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GUIDELINES

ISUOG Practice Guidelines: role of ultrasound in screening for and follow-up of pre-eclampsia

Clinical Standards Committee

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INTRODUCTION

Hypertensive disease of pregnancy affects up to 10% of pregnant women[1] and the pooled global incidence of pre-eclampsia (PE) is approximately 3%[2]. Significant variations between developed and developing countries can be attributed to true differences or differences arising from data acquisition. PE 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 PE[3], the development of effective prediction and prevention strategies has been a major objective of prenatal care and of research.

PE 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 associated strongly with most cases of early and severe PE[4]. In contrast, defective placentation seems to be less important for the development of PE that manifests later in pregnancy, for example after 34 weeks. Compared with pregnancies affected by early-onset disease, in those complicated with PE at or near term, placentae have a significantly lower frequency of histological abnormalities[6], and maternal factors (e.g. metabolic syndrome or chronic hypertension) have a relatively greater significance[4]. Differences between early- and late-onset PE are also seen in risk factors[7], maternal vascular responsiveness[8], screening performance[9] and prevention effectiveness[10].

Increasing insight into the pathophysiology of PE is reflected in current screening strategies, which are based on history, demographics, biomarkers (including blood pressure) and uterine artery Doppler[11].

There are currently more than 10 000 PubMed-indexed articles related to PE screening, illustrating the vast interest in this topic. Fewer than one-fifth of these deal with early screening, this being a development of the last decade. The aim of these Guidelines is to review the latest evidence and, when possible, provide evidence-based recommendations regarding the role of ultrasound in screening and follow-up of PE. The Guidelines 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, these Guidelines were developed with the assumption that the resources required for implementation of screening and follow-up (equipment, examiners, expertise) are available. The steps and procedures described in these Guidelines are not intended to act as a legal standard for clinical service.

TERMINOLOGY: SCREENING *VS* PREDICTION

Although the terms 'screening' and 'prediction' are frequently used interchangeably, screening is in fact a wider process, beginning with invitation of a population to participate and ending with treatment for individuals identified as being at high risk[12]. Prediction, or the calculation of risk for disease, is an integral element of the screening process, but it is not equivalent to 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 screened condition and ultimately to improve the outcome[13]. Screening in prenatal care has been commonly used to offer the option of timely termination of pregnancy to parents of fetuses with untreatable conditions; this is an extension of the World Health Organization's scope of screening, which is prevention of disease. For the purpose of this Guideline, in the context of PE, 'screening' is the preferred term when identification of cases at risk may lead to prevention of its development, whereas 'prediction' is 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 PE should have up-to-date knowledge regarding major risk factors for PE (**GOOD PRACTICE POINT**).

Given that ultrasound screening for PE should not be isolated from the general concept of prenatal care, it is advisable that professionals who screen for PE have up-to-date knowledge about proven risk factors and aim to identify them during screening. A global assessment of risk should encompass four broad areas, including personal risk profile (including age, ethnicity, parity, smoking, medical and obstetric history and conception method), metabolic risk profile (including body mass index (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 PRE-ECLAMPSIA USING ULTRASOUND

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

Which Doppler index to use

Recommendation

- The pulsatility index (PI) should be used for examination of uterine artery resistance in the context of PE screening (**GRADE OF RECOMMENDATION: B**).

As described in the ISUOG Practice Guidelines on the use of Doppler ultrasonography in obstetrics[16], the systolic/diastolic ratio (S/D), resistance index (RI) and PI are the three best-known indices with which to describe arterial flow-velocity waveforms. PI is the index most commonly used; its advantage over RI in evaluation of the uterine artery Doppler waveform is that PI includes in its calculation the averaged value of all maximum velocities during the cardiac cycle, rather than just two points in the cardiac cycle as for RI. Furthermore, PI 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 PE[17], 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 as a screening marker, bilateral notching is not uncommon in normal first-trimester pregnancies, occurring in 43% of cases[19], which reduces its specificity. Likewise, uterine artery notching 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 increased PI, alone or combined with notching, is the most predictive Doppler index for PE[20]. A considerable amount of evidence published since then indicates the superiority of mean uterine artery PI as the preferred Doppler index for PE screening, and this is the index used for screening and prevention in the first trimester[21–23].

First trimester

Recommendation

- Doppler examination of the uterine arteries at $11+0$ to $13+6$ weeks can be performed either transabdominally or transvaginally, according to local preferences and resources (**GOOD PRACTICE POINT**).

Technical advice

- Screening by first-trimester uterine artery PI > 90th centile detects 48% of women who will develop early PE and 26% of those who will develop any PE, for a 10% screen-positive rate (**EVIDENCE LEVEL: 2++**).

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

For the first-trimester transabdominal assessment of uterine artery resistance, a midsagittal section of the uterus and cervix is obtained initially. Using color flow mapping,

the transducer is gently tilted sideways, so that the uterine arteries are identified with high-velocity blood flow along the side of the cervix and uterus (Figure 1). The pulsed-wave Doppler sampling gate should be narrow (set at approximately 2 mm) and positioned on either the ascending or descending branch of the uterine artery at the point closest to the internal cervical os, with an insonation angle $< 30°$[24]. In order to verify that the uterine artery is being examined, the peak systolic velocity should be > 60 cm/s. The PI is measured when at least three identical waveforms are obtained[25,26]. Detailed methodology can be found in a practical advice paper published in this journal[27]. Following this approach, uterine artery PI can be measured in more than 95% of cases[25].

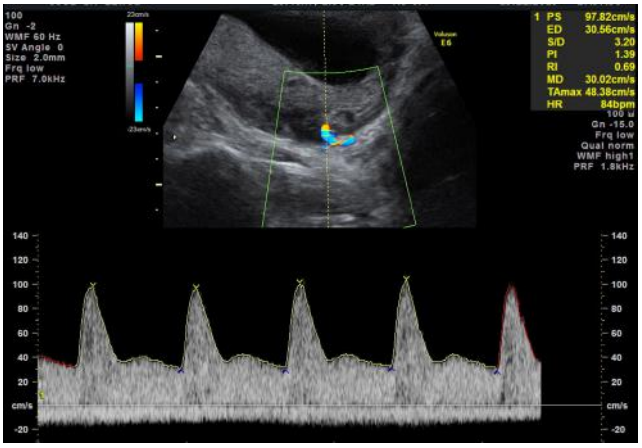

Figure 1 Transabdominal Doppler ultrasound examination of uterine artery in the first trimester. The uterine artery loop is located in a paracervical section, and at least three identical waveforms are recorded, using an insonation angle as close to 0° as possible.

