DO AFTER SCREENING

Recommendation

- There is convincing evidence that low-dose aspirin can significantly decrease the risk for development of early preeclampsia, when commenced at the time of first-trimester screening

Grade: A

First trimester

Currently, the American College of Obstetricians and Gynecologists¹¹², the UK National Institute for Health and Care Excellence (NICE)¹¹³ and the Society of Obstetricians and

Obstetricians of Canada ¹¹⁴, among others, recommend administering low-dose aspirin to women at risk for placental insufficiency, commencing before 16 weeks.

Most of the studies on which current recommendations are based, classified women as high-risk based on historical or medical factors rather than using current screening methods (i.e. maternal factors, Doppler and biochemistry). In 2017, the multicenter ASPRE trial was reported. In this study, 1776 women at high risk for preeclampsia based on first-trimester combined screening were randomized to either aspirin 150 mg at bedtime or placebo ¹⁰. The dose of 150 mg was selected in line with evidence that a significant proportion (10-30%) of patients show aspirin resistance at lower doses ¹¹⁵, and *in vitro* data showing that the optimal dose to improve trophoblast function is the equivalent of 150mg *in vivo* ¹¹⁶. Bedtime administration was based on data indicating the presence of a diurnal effect in response to aspirin, with optimal effectiveness for bedtime administration ¹¹⁷. The ASPRE trial found that aspirin reduced the risk for preeclampsia before 37 weeks by 62% (from 4.3% to 1.6%). Aspirin also reduced the risk of preeclampsia before 34 weeks by 82%, but this effect did not reach statistical significance due to the small absolute rates (0.4% vs. 1.8%) ¹⁰. The beneficial effect of aspirin appeared to depend on the degree of compliance, with the greatest risk reduction observed for compliance $\geq 90\%$ ¹¹⁸.

First-trimester screening and intervention with aspirin appears to be cost-effective, combining the prevention of a significant proportion of early onset cases with cost savings for the health system ¹¹⁹.

Second trimester

Second-trimester prediction appears to be equally or more sensitive ^{70 78} as prediction in the first-trimester, but its value is limited by the lack of effective interventions at this gestational stage. While aspirin commenced in the first trimester appears to reduce the development of preeclampsia ^{120 121}, the same intervention seems ineffective when started after 20 weeks ¹²⁰. Although it is too late to prevent the development of preeclampsia after second trimester prediction, its results can still be useful in guiding further follow-up ^{122 123}. However, the clinical impact of intensified follow-up is yet to be proven. A Spanish trial (N=11667) randomized women who attended routine second-trimester scan to Doppler or non-Doppler groups. It was found that Doppler velocimetry identified 60% of the women who developed preeclampsia, but the intensification of their care did not result in better short-term maternal and perinatal outcomes compared to

women who had not a second-trimester Doppler examination at second-trimester scan

¹²⁴.

Third trimester

Third-trimester prediction can identify the great majority of women who will develop preeclampsia in the subsequent weeks^{80 125}. This policy has been described as part of a longitudinal risk-assessment scheme mainly focused on early detection, which involves detailed screening in the first trimester for stratification for all major obstetric complications, and then contingent screening based on the risk reassessment at each visit^{125 126}. The validation and audit of this strategy is a subject of ongoing research.

WHAT TO DO IN MULTIPLE PREGNANCIES

Recommendation

- Due to increased placental mass in twin pregnancies resulting in a lower mean resistance in the uterine arteries, twin-specific reference ranges should be used for Doppler examination, if available. **Grade: B**
- Combined screening (maternal factors, uterine artery PI, mean arterial pressure, PIGF) the algorithm for singletons can be also used in twins and it can predict more than 95% of women who will develop preeclampsia. The examiner should be aware that this is achieved at the cost of 75% screen-positive rate. **Grade: B**

Twin pregnancy is a risk factor for obstetric complications, including preeclampsia¹²⁷.

The increased placental mass in twin pregnancies results in a lower mean uterine artery resistance compared to singleton pregnancies at the same gestational age¹²⁸⁻¹³⁰. As a result, using reference ranges for singleton pregnancies, which are higher than those for

twins, may result in reduced sensitivity of Doppler screening. A study comparing the two approaches reported that twin-specific ranges resulted in a sensitivity of 36.4%, for 12% false positive rates; if the standard cutoffs for singleton pregnancies were used, the sensitivity would be 18% for 1.7% false positive rate¹³⁰.

Chorionicity could theoretically have an impact on the extent of uterine hemodynamics adaptation, as mono- and dichorionic twins have different placental masses and architecture. Indeed, a survival-time model analysis calculated that, for a reference population standardized for maternal characteristics, the risk for preeclampsia <37 weeks' gestation is 9.0% for dichorionic twins and 14.2% for monochorionic twins, as compared to 0.6% for singleton pregnancies¹³¹. A study in the first trimester reported higher uterine artery resistance in monochorionic compared to dichorionic twins; in fact monochorionic twins had similar resistance as singleton fetuses¹³².

First-trimester uterine artery mean PI is already lower in twin pregnancies^{128 132}.

Excluding cases with subsequent twin-to-twin transfusion syndrome, first-trimester mean uterine artery PI was 46% higher in twin pregnancies that developed early-onset preeclampsia and 22% higher in those developing late preeclampsia, compared to uncomplicated twin pregnancies¹²⁸.

As in the first trimester, second-trimester mean uterine artery PI is lower in twin compared to singleton pregnancies. In a study of dichorionic twin pregnancies from 17 to 38 weeks, the 95th centile for the mean uterine artery PI, measured transabdominally, was 1.21 at 21 weeks, 1.16 at 22 weeks, 1.12 at 23 weeks and 1.09 at 24 weeks¹³³.

Using the transvaginal approach, a cut-off of 1.5 for mean UtA PI at 22-24 weeks, had 33.3% sensitivity for preeclampsia, for 3.3% false positive rate (monochorionic and dichorionic twins)¹²⁹.

As in singleton pregnancies, combined screening has a better performance than each of its individual components. A recent study assessed first-trimester screening with maternal factors, uterine artery PI, mean arterial pressure, PAPP-A and P/IGF and found that the detection rate of preeclampsia requiring delivery before 32 and 37 weeks was 100% and 99%, respectively, at the cost of a screen-positive rate of 75%. The use of twin-specific charts resulted in only a minor increase in the performance of the model¹³¹.

THE USE OF ULTRASOUND IN A PATIENT WITH ESTABLISHED PREECLAMPSIA

Deteriorating fetal status is one of the indication for delivery in preeclampsia; therefore, close fetal surveillance is commonly needed until delivery^{134 135}. Ultrasound is obviously the cornerstone for fetal assessment. However, there are currently no randomized controlled trials, and therefore the optimal surveillance strategy and its impact on outcome need to be determined. The three main components for fetal evaluation in clinical practice are: 1) B-mode ultrasound, 2) Doppler, and 3) fetal heart rate monitoring.¹³⁶

Recommendations

- Given that fetal deterioration is an indication for delivery in established preeclampsia, fetal status should be regularly assessed in these patients. GPP
- The sonographic follow-up in pregnancies affected by preeclampsia includes assessment of fetal growth, biophysical profile and fetal Doppler studies. GPP
- As there are currently no randomized controlled trials, the components, frequency, and impact of ultrasound surveillance in pregnancies affected by preeclampsia are yet to be determined. GPP
- Examination of fetal biometry, amniotic fluid volume, uterine-, umbilical- and middle cerebral artery PI and cerebroplacental ratio, as well as placenta visualization to exclude abruption should be considered in women presenting with headache, abdominal pain, bleeding and reduced fetal movements. GPP
- The same tests should be considered for women admitted for or with suspected preeclampsia, as well as for severe preeclampsia or HELLP syndrome. GPP

Preeclampsia is commonly associated with fetal growth restriction, and these fetuses tend to be delivered earlier and deteriorate faster than growth-restricted fetuses of normotensive mothers¹³⁷. Therefore, the identification and follow-up of fetal growth restriction is of paramount importance for the optimization of perinatal outcome in preeclampsia.

B-mode ultrasound

Biometry

Fetal biometry can be assessed to identify a small-for-gestational-age fetus; and to predict small-for-gestational-age newborns¹³⁸.

Amniotic fluid index

The amount of amniotic fluid can be assessed by the amniotic fluid index (AFI) or by the maximum vertical pocket (MVP): MVP <2 cm and/or AFI <5 cm are considered as cut-off values for the diagnosis of reduced amniotic fluid or oligohydramnios^{139 140}. Compared to AFI, measurement of MVP may result in fewer interventions without increasing adverse perinatal outcomes¹⁴¹.

