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

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THE INTERNATIONAL SOCIETY OF ULTRASOUND in Obstetrics & Gynecology

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 women [1] 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 preeclampsia [3], 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 preeclampsia [4].

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 disease [6] and maternal factors (e.g. metabolic syndrome or chronic hypertension) have a relatively greater significance [4]. Differences in early- and late-onset preeclampsia are also seen in risk factors [7], maternal vascular responsiveness [8], screening performance [9] and prevention effectiveness [10].

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 pressure [11].

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 risk [12]. 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 outcome [13]. 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 values [16].

Uterine artery notching has also been used in screening for preeclampsia [17], 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 pregnancies[19], 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 rate [17], 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 preeclampsia [20]. 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 trimester[21-23].

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	**GPP**
• 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	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 journal [27]. Following this approach, uterine artery PI can be measured in more than 95% of the cases [25] (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 ≤30° [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 be as high as ±35% for the transvaginal and ±40% for the transabdominal approach [30]. Based on such results, the reproducibility of the method should be interpreted as being poor to moderate [31]. 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 examination[27] is imperative to minimize the operator-dependent variability, as systematic error in the measurements can affect screen-positive rate [32].

Technical advice

- The 95th centile for transabdominal uterine artery mean PI between 11+0 and 13+6 weeks is 2.35 — Level of evidence: 2+
- 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 — Level of evidence: 2+
- The uterine artery PI may also be affected by maternal factors, including ethnic origin, BMI and previous preeclampsia — 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 weeks [25], with no- [25] or only a small trend to decrease [30] 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. 1.83 [33], and 1.60 vs. 1.52 [30]. The reason for this may be that TVS ensures a closer proximity to the vessel and lower insonation angles [30] . 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 mm [33].

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 values [35]

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 weeks [25]. 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 neonate [38], 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-off [40].

However, combined screening (maternal factors, maternal mean arterial blood pressure, uterine arteries Doppler, P*l*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° 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 — Level of evidence: 2++
- 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. — Level of evidence: 2+
- 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++

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 ±35%) [30].

The 95th centile of the mean UtA PI with the transabdominal approach has been reported as 1.44 [41] whereas the corresponding value for the transvaginal approach was 1.58 [43] 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 weeks [44].

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 limits [45].

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 factors [46]. 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 growth [17]. 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 notches [42], making their addition to screening not recommendable, although not all studies agree on the latter [47].

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 — Level of evidence: 4
- The 95th centile of mean uterine artery PI is 1.17 for transabdominal scan at 30-34 weeks — 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. — **GPP**
- The mean uterine artery PI should be used for prediction for preeclampsia, if this is offered in the third trimester — **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 rate [50].

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) preeclampsia [54]. 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 PI [55].

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 preeclampsia [56]. 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 studies [58 59]. Three-dimensional placental vascularization indices have also been evaluated [58-62]; however, they can be affected by attenuation due to depth and tissue interfases, 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 calculation [64 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 mm^3 [59 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 analysis [67].

Combined screening strategies

Recommendation

- A combination of maternal factors, maternal arterial blood pressure, uterine artery Doppler and placental growth factor (P*l*GF) 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 abnormalities [11]. 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 pressure [68], 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 (PlGF) [70 73], along with higher resistance in the uterine arteries [74], 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 PlGF increased this rate to 60%, and combined screening with maternal characteristics, uterine artery mean pulsatility index, mean arterial pressure and PlGF 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 PlGF 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 preeclampsia [77]; 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% respectively [78].

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%, respectively [49]. Prior screening in the first and second trimester does not further improve prediction accuracy over that of third-trimester alone [79]. Ethnic origin affects the sensitivity and false positive rate of third-trimester prediction, with both being higher in women of Afro-Caribbean origin [80]. Maternal and biochemical markers become more important for the prediction of preeclampsia in late pregnancy. Thus, among several potential factors, mean arterial pressure, PlGF and sFlt-1 were the ones associated with the prediction of preeclampsia between 30-34 [81] and 35-37 [82] 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 weeks [83]. The sFlt-1/PlGF 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 from [85]. 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 preeclampsia [87-89]. 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 pregnancy [90-101]. 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 biventricular [102] and endothelial function [103], and by the increased risk of cardiovascular morbidity later in life [104-106]. The hazard ratio for developing cardiovascular disease later in life is as high as 5.4 in women who had severe pre-eclampsia/eclampsia [105]. 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 pregnancy [107].