Transvaginal assessment of uterine artery resistance 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 with an angle of insonation $< 30°$[28].

Recommendation

- Standardized methodology, as described in these Guidelines, should be followed for assessment of the uterine artery Doppler indices (**GOOD PRACTICE POINT**).

Adherence to a standardized 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, limits of agreement were found be as high as ±35% for the transvaginal and ±40% for the transabdominal approach[30]. On this basis, the reproducibility of the method should be interpreted as being poor to moderate[31]. Besides differences caused by observers, Doppler indices may change during an examination, due to factors such as uterine contractions and changes in heart rate. Although the effect of such factors cannot be prevented, adherence to a standardized protocol of examination[27] is imperative to minimize the operator-dependent variability, as systematic error in measurements can affect the screen-positive rate[32].

Technical advice

- The 95th centile for mean uterine artery PI obtained using a transabdominal approach between 11 + 0 and 13 + 6 weeks is 2.35 (**EVIDENCE LEVEL: 2+**).
- Uterine artery resistance is higher on transvaginal compared with transabdominal measurement; the 95th centile for mean uterine artery PI obtained using a transvaginal approach is approximately 3.10 for crown–rump lengths (CRL) up to 65 mm, gradually declining with increased CRL thereafter (**EVIDENCE LEVEL: 2+**).
- The uterine artery PI may also be affected by maternal factors, including ethnic origin, BMI and previous PE (**EVIDENCE LEVEL: 2++**).

Recommendation

- Given that maternal factors can affect uterine artery PI, its inclusion in a multifactorial screening model should, whenever feasible, be preferred over its use as a standalone test with absolute cut-offs (**GRADE OF RECOMMENDATION: B**).

The 95th centile of mean uterine artery PI obtained using a transabdominal approach is about 2.35 for the period 11 + 0 to 13 + 6 weeks[25], with no change[25] or only a small trend to decrease[30] over this period. In two comparative studies[30,33], the transvaginal approach gave significantly higher readings compared with the transabdominal approach, with mean PIs of 1.98 *vs* 1.83[33] and 1.60 *vs* 1.52[30]. The reason for this may be that transvaginal ultrasound allows closer proximity of the transducer to the vessel and lower insonation angles[30]. The 95th centile of the mean uterine artery PI obtained transvaginally has been reported as approximately 3.10 for CRLs up to 65 mm, progressively declining thereafter to reach 2.36 at a CRL of 84 mm[33].

In women who do not develop PE, uterine artery PI may be affected by maternal factors, including ethnic origin (African origin is associated with increased PI), BMI (decreasing PI with increasing BMI) and previous PE (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]. An absolute numerical cut-off for uterine artery PI may, therefore, not reflect accurately uterine artery resistance, and it has been suggested that first-trimester uterine artery PI should be expressed as multiples of the median (MoM) rather than absolute values[35].

Recommendation

- Mean uterine artery PI should be the Doppler index of choice for screening in the first trimester (**GRADE OF RECOMMENDATION: B**).

In one of the early studies using the current standard methodology for assessing uterine artery Doppler in the first trimester, a mean PI > 95th centile had a sensitivity of 27% for PE and a sensitivity of 60% for PE requiring delivery before 32 weeks[25]. Subsequent studies used the lowest uterine artery PI (i.e. PI of the side with least resistance) because the point estimates for the area under the receiver–operating characteristics 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 PE)[36]. However, the confidence intervals for the AUCs overlapped, and the superiority of the lowest PI was not confirmed by another large study (AUC, 0.79 for mean and 0.76 for lowest PI for the outcome of early PE, with overlapping CIs)[37]. Both techniques are acceptable, but the mean uterine artery PI is the index most commonly used for first- and second-trimester uterine artery Doppler examination, and the default reference values in most commercial software apply to this.

Bilateral notching has been associated with a 22-fold increased risk for PE and an almost nine-fold increased risk for small-for-gestational-age (SGA) neonate[38]; however, it may be observed in around 50% of pregnant women at 11 + 0 to 13 + 6 weeks[19,25,39]. This marker therefore has a very low specificity for PE.

A recent meta-analysis reported that first-trimester Doppler examination of the uterine arteries can predict 47.8% of cases of early PE (7.9% false-positive rate), 39.2% of cases of early fetal growth restriction (6.7% false-positive rate) and 26.4% of cases of PE at any stage (6.6% false-positive rate), when using as a cut-off the 90th centile of PI or RI[40]. However, combined screening (including maternal factors, maternal mean arterial blood pressure, uterine artery Doppler and placental growth factor (PlGF) measurement) has superior predictive performance (as detailed later) and, if available, should be preferred over Doppler-based screening.

Second trimester

Recommendation

- Doppler examination of the uterine arteries at the second-trimester scan can be performed either transabdominally or transvaginally, according to local preferences and resources (**GOOD PRACTICE POINT**).

Second-trimester Doppler examination of uterine arteries: technique. 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 at least three similar consecutive waveforms are obtained, PI is measured, and the presence or absence of early diastolic notching 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. The probe is then moved into the lateral fornix and the uterine arteries are identified on either side using color Doppler at the level of the internal cervical os. Pulsed-wave Doppler is used to obtain three similar consecutive waveforms. PI and RI can then be measured and the presence or absence of early diastolic notching can be recorded[17]. Examination of the uterine artery Doppler waveform following this approach is feasible in 99% of women[42].

As in the first trimester, using either a transabdominal or a transvaginal approach, care should be taken to maintain the angle of insonation < 30° and the peak systolic velocity > 60 cm/s 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 (**EVIDENCE LEVEL: 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 (**EVIDENCE LEVEL: 2+**).
- The 95th centile of the mean uterine artery PI decreases by about 15% between 20 and 24 weeks, and by <10% between 22 and 24 weeks (**EVIDENCE LEVEL: 2++**).