Fetal movements

As part of the fetal biophysical profile, fetal breathing movements, body / limb movements and muscular tone (i.e. extension and flexion of a fetal extremity or an opening and closing of the hand) should be observed¹⁴². These three components, plus the presence/absence of oligohydramnios and fetal heart rate monitoring constitute the fetal biophysical profile (BPP). Positive findings for each component are assigned a value of 2 with the total BPP ranging from 0 to 10. A BPP score of ≥8 is considered to be a normal BPP and a manifestation of fetal well-being. BPP of 6 is a non-conclusive result, and the test should be repeated. A BPP ≤4 is a non-reassuring fetal test and delivery should be considered^{143 144}. BPP testing is mostly used in the USA, whereas clinical management in Europe is mostly based on Doppler examination. There are no data for the comparative cost-effectiveness of the two methods.

Placenta

Visualization of the placenta might help to exclude signs suggestive of severe preeclampsia, such as a thickened placenta with diffuse echogenicity most probably due to edema, a thin placenta with reduced vascularization,^{145 146} or the presence of cystic regions suggestive of infarctions or hematomas.^{147 148} Women with preeclampsia are at risk of partial or total abruption; therefore, evaluation of the interphase placenta/myometrium is important.^{149 150} Sonographic findings related to placental abruption include retroplacental hematoma (hyperechoic, isoechoic, hypoechoic), preplacental hematoma, increased placental thickness and echogenicity, sub-chorionic collection and marginal collection of blood. However, the sensitivity of ultrasound in diagnosing placental abruption is poor, as approximately 50-75% of these cases may be missed by scan^{151 152}. Chronic abruption, which may be seen as a retroplacental sonolucent area on ultrasound, and oligohydramnios sequence can develop in preeclamptic patients.¹⁵³

Doppler

The four Doppler territories commonly examined for fetal and maternal evaluation are 1)

umbilical artery (UA), 2) middle cerebral artery, 3) ductus venosus, and 4) uterine arteries.

Briefly, absent or reversed end-diastolic (A/RED) velocities in the umbilical artery (UmA) are highly associated with perinatal morbidity/mortality^{154 155}. A reduced middle cerebral artery PI (MCA-PI) <10th percentile is a sign of brain vasodilatation and has been associated with emergency cesarean delivery due to non-reassuring fetal heart rate monitoring in growth restricted fetuses¹⁵⁶⁻¹⁵⁸. A cerebro-placental ratio (CPR) below the 10th percentile is considered to be a sign of hemodynamic redistribution, can be observed even before the UmA is affected and is an indicator for close fetal surveillance¹⁵⁹⁻¹⁶¹. Reversed a-wave in the ductus venosus is a strong manifestation of fetal cardiac deterioration and is associated with a high risk of perinatal mortality and severe neonatal morbidity^{162 163}. The results of the TRUFFLE trial provide insight on the follow-up of growth-restricted fetuses in preeclampsia, as most of its participants had preeclampsia at enrollment, or developed it during their follow-up. It was found that the optimal long-term outcome for growth-restricted fetuses with abnormal umbilical artery flow is achieved when delivery is postponed until the a-wave in the ductus venosus becomes reversed, unless reduced short-term variability on non-stress test is observed meanwhile, which also prompts immediate delivery^{137 164 165}. Increased resistance in the uterine artery flow indicates defective spiral artery transformation and is not useful as an indication for delivery.

Guidelines for fetal Doppler evaluation have been published previously and further details of Doppler evaluation are beyond the scope of this guideline¹⁶.

Technical advice

- Administration of antihypertensive drugs is not associated with significant changes in maternal and fetal Doppler indices
- Antenatal corticosteroids are associated with a transient decrease in the vascular resistance in the umbilical arteries and ductus venosus
- The data about a potential effect of magnesium sulfate on maternal and fetal Doppler indices are inconclusive

Level of evidence: 2+

Level of evidence: 2+

Level of evidence: 2-

No changes in the Doppler waveforms of the uterine and umbilical arteries have been reported associated with the use of labetalol, nifedipine or hydralazine¹⁶⁶⁻¹⁶⁹. However, Grzesiak et al.¹⁷⁰ and Lima et al.¹⁷¹ reported a mild reduction in the MCA-PI after administration of nifedipine with no alteration in the other vascular territories. Methyldopa

also has no effect on the uterine artery resistance in patients with gestational hypertensive disease¹⁷².

The effect of antenatal corticosteroids in the fetal circulation has been extensively documented. A transient reduction in vascular resistance and in the PI of the umbilical artery and the ductus venosus is generally observed. Absent or reversed end-diastolic or atrial velocities generally improve after the administration of corticosteroids; this effect can last for 48-72 hours, but it can be longer in some fetuses. Some authors also reported a mild reduction in the MCA-PI; however, no effect of steroids on the uterine arteries' Doppler waveform has been reported¹⁷³⁻¹⁷⁶

There is no consensus regarding the effect of magnesium sulfate on fetal hemodynamics. Some authors reported a reduction in the PI or in the RI of the umbilical, uterine, and MCA arteries after the administration of magnesium sulfate,¹⁷⁷⁻¹⁷⁹ but others have not seen such an effect.¹⁸⁰

AREAS OF FUTURE RESEARCH

Recommendation

- Doppler studies need to fulfill quality criteria, including prospective data collection, specific scan for research purposes and examination of consecutive patients (i.e. non-opportunistic) recruitment.

Grade: C

Doppler examination of maternal and fetal vessels has been used for about two decades with a significant positive impact on maternal and fetal health. However, both older and newer Doppler studies may be biased, for different reasons. Older studies were performed using ultrasound machines of lower imaging detail than the ones used now, and is not certain whether their results would be identical if newer ultrasound technology had been used. Newer Doppler studies were performed at a time where the value of Doppler was already established and this may have resulted in two forms of bias. The first is intention-to-treat bias, i.e. the Doppler measurements may have affected the management, hence the natural history, of the condition they were only suppose to diagnose. The second is the expected value bias, i.e. as normal ranges of Doppler measurement were becoming available, many examiners might subconsciously have pulled their measurements towards the expected normal range; therefore any retrospective study using these data may have been biased. A recent systematic review¹⁸¹ showed that the vast majority of Doppler studies suffers from methodological limitations and proposes a set of criteria, which should be applied in future high-quality studies. These criteria involve, among others, prospective data collection, specific scan for research purposes and examination of consecutive patients (i.e. non-opportunistic) recruitment¹⁸¹.

Summary of recommendations

Relevant information available to the examiner

- Examiners involved in screening for preeclampsia should have up-to-date knowledge regarding major risk factors for preeclampsia (**Good Practice Point**)

Which Doppler index to use

- The pulsatility index (PI) is the index that should be used for the examination of the uterine artery resistance in the context of preeclampsia screening (**Grade B recommendation**)

First-trimester screening for preeclampsia

- Maternal factors can affect uterine artery PI. Therefore, whenever feasible, inclusion of uterine artery PI in a multifactorial screening model should be preferred over its use as a standalone test with absolute cut-offs (**Grade B recommendation**)
- The mean uterine artery PI should be the Doppler index used for screening in the first trimester (**Grade B recommendation**)

Second-trimester screening for preeclampsia

- The mean uterine artery PI should be used for screening in the second trimester. In case of a unilateral placenta, a unilaterally increased PI does not appear to increase the risk for preeclampsia if the mean PI is within normal limits (**Grade B recommendation**)

Third-trimester screening for preeclampsia

- There are currently no randomized trials on the impact of third-trimester screening for preeclampsia on maternal, fetal and neonatal outcomes; consequently, its implementation into routine practice cannot be recommended at present. (**Good Practice Point**)
- The mean uterine artery PI should be used for prediction for preeclampsia, if this is offered in the third trimester (**Grade B recommendation**)

Longitudinal changes in Doppler indices

- Regarding sequential Doppler examinations, preventive strategies for reducing the risk of preeclampsia are effective if started in the first trimester; therefore, delaying the commencement of preventive strategies to assess the evolution of Doppler in the second trimester should be avoided (**Good Practice Point**)

Placental volume

- Although placental volume and vascularization indices have been tested as predictors for preeclampsia, their limited reproducibility and the fact that their measurement requires special equipment and is time-consuming limit their use for screening (**Good Practice Point**)

Combined screening strategies

- A combination of maternal factors, maternal arterial blood pressure, uterine artery Doppler and placental growth factor (P/IGF) at 11-13 weeks appears to be the most efficient screening model for identification of women at risk of preeclampsia (**Grade B recommendation**).
- Given the superiority of combined screening, the use of Doppler cut-offs as a standalone screening modality should be avoided if combined screening is available (**Grade B recommendation**).
- The transabdominal approach should be preferred for calculating first-trimester individual patient risk, as most screening algorithms were calculated using transabdominal ultrasound (**Good Practice Point**).

Assessment of maternal hemodynamics

- Despite the fact that maternal hemodynamic assessment may be of value in prediction of preeclampsia, there are still few data to support their routine implementation in clinical practice as standalone tests (**Good Practice Point**)

What to do after screening

- There is convincing evidence that low-dose aspirin can significantly decrease the risk for development of early preeclampsia, when commenced at the time of first-trimester screening (**Grade A recommendation**).