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 stiffness [90]. 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 pregnancies [94]. 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 hypertension [94]. Women who subsequently develop preeclampsia have evidence of left ventricular concentric remodelling at mid-gestation [97].

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 populations [111].

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 Gynecologists[112], 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 ≥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, PlGF) 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 preeclampsia [127]. The increased placental mass in twin pregnancies results in a lower mean uterine artery resistance compared to singleton pregnancies at the same gestational age [128-130]. 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 rate [130].

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 pregnancies [131]. 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 fetuses [132].

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 pregnancies [128].

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 weeks [133]. 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 dichrorionic 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*l*GF 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 model[131].

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 mothers [137]. 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 newborns [138].

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 outcomes [141].

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 observed [142]. 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 fetuses [156-158]. 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 surveillance [159-161]. 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 guideline[16].

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Technical advice

- Administration of antihypertensive drugs is not associated with significant changes in maternal and fetal Doppler indices — Level of evidence: 2+
- Antenatal corticosteroids are associated with a transient decrease in the vascular resistance in the umbilical arteries and ductus venosus — Level of evidence: 2+
- The data about a potential effect of magnesium sulfate on maternal and fetal Doppler indices are inconclusive — 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 hydralazine [166-169]. 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 disease [172].

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 reported [173-176]

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 review[181] 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) recruitment [181].

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 pratice 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*l*GF) 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 so 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, PlGF) 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**).

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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.

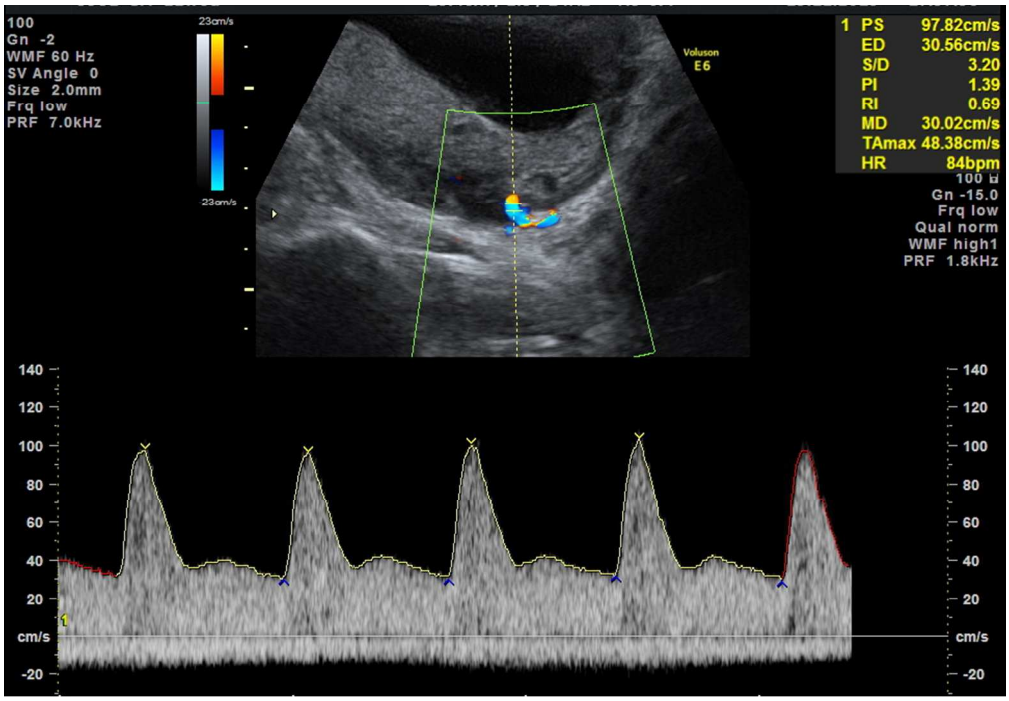

Figure 1. Transabdominal examination of first-trimester uterine artery waveform in the first trimester. The loop of the uterine artery is located at a paracervical section, and at least three identical waveforms are recorded with an insonation angle as close to 0° as possible.

163x112mm (150 x 150 DPI)