Recommendation

- Mean uterine artery PI should be used for prediction of PE. In case of a unilateral placenta, a unilaterally increased PI does not appear to increase the risk for PE if the mean PI is within normal limits (**GRADE OF RECOMMENDATION: B**).

Similar to the first trimester, when the uterine arteries are examined transvaginally, the PI readings are higher compared with those obtained using the transabdominal approach. In a comparative series of 96 women between 20 and 26 weeks, the mean uterine artery PI was 1.07 with the transvaginal and 0.96 with the transabdominal approach. The median angle of insonation was lower using transvaginal ultrasound (10.0° *vs* 17.5°); however, PI being a ratio, the most likely reason for the differences between transabdominal and transvaginal values 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 uterine artery PI at 23 weeks obtained with a transabdominal approach has been reported as 1.44[41], and that obtained with a transvaginal approach as 1.58[43]. The 95th centile of the mean uterine artery PI decreases by about 15% between 20 and 24 weeks, and by < 10% between 22 and 24 weeks[44].

In unilaterally located placentae, resistance to uterine flow on the contralateral side is commonly increased. A unilaterally increased PI does not appear to be associated with a higher risk for PE if the mean PI is within normal limits[45].

Performance of second-trimester prediction of PE. The predictive performance of uterine artery Doppler is better for early-onset PE; a study of more than 32 000 women indicated that, for a false-positive rate of 10%, uterine artery PI alone can predict 85% of cases of early-onset PE, compared with 48% of late-onset cases when combined with maternal factors[46]. Furthermore, the risk for early PE appears to increase with increasing uterine artery resistance; a mean PI of 1.6 was associated with a positive likelihood ratio (LR+) of 3.07, a mean PI of 1.8 with a LR+ of 8.00 and a mean PI of 2.2 with a LR+ of 27.08 (transvaginal measurements)[46]. In general, uterine artery Doppler velocimetry tends to predict better the more severe and complicated cases. For example, mean PI >1.65 (on transvaginal ultrasound) was found to predict 41% of all PE cases, but, when subgroups were analyzed, the prediction rate was 69% for PE with fetal growth restriction and 24% for PE with normal fetal growth[17]. This finding can be explained by the fact that high impedance in the uterine arteries reflects defective placentation, which has a concomitant deleterious effect on fetal growth.

Bilateral diastolic notching in the uterine artery Doppler waveform is also associated with increased risk for PE[17,41,42,46,47]. However, for the same false-positive rate, uterine artery PI is associated with better sensitivity than is notching[42], rendering unnecessary its addition to screening, although not all studies support this[47].

In terms of maternal health, a study of 491 women undergoing transthoracic echocardiography at the time of second-trimester screening for PE, showed that women with mean uterine artery PI > 90th centile (which was 1.25 in that study) had a higher prevalence of previously undiagnosed, functionally significant, cardiac defects (4.4%) compared with women with normal mean uterine artery PI (0.3%). This prevalence was particularly high among migrant women[48].

Third trimester

Technical advice

- Although uterine artery velocimetry can be assessed transvaginally, the most common method of uterine artery Doppler examination in the third trimester uses a transabdominal approach (**EVIDENCE LEVEL: 4**).
- The 95th centile for mean uterine artery PI is 1.17 obtained using a transabdominal approach at 30–34 weeks (**EVIDENCE LEVEL: 2+**).

Recommendations

- There are currently no randomized trials on the impact of third-trimester screening for PE on maternal, fetal and neonatal outcomes; consequently, its implementation into routine practice cannot be recommended at present (**GOOD PRACTICE POINT**).
- Mean uterine artery PI should be used for prediction of PE, if this is offered in the third trimester (**GRADE OF RECOMMENDATION: B**).

The standard method for Doppler examination of the uterine arteries in the third trimester is by a transabdominal approach, similar to the second trimester[24,41].

In a large, multicenter study in the UK, the 90th and 95th centiles for mean uterine artery PIs between 30 + 0 and 34 + 6 weeks were 1.03 and 1.17, respectively[49]. Mean uterine artery PI > 95th centile (5% false-positive rate) alone could predict 54% of PE before 37 weeks and 14% of PE ≥ 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 PE[49]. The same group assessed the effectiveness of screening at 35–37 weeks, finding that uterine artery Doppler alone was a poor predictor for PE; even when it was combined with maternal factors, the detection rate was 26% for a 5% false-positive rate and 37% for 10% false-positive rate[50].

Reversed uterine artery diastolic flow has been reported sporadically in the third trimester and, in cases with placental insufficiency, was associated with adverse outcome, such as progression to eclampsia or intrauterine demise[51,52].

Longitudinal changes in Doppler indices

Technical advice

- Increased uterine artery resistance persisting from first trimester to second trimester may identify women at highest risk for PE (**EVIDENCE LEVEL: 2++**).

Recommendation

- Given that preventive strategies (e.g. low-dose aspirin) for reducing the risk of PE are effective if started in the first trimester, their use should be commenced as soon as possible in women identified as being high-risk, without waiting to assess the evolution of Doppler in the second trimester (**GOOD PRACTICE POINT**).

As well as cross-sectional measurements of Doppler indices, their longitudinal changes have been studied in

the prediction of PE. A study examining sequentially uterine artery Doppler at 11–14 and 19–22 weeks ($n = 870$) reported that 73% of cases with increased PI in the first trimester had normalized by the second trimester. Women with increased PI in both first and second trimesters were at highest risk (37.5%) for adverse pregnancy outcome, i.e. growth restriction or hypertensive disorder. In contrast, women with normal PI in the first trimester had a 95% chance of normal measurements in the second trimester, 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 and first-trimester uterine artery PI, both expressed in MoM for the corresponding gestational ages. An increasing gap between first- and second-trimester uterine artery PI MoM, reflecting defective spiral artery transformation, appeared to be the most accurate predictor for early (AUC, 0.85) and preterm (AUC, 0.79) PE[54]. Another study on 104 women with increased uterine artery PI at 20–22 weeks reported that abnormal findings persisted at 26–28 weeks in 59.6% of cases; women with persistently increased PI had a greater risk for PE (16% *vs* 1%), SGA (32% *vs* 1%) and admission to a neonatal intensive care unit (26% *vs* 4%), compared with women in whom the PI normalized[55].