What to do in multiple pregnancies

- Due to increased placental mass in twin pregnancies resulting in a lower mean resistance in the uterine arteries, twin-specific reference ranges should be used for Doppler examination, if available (**Grade B recommendation**).
- Combined screening (maternal factors, uterine artery PI, mean arterial pressure, PIGF) the algorithm for singletons can be also used in twins and it can predict more than 95% of women who will develop preeclampsia. The examiner should be aware that this is achieved at the cost of 75% screen-positive rate (**Grade B recommendation**).

The use of ultrasound in a patient with established preeclampsia

- Given that fetal deterioration is an indication for delivery in established preeclampsia, fetal status should be regularly assessed in these patients (**Good Practice Point**).
- The sonographic follow-up in pregnancies affected by preeclampsia includes assessment of fetal growth, biophysical profile and fetal Doppler studies (**Good Practice Point**).
- As there are currently no randomized controlled trials, the components, frequency, and impact of ultrasound surveillance in pregnancies affected by preeclampsia are yet to be determined (**Good Practice Point**).
- Examination of fetal biometry, amniotic fluid volume, uterine-, umbilical- and middle cerebral artery PI and cerebroplacental ratio, as well as placenta visualization to exclude abruption should be considered in women presenting with headache, abdominal pain, bleeding and reduced fetal movements (**Good Practice Point**).
- The same tests should be considered for women admitted for or with suspected preeclampsia, as well as for severe preeclampsia or HELLP syndrome (**Good Practice Point**).

Areas of future research

- Doppler studies need to fulfill quality criteria, including prospective data collection, specific scan for research purposes and examination of consecutive patients (i.e. non-opportunistic) recruitment (**Grade C recommendation**).

References

1. Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol* 2009;**33**(3):130-7.
2. Dolea C, AbouZahr C. Global burden of hypertensive disorders of pregnancy in the year 2000. In: WHO, ed. *Evidence and Information for Policy (EIP)*. Geneva: World Health Organization, 2003.
3. WHO. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. Geneva, Switzerland: WHO, 2011.
4. Chaiworapongsa T, Chaemsaihong P, Yeo L, Romero R. Pre-eclampsia part 1: current understanding of its pathophysiology. *Nat Rev Nephrol* 2014;**10**(8):466-80.
5. Melchiorre K, Sharma R, Thilaganathan B. Cardiovascular implications in preeclampsia: an overview. *Circulation* 2014;**130**(8):703-14.
6. Mifsud W, Sebire NJ. Placental pathology in early-onset and late-onset fetal growth restriction. *Fetal Diagn Ther* 2014;**36**(2):117-28.
7. Llurba E, Carreras E, Gratacos E, Juan M, Astor J, Vives A, Hermosilla E, Calero I, Millan P, Garcia-Valdecasas B, Cabero L. Maternal history and uterine artery Doppler in the assessment of risk for development of early- and late-onset preeclampsia and intrauterine growth restriction. *Obstet Gynecol Int* 2009;**2009**:275613.
8. Stergiotou I, Crispi F, Valenzuela-Alcaraz B, Bijnens B, Gratacos E. Patterns of maternal vascular remodeling and responsiveness in early- versus late-onset preeclampsia. *Am J Obstet Gynecol* 2013;**209**(6):558 e1-58 e14.
9. O'Gorman N, Wright D, Syngelaki A, Akolekar R, Wright A, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks gestation. *Am J Obstet Gynecol* 2016;**214**(1):103 e1-03 e12.
10. Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, Akolekar R, Cicero S, Janga D, Singh M, Molina FS, Persico N, Jani JC, Plasencia W, Papaioannou G, Tenenbaum-Gavish K, Meiri H, Gizurarson S, Maclagan K, Nicolaides KH. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. *N Engl J Med* 2017.
11. Baschat AA. First-trimester screening for pre-eclampsia: moving from personalized risk prediction to prevention. *Ultrasound Obstet Gynecol* 2015;**45**(2):119-29.
12. [No_authors_listed]. Screening for various cancers. *Secondary Screening for various cancers* 2018. <http://www.who.int/cancer/detection/variouscancer/en/>.
13. Guidance: Criteria for appraising the viability, effectiveness and appropriateness of a screening programme. *Secondary Guidance: Criteria for appraising the viability, effectiveness and appropriateness of a screening programme* 2015. <https://www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes/criteria-for-appraising-the-viability-effectiveness-and-appropriateness-of-a-screening-programme>.
14. Falco ML, Sivanathan J, Laoreti A, Thilaganathan B, Khalil A. Placental histopathology associated with pre-eclampsia: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2017;**50**(3):295-301.
15. Orabona R, Donzelli CM, Falchetti M, Santoro A, Valcamonico A, Frusca T. Placental histological patterns and uterine artery Doppler velocimetry in pregnancies complicated by early or late pre-eclampsia. *Ultrasound Obstet Gynecol* 2016;**47**(5):580-5.

16. Bhide A, Acharya G, Bilardo CM, Brezinka C, Cafici D, Hernandez-Andrade E, Kalache K, Kingdom J, Kiserud T, Lee W, Lees C, Leung KY, Malinger G, Mari G, Prefumo F, Sepulveda W, Trudinger B. ISUOG practice guidelines: use of Doppler ultrasonography in obstetrics. *Ultrasound Obstet Gynecol* 2013;**41**(2):233-39.
17. Papageorghiou AT, Yu CK, Bindra R, Pandis G, Nicolaides KH, Fetal Medicine Foundation Second Trimester Screening G. Multicenter screening for pre-eclampsia and fetal growth restriction by transvaginal uterine artery Doppler at 23 weeks of gestation. *Ultrasound Obstet Gynecol* 2001;**18**(5):441-9.
18. Brodzki J, Lanne T, Laurini R, Strevens H, Wide-Svensson D, Marsal K. Vascular mechanical properties and endothelial function in pre-eclampsia with special reference to bilateral uterine artery notch. *Acta Obstet Gynecol Scand* 2008;**87**(2):154-62.
19. Melchiorre K, Leslie K, Prefumo F, Bhide A, Thilaganathan B. First-trimester uterine artery Doppler indices in the prediction of small-for-gestational age pregnancy and intrauterine growth restriction. *Ultrasound Obstet Gynecol* 2009;**33**(5):524-9.
20. Cnossen JS, Morris RK, ter Riet G, Mol BW, van der Post JA, Coomarasamy A, Zwinderman AH, Robson SC, Bindels PJ, Kleijnen J, Khan KS. Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: a systematic review and bivariable meta-analysis. *CMAJ* 2008;**178**(6):701-11.
21. Rolnik DL, Wright D, Poon LCY, Syngelaki A, O'Gorman N, de Paco Matallana C, Akolekar R, Cicero S, Janga D, Singh M, Molina FS, Persico N, Jani JC, Plasencia W, Papaioannou G, Tenenbaum-Gavish K, Nicolaides KH. ASPRE trial: performance of screening for preterm pre-eclampsia. *Ultrasound Obstet Gynecol* 2017;**50**(4):492-95.
22. Tan MY, Wright D, Syngelaki A, Akolekar R, Cicero S, Janga D, Singh M, Greco E, Wright A, Maclagan K, Poon LC, Nicolaides KH. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. *Ultrasound Obstet Gynecol* 2018.
23. Tan MY, Poon LC, Rolnik DL, Syngelaki A, de Paco Matallana C, Akolekar R, Cicero S, Janga D, Singh M, Molina FS, Persico N, Jani JC, Plasencia W, Greco E, Papaioannou G, Wright D, Nicolaides KH. Prediction and prevention of small-for-gestational-age neonates: evidence from SPREE and ASPRE. *Ultrasound Obstet Gynecol* 2018.
24. Tayyar A, Guerra L, Wright A, Wright D, Nicolaides KH. Uterine artery pulsatility index in the three trimesters of pregnancy: effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2015;**45**(6):689-97.
25. Martin AM, Bindra R, Curcio P, Cicero S, Nicolaides KH. Screening for pre-eclampsia and fetal growth restriction by uterine artery Doppler at 11-14 weeks of gestation. *Ultrasound Obstet Gynecol* 2001;**18**(6):583-6.
26. Plasencia W, Maiz N, Bonino S, Kaihura C, Nicolaides KH. Uterine artery Doppler at 11 + 0 to 13 + 6 weeks in the prediction of pre-eclampsia. *Ultrasound Obstet Gynecol* 2007;**30**(5):742-9.
27. Khalil A, Nicolaides KH. How to record uterine artery Doppler in the first trimester. *Ultrasound Obstet Gynecol* 2013;**42**(4):478-9.
28. Gomez O, Martinez JM, Figueras F, Del Rio M, Borobio V, Puerto B, Coll O, Cararach V, Vanrell JA. Uterine artery Doppler at 11-14 weeks of gestation to screen for hypertensive disorders and associated complications in an unselected population. *Ultrasound Obstet Gynecol* 2005;**26**(5):490-4.
29. Ridding G, Schluter PJ, Hyett JA, McLennan AC. Uterine artery pulsatility index assessment at 11-13 weeks' gestation. *Fetal Diagn Ther* 2014;**36**(4):299-304.
30. Ferreira AE, Mauad Filho F, Abreu PS, Mauad FM, Araujo Junior E, Martins WP. Reproducibility of first- and second-trimester uterine artery pulsatility index measured by transvaginal and transabdominal ultrasound. *Ultrasound Obstet Gynecol* 2015;**46**(5):546-52.

31. Martins WP, Nastri CO. Interpreting reproducibility results for ultrasound measurements. *Ultrasound Obstet Gynecol* 2014;**43**(4):479-80.
32. Rolnik DL, da Silva Costa F, Sahota D, Hyett J, McLennan A. Quality assessment of uterine artery Doppler measurement in first trimester combined screening for pre-eclampsia. *Ultrasound Obstet Gynecol* 2018.
33. Plasencia W, Barber MA, Alvarez EE, Segura J, Valle L, Garcia-Hernandez JA. Comparative study of transabdominal and transvaginal uterine artery Doppler pulsatility indices at 11-13 + 6 weeks. *Hypertens Pregnancy* 2011;**30**(4):414-20.
34. Resnik R, Killam AP, Battaglia FC, Makowski EL, Meschia G. The stimulation of uterine blood flow by various estrogens. *Endocrinology* 1974;**94**(4):1192-6.
35. Poon LC, Nicolaides KH. Early prediction of preeclampsia. *Obstet Gynecol Int* 2014;**2014**:297397.
36. Poon LC, Staboulidou I, Maiz N, Plasencia W, Nicolaides KH. Hypertensive disorders in pregnancy: screening by uterine artery Doppler at 11-13 weeks. *Ultrasound Obstet Gynecol* 2009;**34**(2):142-8.
37. Napolitano R, Rajakulasingam R, Memmo A, Bhide A, Thilaganathan B. Uterine artery Doppler screening for pre-eclampsia: comparison of the lower, mean and higher first-trimester pulsatility indices. *Ultrasound Obstet Gynecol* 2011;**37**(5):534-7.
38. Harrington K, Carpenter RG, Goldfrad C, Campbell S. Transvaginal Doppler ultrasound of the uteroplacental circulation in the early prediction of pre-eclampsia and intrauterine growth retardation. *Br J Obstet Gynaecol* 1997;**104**(6):674-81.
39. Alves JA, Silva BY, de Sousa PC, Maia SB, Costa Fda S. Reference range of uterine artery Doppler parameters between the 11th and 14th pregnancy weeks in a population sample from Northeast Brazil. *Rev Bras Ginecol Obstet* 2013;**35**(8):357-62.
40. Velauthar L, Plana MN, Kalidindi M, Zamora J, Thilaganathan B, Illanes SE, Khan KS, Aquilina J, Thangaratinam S. First-trimester uterine artery Doppler and adverse pregnancy outcome: a meta-analysis involving 55,974 women. *Ultrasound Obstet Gynecol* 2014;**43**(5):500-7.
41. Albaiges G, Missfelder-Lobos H, Lees C, Parra M, Nicolaides KH. One-stage screening for pregnancy complications by color Doppler assessment of the uterine arteries at 23 weeks' gestation. *Obstet Gynecol* 2000;**96**(4):559-64.
42. Papageorghiou AT, Yu CK, Erasmus IE, Cuckle HS, Nicolaides KH. Assessment of risk for the development of pre-eclampsia by maternal characteristics and uterine artery Doppler. *BJOG* 2005;**112**(6):703-9.
43. Yu CK, Khouri O, Onwudiwe N, Spiliopoulos Y, Nicolaides KH, Fetal Medicine Foundation Second-Trimester Screening G. Prediction of pre-eclampsia by uterine artery Doppler imaging: relationship to gestational age at delivery and small-for-gestational age. *Ultrasound Obstet Gynecol* 2008;**31**(3):310-3.
44. Gomez O, Figueras F, Fernandez S, Bennasar M, Martinez JM, Puerto B, Gratacos E. Reference ranges for uterine artery mean pulsatility index at 11-41 weeks of gestation. *Ultrasound Obstet Gynecol* 2008;**32**(2):128-32.
45. Contro E, Maroni E, Cera E, Youssef A, Bellussi F, Pilu G, Rizzo N, Pelusi G, Ghi T. Unilaterally increased uterine artery resistance, placental location and pregnancy outcome. *Eur J Obstet Gynecol Reprod Biol* 2010;**153**(2):143-7.
46. Yu CK, Smith GC, Papageorghiou AT, Cacho AM, Nicolaides KH, Fetal Medicine Foundation Second Trimester Screening G. An integrated model for the prediction of preeclampsia using maternal factors and uterine artery Doppler velocimetry in unselected low-risk women. *Am J Obstet Gynecol* 2005;**193**(2):429-36.
47. Espinoza J, Kusanovic JP, Bahado-Singh R, Gervasi MT, Romero R, Lee W, Vaisbuch E, Mazaki-Tovi S, Mittal P, Gotsch F, Erez O, Gomez R, Yeo L, Hassan SS. Should bilateral uterine artery notching be used in the risk assessment for preeclampsia, small-

- for-gestational-age, and gestational hypertension? *J Ultrasound Med* 2010;**29**(7):1103-15.
48. Melchiorre K, Sutherland GR, Liberati M, Bhide A, Thilaganathan B. Prevalence of maternal cardiac defects in women with high-resistance uterine artery Doppler indices. *Ultrasound Obstet Gynecol* 2011;**37**(3):310-6.
 49. Tsiakkas A, Saiid Y, Wright A, Wright D, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 30-34 weeks' gestation. *Am J Obstet Gynecol* 2016;**215**(1):87 e1-87 e17.
 50. Andrietti S, Silva M, Wright A, Wright D, Nicolaides KH. Competing-risks model in screening for pre-eclampsia by maternal factors and biomarkers at 35-37 weeks' gestation. *Ultrasound Obstet Gynecol* 2016;**48**(1):72-9.
 51. Lau WL, Lam HS, Leung WC. Reversed diastolic flow in the uterine artery - a new Doppler finding related to placental insufficiency? *Ultrasound Obstet Gynecol* 2007;**29**(2):232-5.
 52. Ekici E, Vicdan K, Dayan H, Danisman N, Gokmen O. Reverse end-diastolic uterine artery velocity in a pregnant woman complicated by mild preeclampsia and severe growth retardation. *Eur J Obstet Gynecol Reprod Biol* 1996;**66**(1):79-82.
 53. Gomez O, Figueras F, Martinez JM, del Rio M, Palacio M, Eixarch E, Puerto B, Coll O, Cararach V, Vanrell JA. Sequential changes in uterine artery blood flow pattern between the first and second trimesters of gestation in relation to pregnancy outcome. *Ultrasound Obstet Gynecol* 2006;**28**(6):802-8.
 54. Napolitano R, Melchiorre K, Arcangeli T, Dias T, Bhide A, Thilaganathan B. Screening for pre-eclampsia by using changes in uterine artery Doppler indices with advancing gestation. *Prenat Diagn* 2012;**32**(2):180-4.
 55. Ghi T, Contro E, Youssef A, Giorgetta F, Farina A, Pilu G, Pelusi G. Persistence of increased uterine artery resistance in the third trimester and pregnancy outcome. *Ultrasound Obstet Gynecol* 2010;**36**(5):577-81.
 56. Hafner E, Metzenbauer M, Hofinger D, Stonek F, Schuchter K, Waldhor T, Philipp K. Comparison between three-dimensional placental volume at 12 weeks and uterine artery impedance/notching at 22 weeks in screening for pregnancy-induced hypertension, pre-eclampsia and fetal growth restriction in a low-risk population. *Ultrasound Obstet Gynecol* 2006;**27**(6):652-7.
 57. Rizzo G, Capponi A, Cavicchioni O, Vendola M, Arduini D. First trimester uterine Doppler and three-dimensional ultrasound placental volume calculation in predicting pre-eclampsia. *Eur J Obstet Gynecol Reprod Biol* 2008;**138**(2):147-51.
 58. Odeh M, Ophir E, Maximovsky O, Grinin V, Bornstein J. Placental volume and three-dimensional power Doppler analysis in prediction of pre-eclampsia and small for gestational age between Week 11 and 13 weeks and 6 days of gestation. *Prenat Diagn* 2011;**31**(4):367-71.
 59. Odibo AO, Goetzinger KR, Huster KM, Christiansen JK, Odibo L, Tuuli MG. Placental volume and vascular flow assessed by 3D power Doppler and adverse pregnancy outcomes. *Placenta* 2011;**32**(3):230-4.
 60. Hafner E, Metzenbauer M, Stumpfflen I, Waldhor T, Philipp K. First trimester placental and myometrial blood perfusion measured by 3D power Doppler in normal and unfavourable outcome pregnancies. *Placenta* 2010;**31**(9):756-63.
 61. Plasencia W, Gonzalez-Davila E, Gonzalez Lorenzo A, Armas-Gonzalez M, Padron E, Gonzalez-Gonzalez NL. First trimester placental volume and vascular indices in pregnancies complicated by preeclampsia. *Prenat Diagn* 2015;**35**(12):1247-54.
 62. Demers S, Girard M, Roberge S, Tetu A, Giguere Y, Forest JC, Bujold E. First-Trimester Placental and Myometrial Blood Perfusion Measured by Three-Dimensional Power Doppler in Preeclampsia. *Am J Perinatol* 2015;**32**(10):920-6.