A problem with sequential assessment of Doppler is that the window of opportunity for preventative intervention (i.e. gestational age < 16 weeks) is missed if intervention is delayed pending a subsequent scan.

Placental volume

Recommendation

- Although placental volume and vascularization indices have been assessed as predictors for PE, they cannot be recommended for screening purposes given that their reproducibility is limited, they require special equipment and they are time-consuming (**GOOD PRACTICE POINT**).

Shortly after the introduction of three-dimensional ultrasound, first-trimester placental volume was tested as a potential predictor of PE. In one of the initial studies, placental volume at 12 weeks was compared with uterine artery Doppler examination at 22 weeks; the predictive performances of these two methods were: 20% and 28%, respectively, for PE without SGA; 31% and 46%, respectively, for PE with SGA; and 50% and 50%, respectively, for early PE[56]. Similarly, placental volume had predictive performance comparable to that of first-trimester mean uterine artery PI for PE (56% *vs* 50%) and for PE requiring delivery before 32 weeks (67% *vs* 67%)[57]. However, these findings have not been confirmed by other 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 interfaces, the use of different ultrasound settings and the lack of robust reproducibility (intra- and interobserver intraclass correlation coefficients, < 0.48 and < 0.66, respectively)[63], all of which limit their clinical applicability.

Although good reproducibility is reported for placental volume calculation[64,65], normal values vary considerably (first-trimester mean placental volume has been reported to range from 45 to 74 mL[59,61,64–66]). Moreover, placental volume calculation is currently a non-automated measurement subject to operator variability, and can be time-consuming, depending on the number of frames used for volume analysis[67].

COMBINED SCREENING STRATEGIES

Recommendations

- A combination of maternal factors, maternal arterial blood pressure, uterine artery Doppler and PlGF level at 11–13 weeks appears to be the most efficient screening model for identification of women at risk of PE (**GRADE OF RECOMMENDATION: 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 OF RECOMMENDATION: B**).
- The transabdominal approach is preferred for calculating first-trimester individual patient risk, as most screening algorithms were developed using this approach (**GOOD PRACTICE POINT**).

Maternal risk factors (history, demographics, cardiovascular and metabolic profile) and placental markers (uterine artery resistance and biomarkers) for the development of PE have been identified. 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 tailoring management accordingly, similar to screening for chromosomal abnormalities[11]. On a population basis, combined screening aims at improving on the sensitivity of single-marker screening and, at the same time, reducing the false-positive rate.

Combined screening has been the subject of approximately 400 PubMed articles up to April 2018. Multiple studies have shown that women who go on to develop PE 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] and PlGF[70,73], along with higher resistance in the uterine arteries[74], compared with women who do not. For all these predictors, the performance was better for early than for late PE[9,70], and was better when assessed later in pregnancy than at 11–13 weeks, i.e. closer to the development of PE[68–71,73–75].

Data from almost 36 000 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 and smoking) could predict 49% of PE < 37 weeks. The addition of

PlGF increased this rate to 60%, and combined screening with maternal characteristics, mean uterine artery PI, mean arterial pressure and PlGF at 11–13 weeks predicted 75% of cases of PE < 37 weeks and 47% of cases of PE ≥ 37 weeks[9]. The same protocol was used in the context of the ASPRE trial[21,76]; in this trial, combined screening was followed by randomization to aspirin or placebo in those at high risk. This algorithm, combining maternal factors, mean arterial pressure, mean uterine artery PI and PlGF, achieved a 100% detection rate for PE developing < 32 weeks, 75% detection for PE developing < 37 weeks and 43% detection for PE developing ≥ 37 weeks, for a 10% false-positive rate. The fetal fraction of cell-free DNA in the maternal circulation is also significantly associated with maternal and fetal risk factors for PE, and there is a significant relationship between low fraction and increased risk for PE[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 many as 100% of women who will develop early PE for a false-positive rate of 10%; the sensitivity for late PE and gestational hypertension is 56.4% and 54.1%, respectively[78].

In the third trimester, a combination of maternal factors and sFlt-1 level may predict 83% and 38% of PE before and after 37 weeks, respectively, for a false-positive rate of 5%; the corresponding figures for a 10% false-positive rate are 94% and 51%, respectively[49]. Prior screening in the first and/or second trimesters does not further improve prediction accuracy over that of third-trimester screening 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 PE in late pregnancy. Thus, among several potential factors, mean arterial pressure, PlGF and sFlt-1 were the ones associated with the prediction of PE between 30–34 weeks[81] and 35–37 weeks[82]. In contrast, the addition of uterine artery PI and maternal cardiovascular parameters did not improve the prediction of PE after 35–36 weeks[83]. The sFlt-1/PlGF ratio as a standalone marker can predict more than 75% of cases which will develop PE within 4 weeks, but its sensitivity is significantly higher at 31–34 than at 35–37 weeks (false-positive rate, 1.7% *vs* 9.6%)[84].

A common concern with combined screening models is that they may perform differently when applied prospectively in populations different from the ones from which they were derived[85]. The performance of the combined screening model used for the ASPRE trial (maternal factors, mean arterial pressure, mean uterine artery PI, PlGF) was practically identical when applied to the dataset used for its development and the actual clinical trial[9,76]. In fact, this screening model was found to be considerably more efficient for the prediction of early PE than were 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 PE, there are still too few data to support its routine implementation in clinical practice as a standalone test (**GOOD PRACTICE POINT**).