63. Martins WP, Lima JC, Welsh AW, Araujo Junior E, Miyague AH, Filho FM, Raine-Fenning NJ. Three-dimensional Doppler evaluation of single spherical samples from the placenta: intra- and interobserver reliability. *Ultrasound Obstet Gynecol* 2012;**40**(2):200-6.
64. Burstein E, Sheiner E, HersHKovitz R. Three-dimensional placental volume measurements between 11 and 13 weeks' gestation. *Am J Perinatol* 2009;**26**(2):169-71.
65. Cabezas Lopez E, Martinez-Payo C, Engels Calvo V, San Frutos Llorente L, Perez-Medina T. Reproducibility of first trimester three-dimensional placental measurements. *Eur J Obstet Gynecol Reprod Biol* 2016;**201**:156-60.
66. Aye CY, Stevenson GN, Impey L, Collins SL. Comparison of 2-D and 3-D estimates of placental volume in early pregnancy. *Ultrasound Med Biol* 2015;**41**(3):734-40.
67. Martins WP, Ferriani RA, Ferreira AC, Spara P, Pinheiro Filho L, dos Reis RM, Filho FM. [The reproducibility of VOCAL endometrial volume measurement - importance of the step rotation]. *Rev Bras Ginecol Obstet* 2006;**28**:38-43.
68. Tayyar A, Krithinakis K, Wright A, Wright D, Nicolaidis KH. Mean arterial pressure at 12, 22, 32 and 36 weeks' gestation in screening for pre-eclampsia. *Ultrasound Obstet Gynecol* 2016;**47**(5):573-9.
69. Tsiakkas A, Mendez O, Wright A, Wright D, Nicolaidis KH. Maternal serum soluble fms-like tyrosine kinase-1 at 12, 22, 32 and 36 weeks' gestation in screening for pre-eclampsia. *Ultrasound Obstet Gynecol* 2016;**47**(4):478-83.
70. Khalil A, Maiz N, Garcia-Mandujano R, Penco JM, Nicolaidis KH. Longitudinal changes in maternal serum placental growth factor and soluble fms-like tyrosine kinase-1 in women at increased risk of pre-eclampsia. *Ultrasound Obstet Gynecol* 2016;**47**(3):324-31.
71. Bredaki FE, Mataliotakis M, Wright A, Wright D, Nicolaidis KH. Maternal serum alpha-fetoprotein at 12, 22 and 32 weeks' gestation in screening for pre-eclampsia. *Ultrasound Obstet Gynecol* 2016;**47**(4):466-71.
72. Spencer K, Cowans NJ, Nicolaidis KH. Low levels of maternal serum PAPP-A in the first trimester and the risk of pre-eclampsia. *Prenat Diagn* 2008;**28**(1):7-10.
73. Tsiakkas A, Cazacu R, Wright A, Wright D, Nicolaidis KH. Maternal serum placental growth factor at 12, 22, 32 and 36 weeks' gestation in screening for pre-eclampsia. *Ultrasound Obstet Gynecol* 2016;**47**(4):472-7.
74. O'Gorman N, Tampakoudis G, Wright A, Wright D, Nicolaidis KH. Uterine artery pulsatility index at 12, 22, 32 and 36 weeks' gestation in screening for pre-eclampsia. *Ultrasound Obstet Gynecol* 2016;**47**(5):565-72.
75. Wright A, Guerra L, Pellegrino M, Wright D, Nicolaidis KH. Maternal serum PAPP-A and free beta-hCG at 12, 22 and 32 weeks' gestation in screening for pre-eclampsia. *Ultrasound Obstet Gynecol* 2016;**47**(6):762-7.
76. O'Gorman N, Wright D, Poon LC, Rolnik DL, Syngelaki A, Wright A, Akolekar R, Cicero S, Janga D, Jani J, Molina FS, de Paco Matallana C, Papantoniou N, Persico N, Plasencia W, Singh M, Nicolaidis KH. Accuracy of competing risks model in screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. *Ultrasound Obstet Gynecol* 2017.
77. Rolnik DL, da Silva Costa F, Lee TJ, Schmid M, McLennan AC. Association between fetal fraction on cell-free DNA testing and first trimester markers for pre-eclampsia. *Ultrasound Obstet Gynecol* 2018.
78. Onwudiwe N, Yu CK, Poon LC, Spiliopoulos I, Nicolaidis KH. Prediction of pre-eclampsia by a combination of maternal history, uterine artery Doppler and mean arterial pressure. *Ultrasound Obstet Gynecol* 2008;**32**(7):877-83.
79. Andrietti S, Carlucci S, Wright A, Wright D, Nicolaidis KH. Repeat measurements of uterine artery pulsatility index, mean arterial pressure and serum placental growth factor at 12, 22 and 32 weeks in prediction of pre-eclampsia. *Ultrasound Obstet Gynecol* 2017;**50**(2):221-27.

80. Panaitescu A, Ciobanu A, Syngelaki A, Wright A, Wright D, Nicolaides KH. Screening for pre-eclampsia at 35-37 weeks' gestation. *Ultrasound Obstet Gynecol* 2018.
81. Valino N, Giunta G, Gallo DM, Akolekar R, Nicolaides KH. Biophysical and biochemical markers at 30-34 weeks' gestation in the prediction of adverse perinatal outcome. *Ultrasound Obstet Gynecol* 2016;**47**(2):194-202.
82. Valino N, Giunta G, Gallo DM, Akolekar R, Nicolaides KH. Biophysical and biochemical markers at 35-37 weeks' gestation in the prediction of adverse perinatal outcome. *Ultrasound Obstet Gynecol* 2016;**47**(2):203-9.
83. Guy GP, Ling HZ, Garcia P, Poon LC, Nicolaides KH. Maternal cardiac function at 35-37 weeks' gestation: prediction of pre-eclampsia and gestational hypertension. *Ultrasound Obstet Gynecol* 2017;**49**(1):61-66.
84. Dragan I, Wright D, Fiolna M, Leipold G, Nicolaides KH. Development of pre-eclampsia within 4 weeks of sFlt-1/PIGF ratio > 38: comparison of performance at 31-34 vs 35-37 weeks' gestation. *Ultrasound Obstet Gynecol* 2017;**49**(2):209-12.
85. Oliveira N, Magder LS, Blitzer MG, Baschat AA. First-trimester prediction of pre-eclampsia: external validity of algorithms in a prospectively enrolled cohort. *Ultrasound Obstet Gynecol* 2014;**44**(3):279-85.
86. O'Gorman N, Wright D, Poon LC, Rolnik DL, Syngelaki A, de Alvarado M, Carbone IF, Dutemeyer V, Fiolna M, Frick A, Karagiannis N, Mastrodimas S, de Paco Matallana C, Papaioannou G, Pazos A, Plasencia W, Nicolaides KH. Multicenter screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks' gestation: comparison to NICE guidelines and ACOG recommendations. *Ultrasound Obstet Gynecol* 2017.
87. Magnussen EB, Vatten LJ, Lund-Nilsen TI, Salvesen KA, Davey Smith G, Romundstad PR. Prepregnancy cardiovascular risk factors as predictors of pre-eclampsia: population based cohort study. *BMJ* 2007;**335**(7627):978.
88. Hale SA, Badger GJ, McBride C, Magness R, Bernstein IM. Prepregnancy Vascular Dysfunction in Women who Subsequently Develop Hypertension During Pregnancy. *Pregnancy Hypertens* 2013;**3**(2):140-45.
89. Mahendru AA, Everett TR, Wilkinson IB, Lees CC, McEniery CM. A longitudinal study of maternal cardiovascular function from preconception to the postpartum period. *J Hypertens* 2014;**32**(4):849-56.
90. Hausvater A, Giannone T, Sandoval YH, Doonan RJ, Antonopoulos CN, Matsoukis IL, Petridou ET, Daskalopoulou SS. The association between preeclampsia and arterial stiffness. *J Hypertens* 2012;**30**(1):17-33.
91. Khalil A, Akolekar R, Syngelaki A, Elkhouli M, Nicolaides KH. Maternal hemodynamics at 11-13 weeks' gestation and risk of pre-eclampsia. *Ultrasound Obstet Gynecol* 2012;**40**(1):28-34.
92. Khalil A, Garcia-Mandujano R, Maiz N, Elkhouli M, Nicolaides KH. Longitudinal changes in maternal hemodynamics in a population at risk for pre-eclampsia. *Ultrasound Obstet Gynecol* 2014;**44**(2):197-204.
93. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. *Hypertension* 2008;**52**(5):873-80.
94. De Paco C, Kametas N, Rencoret G, Strobl I, Nicolaides KH. Maternal cardiac output between 11 and 13 weeks of gestation in the prediction of preeclampsia and small for gestational age. *Obstet Gynecol* 2008;**111**(2 Pt 1):292-300.
95. Melchiorre K, Sutherland GR, Liberati M, Thilaganathan B. Preeclampsia is associated with persistent postpartum cardiovascular impairment. *Hypertension* 2011;**58**(4):709-15.
96. Melchiorre K, Sutherland GR, Baltabaeva A, Liberati M, Thilaganathan B. Maternal cardiac dysfunction and remodeling in women with preeclampsia at term. *Hypertension* 2011;**57**(1):85-93.

97. Melchiorre K, Sutherland G, Sharma R, Nanni M, Thilaganathan B. Mid-gestational maternal cardiovascular profile in preterm and term pre-eclampsia: a prospective study. *BJOG* 2013;**120**(4):496-504.
98. Stott D, Nzelu O, Nicolaides KH, Kametas NA. Maternal haemodynamics in normal pregnancies and in pregnancies affected by pre-eclampsia. *Ultrasound Obstet Gynecol* 2017.
99. Gagliardi G, Tiralongo GM, LoPresti D, Pisani I, Farsetti D, Vasapollo B, Novelli GP, Andreoli A, Valensise H. Screening for pre-eclampsia in the first trimester: role of maternal hemodynamics and bioimpedance in non-obese patients. *Ultrasound Obstet Gynecol* 2017;**50**(5):584-88.
100. Milic NM, Milin-Lazovic J, Weissgerber TL, Trajkovic G, White WM, Garovic VD. Preclinical atherosclerosis at the time of pre-eclamptic pregnancy and up to 10 years postpartum: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2017;**49**(1):110-15.
101. De Haas S, Ghossein-Doha C, Geerts L, van Kuijk SMJ, van Drongelen J, Spaanderman MEA. Cardiac remodeling in normotensive pregnancy and in pregnancy complicated by hypertension: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2017;**50**(6):683-96.
102. Orabona R, Vizzardi E, Sciatti E, Bonadei I, Valcamonico A, Metra M, Frusca T. Insights into cardiac alterations after pre-eclampsia: an echocardiographic study. *Ultrasound Obstet Gynecol* 2017;**49**(1):124-33.
103. Breetveld NM, Ghossein-Doha C, van Neer J, Sengers M, Geerts L, van Kuijk SMJ, van Dijk AP, van der Vlugt MJ, Heidema WM, Brunner-La Rocca HP, Scholten RR, Spaanderman MEA. Decreased endothelial function and increased subclinical heart failure in women several years after pre-eclampsia. *Ultrasound Obstet Gynecol* 2017.
104. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ* 2007;**335**(7627):974.
105. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. *Am Heart J* 2008;**156**(5):918-30.
106. Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. *Eur J Epidemiol* 2013;**28**(1):1-19.
107. Ghossein-Doha C, Spaanderman ME, Al Doulah R, Van Kuijk SM, Peeters LL. Maternal cardiac adaptation to subsequent pregnancy in formerly pre-eclamptic women according to recurrence of pre-eclampsia. *Ultrasound Obstet Gynecol* 2016;**47**(1):96-103.
108. Poon LC, Karagiannis G, Leal A, Romero XC, Nicolaides KH. Hypertensive disorders in pregnancy: screening by uterine artery Doppler imaging and blood pressure at 11-13 weeks. *Ultrasound Obstet Gynecol* 2009;**34**(5):497-502.
109. Savvidou MD, Hingorani AD, Tsikas D, Frolich JC, Vallance P, Nicolaides KH. Endothelial dysfunction and raised plasma concentrations of asymmetric dimethylarginine in pregnant women who subsequently develop pre-eclampsia. *Lancet* 2003;**361**(9368):1511-7.
110. Noori M, Donald AE, Angelakopoulou A, Hingorani AD, Williams DJ. Prospective study of placental angiogenic factors and maternal vascular function before and after preeclampsia and gestational hypertension. *Circulation* 2010;**122**(5):478-87.
111. Foo FL, McEnery CM, Lees C, Khalil A, International Working Group on Maternal H. Assessment of arterial function in pregnancy: recommendations of the International Working Group on Maternal Hemodynamics. *Ultrasound Obstet Gynecol* 2017;**50**(3):324-31.

112. ACOG Committee Opinion No. 743: Low-Dose Aspirin Use During Pregnancy. *Obstet Gynecol* 2018;**132**(1):e44-e52.
113. NICE. Clinical Guideline 107. Hypertension in pregnancy: diagnosis and management. Secondary Clinical Guideline 107. Hypertension in pregnancy: diagnosis and management 2011. <https://www.nice.org.uk/guidance/cg107/chapter/1-Guidance#reducing-the-risk-of-hypertensive-disorders-in-pregnancy>.
114. Lausman A, McCarthy FP, Walker M, Kingdom J. Screening, diagnosis, and management of intrauterine growth restriction. *J Obstet Gynaecol Can* 2012;**34**(1):17-28.
115. Caron N, Rivard GE, Michon N, Morin F, Pilon D, Moutquin JM, Rey E. Low-dose ASA response using the PFA-100 in women with high-risk pregnancy. *J Obstet Gynaecol Can* 2009;**31**(11):1022-7.
116. Panagodage S, Yong HE, Da Silva Costa F, Borg AJ, Kalionis B, Brennecke SP, Murthi P. Low-Dose Acetylsalicylic Acid Treatment Modulates the Production of Cytokines and Improves Trophoblast Function in an in Vitro Model of Early-Onset Preeclampsia. *Am J Pathol* 2016;**186**(12):3217-24.
117. Ayala DE, Ucieda R, Hermida RC. Chronotherapy with low-dose aspirin for prevention of complications in pregnancy. *Chronobiol Int* 2013;**30**(1-2):260-79.
118. Wright D, Poon LC, Rolnik DL, Syngelaki A, Delgado JL, Vojtassakova D, de Alvarado M, Kapeti E, Rehal A, Pazos A, Carbone IF, Dutemeyer V, Plasencia W, Papantoniou N, Nicolaides KH. Aspirin for Evidence-Based Preeclampsia Prevention trial: influence of compliance on beneficial effect of aspirin in prevention of preterm preeclampsia. *Am J Obstet Gynecol* 2017;**217**(6):685 e1-85 e5.
119. Orved D, Hawkins TL, Johnson JA, Hyett J, Metcalfe A. The cost-effectiveness of first trimester screening and early preventative use of aspirin in women at high risk of early onset pre-eclampsia. *Ultrasound Obstet Gynecol* 2018.
120. Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, Forest JC, Giguere Y. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *Obstet Gynecol* 2010;**116**(2 Pt 1):402-14.
121. Roberge S, Demers S, Nicolaides KH, Bureau M, Cote S, Bujold E. Prevention of preeclampsia by low-molecular-weight heparin in addition to aspirin: a meta-analysis. *Ultrasound Obstet Gynecol* 2016;**47**(5):548-53.
122. Litwinska M, Wright D, Efeturk T, Ceccacci I, Nicolaides KH. Proposed clinical management of pregnancies after combined screening for pre-eclampsia at 19-24 weeks' gestation. *Ultrasound Obstet Gynecol* 2017;**50**(3):367-72.
123. Litwinska M, Syngelaki A, Wright A, Wright D, Nicolaides KH. Management of pregnancies after combined screening for pre-eclampsia at 19-24 weeks' gestation. *Ultrasound Obstet Gynecol* 2018.
124. Garcia B, Llurba E, Valle L, Gomez-Roig MD, Juan M, Perez-Matos C, Fernandez M, Garcia-Hernandez JA, Alijotas-Reig J, Higuera MT, Calero I, Goya M, Perez-Hoyos S, Carreras E, Cabero L. Do knowledge of uterine artery resistance in the second trimester and targeted surveillance improve maternal and perinatal outcome? UTOPIA study: a randomized controlled trial. *Ultrasound Obstet Gynecol* 2016;**47**(6):680-9.
125. Wright D, Dragan I, Syngelaki A, Akolekar R, Nicolaides KH. Proposed clinical management of pregnancies after combined screening for preeclampsia at 30-34 weeks' gestation. *Ultrasound Obstet Gynecol* 2016.
126. Nicolaides KH. Turning the pyramid of prenatal care. *Fetal Diagn Ther* 2011;**29**(3):183-96.
127. Francisco C, Wright D, Benko Z, Syngelaki A, Nicolaides KH. Hidden high rate of preeclampsia in twin compared to singleton pregnancies. *Ultrasound Obstet Gynecol* 2017.