Cardiovascular adaptation plays a critical role in the hemodynamic changes observed in normal pregnancy. Failure of this adaptation, and possibly subclinical prepregnancy cardiovascular dysfunction, have been associated with the risk of developing PE[87–89]. Women who develop PE have prepregnancy cardiovascular risk factors, demonstrating increased arterial stiffness and impaired cardiac function at the time of the clinical diagnosis, as well as several weeks before clinical onset of the pathology and several months after the index pregnancy[90–101]. The cardiovascular implications of PE appear to continue long-term, as shown both by increased frequency of prolonged subclinical impairment of systolic biventricular[102] and endothelial[103] function, 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 PE/eclampsia[105]. Moreover, compared to women without recurrent disease, women who develop PE 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 between women with PE and those with normal pregnancy. In a systematic review of 23 studies evaluating arterial stiffness in association with hypertensive disease of pregnancy[90], women with PE had elevated arterial stiffness both during and after pregnancy, and to a greater extent than those with gestational hypertension. Interestingly, more severe PE was associated with greater arterial stiffness[90]. Both pulse-wave velocity analysis and the augmentation index have also been observed to be higher in the subclinical stage (as early as 11 weeks) in women who go on to develop PE[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 PE, 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 PE[109,110].

Cardiac output was significantly higher at 11–13 weeks in women who later developed PE or gestational hypertension, compared with that in women with uncomplicated pregnancy[94]. When combined with other maternal variables, for a 10% false-positive rate, the detection rate was 43.4% for all types of PE, 52% for PE without a SGA fetus and 23.3% for gestational hypertension[94]. Women who subsequently develop PE have evidence of left ventricular concentric remodeling in mid-gestation[97].

Despite the fact that maternal hemodynamics are promising screening markers of PE, 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 being performed increasingly in PE studies, it is imperative that relevant devices and techniques are used appropriately in pregnant populations[111].

MANAGEMENT AFTER SCREENING

Recommendation

- There is convincing evidence that low-dose aspirin can decrease significantly the risk for development of early PE, when administration commences at the time of first-trimester screening (**GRADE OF RECOMMENDATION: A**).

First trimester

Currently, the American College of Obstetricians and Gynecologists (ACOG)[112], the UK National Institute for Health and Care Excellence (NICE)[113] and the Society of Obstetricians and Gynaecologists of Canada (SOGC)[114], among others, recommend administering low-dose aspirin, commencing before 16 weeks, to women at risk for placental insufficiency.

Most of the studies on which current recommendations are based classified women as high risk according to historical or medical factors rather than using current screening methods (i.e. maternal factors, Doppler and biochemistry). In the ASPRE study, 1776 women at high risk for PE based on first-trimester combined screening were randomized to either aspirin (150 mg daily at bedtime) or placebo, from 11–14 weeks to 36 weeks' gestation[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 150 mg *in vivo*[116]. The timing of 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 PE before 37 weeks by 62% (from 4.3% to 1.6%). Aspirin also reduced the risk of PE before 34 weeks by 82%, but this effect did not reach statistical significance due to the low 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 in women with 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 of PE appears to be at least as 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 PE[120,121], the same intervention seems ineffective when started after 20 weeks[120]. Although it is too late to prevent the development of PE after second-trimester prediction, the knowledge can still be useful in guiding follow-up and management of a pregnancy at risk[122,123]. However, the clinical impact of intensified follow-up has yet to be proven. A Spanish trial randomized 11 667 women who attended for a routine second-trimester scan to Doppler or non-Doppler group. It was found that Doppler velocimetry identified 60% of the women who went on to develop PE, but the intensification of their care did not result in better short-term maternal or perinatal outcome compared with that of women who did not have a Doppler examination at the second-trimester scan[124].

Third trimester

Third-trimester testing can identify the majority of women who will develop PE in the subsequent weeks[80,125]. It has been described as part of a longitudinal risk-assessment scheme focused mainly 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 the subject of ongoing research.

MULTIPLE PREGNANCY

Recommendations

- Due to increased placental mass in twin pregnancy, resulting in lower mean resistance in the uterine arteries, twin-specific reference ranges should be used for Doppler examination, if available (**GRADE OF RECOMMENDATION: B**).
- The combined screening (maternal factors, uterine artery PI, mean blood pressure, PlGF) algorithm for singletons can also be used in twins and can identify more than 95% of women with twin pregnancy who will develop PE. However, the examiner should be aware

that this is achieved at the cost of a 75% screen-positive rate (**GRADE OF RECOMMENDATION: B**).

Twin pregnancy is a risk factor for obstetric complications, including PE[127]. The increased placental mass in twin pregnancy results in a lower mean uterine artery resistance compared with that of singleton pregnancy at the same gestational age[128–131], and this can be observed even during the first trimester[128,132]. Consequently, 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 a 12% false-positive rate; if the standard cut-offs for singleton pregnancy were used, the sensitivity would be 18% for a 1.7% false-positive rate[130].

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 PE and 22% higher in those developing late PE, compared with uncomplicated twin pregnancies[128].

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 uterine artery PI at 22–24 weeks had a sensitivity for PE of 33.3%, for a 3.3% false-positive rate (monochorionic and dichorionic twins)[129].

Chorionicity could theoretically have an impact on the extent of uterine hemodynamic 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 PE < 37 weeks' gestation is 8% for dichorionic twins and 14% for monochorionic twins, as compared with 0.6% for singleton pregnancy[127]. A study in the first trimester reported higher uterine artery resistance in monochorionic compared with dichorionic twins; in fact, monochorionic twins had similar resistance to that of singleton fetuses[132].

As in singleton pregnancy, combined screening in twin pregnancy performs better than does each of its individual components. A recent study assessed first-trimester screening with maternal factors, uterine artery PI, mean arterial pressure, PAPP-A and PlGF, and found that the detection rate of PE 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].

USE OF ULTRASOUND IN PATIENTS WITH ESTABLISHED PRE-ECLAMPSIA

Deteriorating fetal status is one of the indications for delivery in PE; therefore, close fetal surveillance is needed until delivery[134,135]. Ultrasound is the cornerstone for fetal assessment. However, as yet there have been no randomized controlled trials; 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 PE, fetal status should be assessed regularly in these patients (**GOOD PRACTICE POINT**).
- The sonographic follow-up in pregnancies affected by PE includes assessment of fetal growth and biophysical profile, and fetal Doppler studies (**GOOD PRACTICE POINT**).
- As there have been no randomized controlled trials, the components, frequency and impact of ultrasound surveillance in pregnancies affected by PE have yet to be determined (**GOOD PRACTICE POINT**).
- Examination of fetal biometry, amniotic fluid volume, uterine artery, umbilical artery (UA) and fetal middle cerebral artery (MCA) PI and cerebroplacental ratio (CPR), as well as placental visualization to exclude abruption, should be considered in women presenting with headache, abdominal pain, bleeding and/or reduced fetal movements (**GOOD PRACTICE POINT**).
- The same tests should be considered for women admitted for PE or with suspected PE, as well as for those with severe PE or HELLP syndrome (**GOOD PRACTICE POINT**).

PE is commonly associated with fetal growth restriction, and these fetuses tend to be delivered earlier and deteriorate faster compared with 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 PE.

B-mode ultrasound

Biometry. Fetal biometry can be assessed to identify a SGA fetus and to predict SGA 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 with AFI, measurement of MVP may result in fewer interventions without increasing adverse perinatal outcome[141].

Fetal movements. As part of the fetal biophysical profile, fetal breathing movements, body/limb movements

and muscular tone (e.g. extension and flexion of a fetal extremity or opening and closing of the hand) should be observed[142]. These three components, plus the assessment of amniotic fluid volume and fetal heart rate, constitute the fetal biophysical profile. Positive findings for each component are assigned a value of 2, with the total biophysical profile score (BPP score) ranging from 0 to 10. A BPP score ≥ 8 is considered to be normal and a manifestation of fetal wellbeing. A BPP score of 6 is an inconclusive result, and the test should be repeated. A BPP score ≤ 4 is a non-reassuring fetal test result, and delivery should be considered[143,144]. Biophysical profile testing is used mostly in the USA, whereas clinical management in Europe is based mostly 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 PE, such as a thickened placenta with diffuse echogenicity most probably due to edema, a thin placenta with reduced vascularization[145,146], or cystic regions suggestive of infarctions or hematomas[147,148]. Women with PE are at risk of partial or total abruption; therefore, evaluation of the placenta–myometrium interface is important[149,150]. Sonographic findings related to placental abruption include retroplacental hematoma (hyperechoic, isoechoic, hypoechoic), preplacental hematoma, increased placental thickness and echogenicity, subchorionic 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 ultrasound examination[151,152]. Chronic abruption, which may be seen as a retroplacental sonolucent area on ultrasound imaging, and oligohydramnios sequence can develop in PE patients[153].

Doppler

The four Doppler territories commonly examined for fetal and maternal evaluation are: (1) UA, (2) fetal MCA, (3) fetal ductus venosus and (4) uterine arteries.

Briefly, absent or reversed end-diastolic velocity in the UA is strongly associated with perinatal morbidity/mortality[154,155]. Reduced MCA-PI $< 10^{th}$ percentile is a sign of brain vasodilatation and has been associated with emergency Cesarean delivery due to non-reassuring fetal heart rate in growth-restricted fetuses[156–158]. CPR $< 10^{th}$ percentile is considered to be a sign of hemodynamic redistribution, can be observed even before the UA 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 into the follow-up of growth-restricted fetuses in PE, as most of its participants either had PE at enrollment or developed it during their follow-up. It was found that optimal long-term outcome for growth-restricted fetuses with abnormal UA 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, prompting immediate delivery[137,164,165]. Increased resistance in the uterine arteries indicates defective spiral artery transformation and is not useful as an indication for delivery.

Guidelines for fetal Doppler evaluation have been published previously[16]; further details of Doppler evaluation are beyond the scope of these Guidelines.

Technical advice

- Administration of antihypertensive drugs is not associated with significant changes in maternal and fetal Doppler indices (**EVIDENCE LEVEL: 2+**).
- Antenatal corticosteroids are associated with a transient decrease in vascular resistance in the UA and ductus venosus (**EVIDENCE LEVEL: 2+**).
- Data regarding a potential effect of magnesium sulfate on maternal and fetal Doppler indices are inconclusive (**EVIDENCE LEVEL: 2–**).

Use of labetalol, nifedipine or hydralazine has not been found to be associated with changes in uterine artery or UA Doppler waveforms[166–169]. However, Grzesiak *et al.*[170] and Lima *et al.*[171] reported a mild reduction in MCA-PI after administration of nifedipine, with no alteration in the other vascular territories. Methyldopa also has no effect on uterine artery resistance in patients with gestational hypertensive disease[172].

The effect of antenatal corticosteroids in the fetal circulation has been documented extensively. A transient reduction in vascular resistance and in UA-PI and ductus venosus-PI is generally observed. Absent or reversed end-diastolic or atrial velocities generally improve after the administration of corticosteroids; this effect generally lasts for 48–72 hours, but it can be longer in some fetuses. Some have also reported a mild reduction in MCA-PI; however, no effect of steroids on the uterine artery Doppler waveform has been reported[173–176].

There is no consensus regarding the effect of magnesium sulfate on fetal hemodynamics. Some studies found a reduction in PI or in RI of the UA, uterine artery and MCA after the administration of magnesium sulfate[177–179], but others found no such effect[180].

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 OF RECOMMENDATION: C**).

Doppler examination of maternal and fetal vessels has been in use 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 with lower image resolution than the ones used now, and it is not certain whether results would be the same if newer ultrasound technology had been used. Newer Doppler studies were performed at a time when the value of Doppler was already established and this may have resulted in two forms of bias: intention-to-treat bias, i.e. the Doppler findings may have affected the management, and hence the natural history, of any condition diagnosed; and expected-value bias, i.e. as normal ranges of Doppler measurements became available, examiners might subconsciously have adjusted their measurements towards the expected normal range, potentially biasing any retrospective study using these data. A recent systematic review[181] showed that the vast majority of Doppler studies suffer from methodological limitations, and proposed a set of criteria which should be applied in future high-quality studies. These criteria involve, among others: prospective data collection, a 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 PE should have up-to-date knowledge regarding major risk factors for PE (**GOOD PRACTICE POINT**).