128. Rizzo G, Pietrolucci ME, Aiello E, Capponi A, Arduini D. Uterine artery Doppler evaluation in twin pregnancies at 11 + 0 to 13 + 6 weeks of gestation. *Ultrasound Obstet Gynecol* 2014;**44**(5):557-61.
129. Yu CK, Papageorgiou AT, Boli A, Cacho AM, Nicolaidis KH. Screening for pre-eclampsia and fetal growth restriction in twin pregnancies at 23 weeks of gestation by transvaginal uterine artery Doppler. *Ultrasound Obstet Gynecol* 2002;**20**(6):535-40.
130. Geipel A, Berg C, Germer U, Katalinic A, Krapp M, Smrcek J, Gembruch U. Doppler assessment of the uterine circulation in the second trimester in twin pregnancies: prediction of pre-eclampsia, fetal growth restriction and birth weight discordance. *Ultrasound Obstet Gynecol* 2002;**20**(6):541-5.
131. Francisco C, Wright D, Benko Z, Syngelaki A, Nicolaidis KH. Competing risks model in screening for preeclampsia in twin pregnancies by maternal factors and biomarkers at 11-13 weeks' gestation. *Ultrasound Obstet Gynecol* 2017.
132. Svirsky R, Yagel S, Ben-Ami I, Cuckle H, Klug E, Maymon R. First trimester markers of preeclampsia in twins: maternal mean arterial pressure and uterine artery Doppler pulsatility index. *Prenat Diagn* 2014;**34**(10):956-60.
133. Geipel A, Hennemann F, Fimmers R, Willruth A, Lato K, Gembruch U, Berg C. Reference ranges for Doppler assessment of uterine artery resistance and pulsatility indices in dichorionic twin pregnancies. *Ultrasound Obstet Gynecol* 2011;**37**(6):663-7.
134. Shear RM, Rinfret D, Leduc L. Should we offer expectant management in cases of severe preterm preeclampsia with fetal growth restriction? *Am J Obstet Gynecol* 2005;**192**(4):1119-25.
135. Belghiti J, Kayem G, Tsatsaris V, Goffinet F, Sibai BM, Haddad B. Benefits and risks of expectant management of severe preeclampsia at less than 26 weeks gestation: the impact of gestational age and severe fetal growth restriction. *Am J Obstet Gynecol* 2011;**205**(5):465 e1-6.
136. American College of O, Gynecologists. ACOG Practice Bulletin No. 125: Chronic hypertension in pregnancy. *Obstet Gynecol* 2012;**119**(2 Pt 1):396-407.
137. Lees C, Marlow N, Arabin B, Bilardo CM, Brezinka C, Derks JB, Duvkot J, Frusca T, Diemert A, Ferrazzi E, Ganzevoort W, Hecher K, Martinelli P, Ostermayer E, Papageorgiou AT, Schlembach D, Schneider KT, Thilaganathan B, Todros T, van Wassenaer-Leemhuis A, Valcamonica A, Visser GH, Wolf H, Group T. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). *Ultrasound Obstet Gynecol* 2013;**42**(4):400-8.
138. Sovio U, White IR, Dacey A, Pasupathy D, Smith GC. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. *Lancet* 2015;**386**(10008):2089-97.
139. Williams K. Amniotic fluid assessment. *Obstet Gynecol Surv* 1993;**48**(12):795-800.
140. Moise KJ, Jr. Toward consistent terminology: assessment and reporting of amniotic fluid volume. *Semin Perinatol* 2013;**37**(5):370-4.
141. Lim KI, Butt K, Naud K, Smithies M. Amniotic Fluid: Technical Update on Physiology and Measurement. *J Obstet Gynaecol Can* 2017;**39**(1):52-58.
142. Manning FA. Fetal biophysical profile: a critical appraisal. *Clin Obstet Gynecol* 2002;**45**(4):975-85.
143. Chari RS, Friedman SA, O'Brien JM, Sibai BM. Daily antenatal testing in women with severe preeclampsia. *Am J Obstet Gynecol* 1995;**173**(4):1207-10.
144. Ullah N, Usman M, Khan AR. Sonographic biophysical profile in detection of foetal hypoxia in 100 cases of suspected high risk pregnancy. *J Ayub Med Coll Abbottabad* 2010;**22**(3):77-80.

145. Predoi CG, Grigoriu C, Vladescu R, Mihart AE. Placental damages in preeclampsia - from ultrasound images to histopathological findings. *J Med Life* 2015;**8 Spec Issue**:62-5.
146. Chen CY, Wang KG, Chen CP. Alteration of vascularization in preeclamptic placentas measured by three-dimensional power Doppler ultrasound. *J Matern Fetal Neonatal Med* 2013;**26**(16):1616-22.
147. Proctor LK, Whittle WL, Keating S, Viero S, Kingdom JC. Pathologic basis of echogenic cystic lesions in the human placenta: role of ultrasound-guided wire localization. *Placenta* 2010;**31**(12):1111-5.
148. Auriolles-Garibay A, Hernandez-Andrade E, Romero R, Qureshi F, Ahn H, Jacques SM, Garcia M, Yeo L, Hassan SS. Prenatal diagnosis of a placental infarction hematoma associated with fetal growth restriction, preeclampsia and fetal death: clinicopathological correlation. *Fetal Diagn Ther* 2014;**36**(2):154-61.
149. Ananth CV. Ischemic placental disease: a unifying concept for preeclampsia, intrauterine growth restriction, and placental abruption. *Semin Perinatol* 2014;**38**(3):131-2.
150. Minire A, Mirton M, Imri V, Lauren M, Aferdita M. Maternal complications of preeclampsia. *Med Arch* 2013;**67**(5):339-41.
151. Glantz C, Purnell L. Clinical utility of sonography in the diagnosis and treatment of placental abruption. *J Ultrasound Med* 2002;**21**(8):837-40.
152. Jha P, Melendres G, Bijan B, Ormsby E, Chu L, Li CS, McGahan J. Trauma in pregnant women: assessing detection of post-traumatic placental abruption on contrast-enhanced CT versus ultrasound. *Abdom Radiol (NY)* 2016.
153. Walker M, Whittle W, Keating S, Kingdom J. Sonographic diagnosis of chronic abruption. *J Obstet Gynaecol Can* 2010;**32**(11):1056-8.
154. Hartung J, Kalache KD, Heyna C, Heling KS, Kuhlig M, Wauer R, Bollmann R, Chaoui R. Outcome of 60 neonates who had ARED flow prenatally compared with a matched control group of appropriate-for-gestational age preterm neonates. *Ultrasound Obstet Gynecol* 2005;**25**(6):566-72.
155. Montenegro N, Santos F, Tavares E, Matias A, Barros H, Leite LP. Outcome of 88 pregnancies with absent or reversed end-diastolic blood flow (ARED flow) in the umbilical arteries. *Eur J Obstet Gynecol Reprod Biol* 1998;**79**(1):43-6.
156. Prior T, Mullins E, Bennett P, Kumar S. Prediction of intrapartum fetal compromise using the cerebroumbilical ratio: a prospective observational study. *Am J Obstet Gynecol* 2013;**208**(2):124 e1-6.
157. Cruz-Martinez R, Figueras F, Hernandez-Andrade E, Oros D, Gratacos E. Fetal brain Doppler to predict cesarean delivery for nonreassuring fetal status in term small-for-gestational-age fetuses. *Obstet Gynecol* 2011;**117**(3):618-26.
158. Eser A, Zulfikaroglu E, Eserdag S, Kilic S, Danisman N. Predictive value of middle cerebral artery to uterine artery pulsatility index ratio in preeclampsia. *Arch Gynecol Obstet* 2011;**284**(2):307-11.
159. Piazze J, Padula F, Cerekja A, Cosmi EV, Anceschi MM. Prognostic value of umbilical-middle cerebral artery pulsatility index ratio in fetuses with growth restriction. *Int J Gynaecol Obstet* 2005;**91**(3):233-7.
160. Mose JC. The role of maternal & fetal doppler in pre-eclampsia. *Pregnancy Hypertens* 2014;**4**(3):242.
161. Yalti S, Oral O, Gurbuz B, Ozden S, Atar F. Ratio of middle cerebral to umbilical artery blood velocity in preeclamptic & hypertensive women in the prediction of poor perinatal outcome. *Indian J Med Res* 2004;**120**(1):44-50.
162. Cruz-Lemini M, Crispi F, Van Mieghem T, Pedraza D, Cruz-Martinez R, Acosta-Rojas R, Figueras F, Parra-Cordero M, Deprest J, Gratacos E. Risk of perinatal death in early-onset intrauterine growth restriction according to gestational age and cardiovascular Doppler indices: a multicenter study. *Fetal Diagn Ther* 2012;**32**(1-2):116-22.