Screening for pre-eclampsia using ultrasound

Which Doppler index to use

- The PI should be used for examination of uterine artery resistance in the context of PE screening (**GRADE OF RECOMMENDATION: B**).

First trimester

- Doppler examination of the uterine arteries at 11 + 0 to 13 + 6 weeks can be performed either transabdominally or transvaginally, according to local preferences and resources (**GOOD PRACTICE POINT**).
- Standardized methodology, as described in these Guidelines, should be followed for assessment of the uterine artery Doppler indices (**GOOD PRACTICE POINT**).
- Mean uterine artery PI should be the Doppler index of choice for screening in the first trimester (**GRADE OF RECOMMENDATION: B**).
- Given that maternal factors can affect uterine artery PI, its inclusion in a multifactorial screening model should, whenever feasible, be preferred over its use as a standalone test with absolute cut-offs (**GRADE OF RECOMMENDATION: B**).

Second trimester

- Doppler examination of the uterine arteries at the second-trimester scan can be performed either transabdominally or transvaginally, according to local preferences and resources (**GOOD PRACTICE POINT**).
- Mean uterine artery PI should be used for prediction of PE. In case of a unilateral placenta, a unilaterally increased PI does not appear to increase the risk for PE if the mean PI is within normal limits (**GRADE OF RECOMMENDATION: B**).

Third trimester

- There are currently no randomized trials on the impact of third-trimester screening for PE on maternal, fetal and neonatal outcomes; consequently, its implementation into routine practice cannot be recommended at present (**GOOD PRACTICE POINT**).
- Mean uterine artery PI should be used for prediction of PE, if this is offered in the third trimester (**GRADE OF RECOMMENDATION: B**).

Longitudinal changes in Doppler indices

- Given that preventive strategies (e.g. low-dose aspirin) for reducing the risk of PE are effective if started in the first trimester, their use should be commenced as soon as possible in women identified as being high-risk, without waiting to assess the evolution of Doppler in the second trimester (**GOOD PRACTICE POINT**).

Placental volume

- Although placental volume and vascularization indices have been assessed as predictors for PE, they cannot be recommended for screening purposes given that their reproducibility is limited, they require special equipment and they are time-consuming (**GOOD PRACTICE POINT**).

Combined screening strategies

- A combination of maternal factors, maternal arterial blood pressure, uterine artery Doppler and PlGF level at 11–13 weeks appears to be the most efficient screening model for identification of women at risk of PE (**GRADE OF RECOMMENDATION: 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 OF RECOMMENDATION: B**).
- The transabdominal approach is preferred for calculating first-trimester individual patient risk, as most screening algorithms were developed using this approach (**GOOD PRACTICE POINT**).

Assessment of maternal hemodynamics

- Despite the fact that maternal hemodynamic assessment may be of value in prediction of PE, there are still few data to support its routine implementation in

clinical practice as a standalone test (**GOOD PRACTICE POINT**).

Management after screening

- There is convincing evidence that low-dose aspirin can decrease significantly the risk for development of early PE, when administration commences at the time of first-trimester screening (**GRADE OF RECOMMENDATION: A**).

Multiple pregnancy

- Due to increased placental mass in twin pregnancy, resulting in lower mean resistance in the uterine arteries, twin-specific reference ranges should be used for Doppler examination, if available (**GRADE OF RECOMMENDATION: B**).
- The combined screening (maternal factors, uterine artery PI, mean blood pressure, PlGF) algorithm for singletons can also be used in twins and can identify more than 95% of women with twin pregnancy who will develop PE. However, the examiner should be aware that this is achieved at the cost of a 75% screen-positive rate (**GRADE OF RECOMMENDATION: B**).

Use of ultrasound in patients with established pre-eclampsia

- Given that fetal deterioration is an indication for delivery in established PE, fetal status should be assessed regularly in these patients (**GOOD PRACTICE POINT**).
- The sonographic follow-up in pregnancies affected by PE includes assessment of fetal growth and biophysical profile, and fetal Doppler studies (**GOOD PRACTICE POINT**).
- As there have been no randomized controlled trials, the components, frequency and impact of ultrasound surveillance in pregnancies affected by PE have yet to be determined (**GOOD PRACTICE POINT**).
- Examination of fetal biometry, amniotic fluid volume, uterine artery, UA and MCA PI and CPR, as well as placental visualization to exclude abruption, should be considered in women presenting with headache, abdominal pain, bleeding and/or reduced fetal movements (**GOOD PRACTICE POINT**).
- The same tests should be considered for women admitted for PE or with suspected PE, as well as for those with severe PE or HELLP syndrome (**GOOD PRACTICE POINT**).

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 OF RECOMMENDATION: C**).

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REFERENCES

1. Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol* 2009; **33**: 130–137.