163. Baschat AA. Ductus venosus Doppler for fetal surveillance in high-risk pregnancies. *Clin Obstet Gynecol* 2010;**53**(4):858-68.
164. Lees CC, Marlow N, van Wassenaer-Leemhuis A, Arabin B, Bilardo CM, Brezinka C, Calvert S, Derks JB, Diemert A, Duvekot JJ, Ferrazzi E, Frusca T, Ganzevoort W, Hecher K, Martinelli P, Ostermayer E, Papageorghiou AT, Schlembach D, Schneider KT, Thilaganathan B, Todros T, Valcamonico A, Visser GH, Wolf H, group Ts. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. *Lancet* 2015;**385**(9983):2162-72.
165. Bilardo CM, Hecher K, Visser GHA, Papageorghiou AT, Marlow N, Thilaganathan B, Van Wassenaer-Leemhuis A, Todros T, Marsal K, Frusca T, Arabin B, Brezinka C, Derks JB, Diemert A, Duvekot JJ, Ferrazzi E, Ganzevoort W, Martinelli P, Ostermayer E, Schlembach D, Valensise H, Thornton J, Wolf H, Lees C, Group T. Severe fetal growth restriction at 26-32 weeks: key messages from the TRUFFLE study. *Ultrasound Obstet Gynecol* 2017;**50**(3):285-90.
166. Baggio MR, Martins WP, Calderon AC, Berezowski AT, Marcolin AC, Duarte G, Cavalli RC. Changes in fetal and maternal Doppler parameters observed during acute severe hypertension treatment with hydralazine or labetalol: a randomized controlled trial. *Ultrasound Med Biol* 2011;**37**(1):53-8.
167. Erkinaro T, Haapsamo M, Kavasmaa T, Makikallio K, Acharya G, Rasanen J. Fetal cardiac function after labetalol or pindolol for maternal hypertension in a sheep model of increased placental vascular resistance. *Eur J Obstet Gynecol Reprod Biol* 2013;**166**(1):18-22.
168. Ulubasoglu H, Ozmen Bayar U, Kaya C, Ungan B. The effect of nifedipine tocolysis on Doppler indices of the uterine and umbilical arteries. *J Clin Ultrasound* 2015;**43**(5):322-6.
169. de Heus R, Mulder EJ, Derks JB, Visser GH. The effects of the tocolytics atosiban and nifedipine on fetal movements, heart rate and blood flow. *J Matern Fetal Neonatal Med* 2009;**22**(6):485-90.
170. Grzesiak M, Ahmed RB, Wilczynski J. 48-hours administration of nifedipine in spontaneous preterm labor - Doppler blood flow assessment of placental and fetal circulation. *Neuro Endocrinol Lett* 2013;**34**(7):687-92.
171. Lima MM, Souza AS, Diniz C, Porto AM, Amorim MM, Moron AF. Doppler velocimetry of the uterine, umbilical and fetal middle cerebral arteries in pregnant women undergoing tocolysis with oral nifedipine. *Ultrasound Obstet Gynecol* 2009;**34**(3):311-5.
172. Khalil A, Harrington K, Muttukrishna S, Jauniaux E. Effect of antihypertensive therapy with alpha-methyldopa on uterine artery Doppler in pregnancies with hypertensive disorders. *Ultrasound Obstet Gynecol* 2010;**35**(6):688-94.
173. Thuring A, Malcus P, Marsal K. Effect of maternal betamethasone on fetal and uteroplacental blood flow velocity waveforms. *Ultrasound Obstet Gynecol* 2011;**37**(6):668-72.
174. Nozaki AM, Francisco RP, Fonseca ES, Miyadahira S, Zugaib M. Fetal hemodynamic changes following maternal betamethasone administration in pregnancies with fetal growth restriction and absent end-diastolic flow in the umbilical artery. *Acta Obstet Gynecol Scand* 2009;**88**(3):350-4.
175. Shojaei K, Mohammadi N. Comparing the effects of antenatal betamethasone on Doppler velocimetry between intrauterine growth restriction with and without preeclampsia. *Glob J Health Sci* 2015;**7**(2):344-50.
176. Piazze J, Dillon KC, Cerekja A. Betamethasone effects on umbilical arteries and ductus venosus Doppler velocity waveforms in growth-restricted fetuses. *J Matern Fetal Neonatal Med* 2012;**25**(7):1179-82.
177. Souza AS, Amorim MM, Coutinho IC, Lima MM, Noronha Neto C, Figueroa JN. Effect of the loading dose of magnesium sulfate (MgSO₄) on the parameters of Doppler flow

- velocity in the uterine, umbilical and middle cerebral arteries in severe preeclampsia. *Hypertens Pregnancy* 2010;**29**(2):123-34.
178. Souza AS, Amorim MM, Coelho IC, Lima MM, Noronha Neto C, Figueroa JN. [Doppler of the umbilical and fetal middle cerebral arteries after magnesium sulfate in preeclampsia]. *Rev Assoc Med Bras* (1992) 2008;**54**(3):232-7.
179. Farshchian N, Rezavand N, Mohammadi S. Effect of magnesium sulfate on Doppler parameters of fetal umbilical and middle cerebral arteries in women with severe preeclampsia. *J Clin Imaging Sci* 2012;**2**:85.
180. Twickler DM, McIntire DD, Alexander JM, Leveno KJ. Effects of magnesium sulfate on preterm fetal cerebral blood flow using Doppler analysis: a randomized controlled trial. *Obstet Gynecol* 2010;**115**(1):21-5.
181. Oros D, Ruiz-Martinez S, Staines Urias E, Conde-Agudelo A, Villar J, Fabre E, Papageorghiou AT. Reference ranges for Doppler indices of umbilical and middle cerebral arteries and cerebroplacental ratio: a systematic review. *Ultrasound Obstet Gynecol* 2018.

For Peer Review

Classification of evidence levels

- 1++** High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
- 1+** Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
- 1-** Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
- 2++** High-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
- 2+** Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
- 2-** Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
- 3** Non-analytical studies, e.g. case reports, case series
- 4** Expert opinion

Grades of recommendations

- A** At least one meta-analysis, systematic review or randomised controlled trial rated as 1++ and directly applicable to the target population; or a systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
- B** A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
- C** A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
- D** Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+
- GPP** Recommended best practice based on the clinical experience of the guideline development group

Legend for figure

Figure 1. Transabdominal examination of first-trimester uterine artery waveform. The loop of the uterine artery is located at a paracervical section, and at least three identical waveforms are recorded with an insonation angle as close to 0° as possible.

For Peer Review

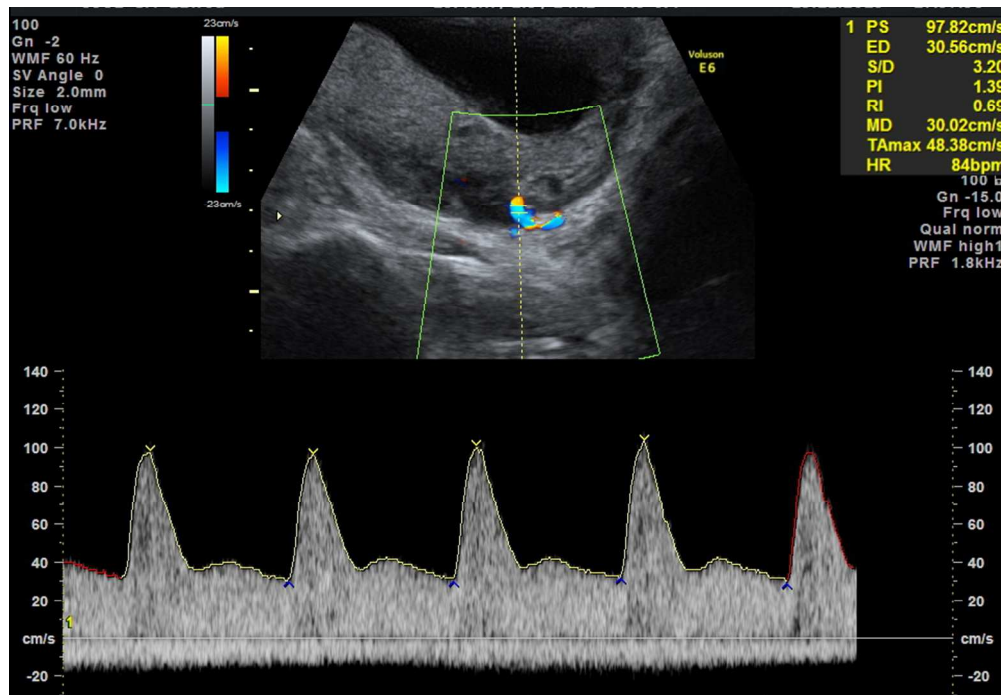


Figure 1. Transabdominal examination of first-trimester uterine artery waveform in the first trimester. The loop of the uterine artery is located at a paracervical section, and at least three identical waveforms are recorded with an insonation angle as close to 0° as possible.

163x112mm (150 x 150 DPI)