2. Dolea C, AbouZahr C. *Global burden of hypertensive disorders of pregnancy in the year 2000. Evidence and Information for Policy (EIP)*. World Health Organization: Geneva, 2003. http://www.who.int/healthinfo/statistics/bod_hypertensivedisordersofpregnancy.pdf
3. WHO. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. WHO: Geneva, Switzerland, 2011. http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241548335/en/
4. Chaiworapongsa T, Chaemsaithong P, Yeo L, Romero R. Pre-eclampsia part 1: current understanding of its pathophysiology. *Nat Rev Nephrol* 2014; **10**: 466–480.
5. Melchiorre K, Sharma R, Thilaganathan B. Cardiovascular implications in preeclampsia: an overview. *Circulation* 2014; **130**: 703–714.
6. Mifsud W, Sebire NJ. Placental pathology in early-onset and late-onset fetal growth restriction. *Fetal Diagn Ther* 2014; **36**: 117–128.
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**: 558.e1–14.
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**: 103.e1–12.
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; **377**: 613–622.
11. Baschat AA. First-trimester screening for pre-eclampsia: moving from personalized risk prediction to prevention. *Ultrasound Obstet Gynecol* 2015; **45**: 119–129.
12. World Health Organization. Screening for various cancers. Secondary screening for various cancers 2018. http: //www.who.int/cancer/detection/variouscancer/en/.
13. Public Health England. 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**: 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**: 580–585.
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**: 233–239.
17. Papageorghiou AT, Yu CK, Bindra R, Pandis G, Nicolaides KH, Fetal Medicine Foundation Second-Trimester Screening Group. Multicenter screening for pre-eclampsia and fetal growth restriction by transvaginal uterine artery Doppler at 23 weeks of gestation. *Ultrasound Obstet Gynecol* 2001; **18**: 441–449.
18. Brodszki J, Lanne T, Laurini R, Strevens H, Wide-Swensson 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**: 154–162.
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**: 524–529.
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**: 701–711.
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**: 492–495.
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; **51**: 743–750.
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; **52**: 52–59.
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**: 689–697.
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**: 583–586.
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**: 742–749.
27. Khalil A, Nicolaides KH. How to record uterine artery Doppler in the first trimester. *Ultrasound Obstet Gynecol* 2013; **42**: 478–479.
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**: 490–494.
29. Ridding G, Schluter PJ, Hyett JA, McLennan AC. Uterine artery pulsatility index assessment at 11–13 weeks' gestation. *Fetal Diagn Ther* 2014; **36**: 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**: 546–552.
31. Martins WP, Nastri CO. Interpreting reproducibility results for ultrasound measurements. *Ultrasound Obstet Gynecol* 2014; **43**: 479–480.
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. DOI: 10.1002/uog.19116.
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**: 414–420.
34. Resnik R, Killam AP, Battaglia FC, Makowski EL, Meschia G. The stimulation of uterine blood flow by various estrogens. *Endocrinology* 1974; **94**: 1192–1196.
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**: 142–148.
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**: 534–537.
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**: 674–681.
39. Alves JA, Silva BY, de Sousa PC, Maia SB, Costa F da 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**: 357–362.
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**: 500–507.
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**: 559–564.
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**: 703–709.
43. Yu CK, Khouri O, Onwudiwe N, Spiliopoulos Y, Nicolaides KH, Fetal Medicine Foundation Second-Trimester Screening Group. 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**: 310–313.
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**: 128–132.
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**: 143–147.
46. Yu CK, Smith GC, Papageorghiou AT, Cacho AM, Nicolaides KH, Fetal Medicine Foundation Second-Trimester Screening Group. 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**: 429–436.
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**: 1103–1115.
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**: 310–316.
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**: 87.e1–17.
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**: 72–79.
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**: 232–235.
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**: 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**: 802–808.

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**: 180–184.
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**: 577–581.
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**: 652–657.
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**: 147–151.
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**: 367–371.
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**: 230–234.
60. Hafner E, Metzenbauer M, Stumpflen 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**: 756–763.
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**: 1247–1254.
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**: 920–926.
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**: 200–206.
64. Burstein E, Sheiner E, Hershkovitz R. Three-dimensional placental volume measurements between 11 and 13 weeks' gestation. *Am J Perinatol* 2009; **26**: 169–171.
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**: 156–160.
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**: 734–740.
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, Nicolaides KH. Mean arterial pressure at 12, 22, 32 and 36 weeks' gestation in screening for pre-eclampsia. *Ultrasound Obstet Gynecol* 2016; **47**: 573–579.
69. Tsiakkas A, Mendez O, Wright A, Wright D, Nicolaides 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**: 478–483.
70. Khalil A, Maiz N, Garcia-Mandujano R, Penco JM, Nicolaides 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**: 324–331.
71. Bredaki FE, Mataliotakis M, Wright A, Wright D, Nicolaides KH. Maternal serum alpha-fetoprotein at 12, 22 and 32 weeks' gestation in screening for pre-eclampsia. *Ultrasound Obstet Gynecol* 2016; **47**: 466–471.
72. Spencer K, Cowans NJ, Nicolaides KH. Low levels of maternal serum PAPP-A in the first trimester and the risk of pre-eclampsia. *Prenat Diagn* 2008; **28**: 7–10.
73. Tsiakkas A, Cazacu R, Wright A, Wright D, Nicolaides KH. Maternal serum placental growth factor at 12, 22, 32 and 36 weeks' gestation in screening for pre-eclampsia. *Ultrasound Obstet Gynecol* 2016; **47**: 472–477.
74. O'Gorman N, Tampakoudis G, Wright A, Wright D, Nicolaides KH. Uterine artery pulsatility index at 12, 22, 32 and 36 weeks' gestation in screening for pre-eclampsia. *Ultrasound Obstet Gynecol* 2016; **47**: 565–572.
75. Wright A, Guerra L, Pellegrino M, Wright D, Nicolaides 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**: 762–767.
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, Nicolaides 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; **49**: 751–755.
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. DOI: 10.1002/uog.18993.
78. Onwudiwe N, Yu CK, Poon LC, Spiliopoulos I, Nicolaides KH. Prediction of pre-eclampsia by a combination of maternal history, uterine artery Doppler and mean arterial pressure. *Ultrasound Obstet Gynecol* 2008; **32**: 877–883.
79. Andrietti S, Carlucci S, Wright A, Wright D, Nicolaides 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**: 221–227.
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; **52**: 501–506.
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**: 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**: 203–209.
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**: 61–66.
84. Dragan I, Wright D, Fiolna M, Leipold G, Nicolaides KH. Development of pre-eclampsia within 4 weeks of sFlt-1/PlGF ratio > 38: comparison of performance at 31–34 vs 35–37 weeks' gestation. *Ultrasound Obstet Gynecol* 2017; **49**: 209–212.
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**: 279–285.
86. O'Gorman N, Wright D, Poon LC, Rolnik DL, Syngelaki A, de Alvarado M, Carbone IF, Dutemeyer V, Fiolna M, Frick A, Karagiotis N, Mastrodima S, de Paco Matallana C, Papaioannou G, Pazos A, Plasencia W, Nicolaides KH. Multicenter screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks' gestation: comparison with NICE guidelines and ACOG recommendations. *Ultrasound Obstet Gynecol* 2017; **49**: 756–760.
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**: 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**: 140–145.
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**: 849–856.
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**: 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**: 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**: 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**: 873–880.
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**: 292–300.
95. Melchiorre K, Sutherland GR, Liberati M, Thilaganathan B. Preeclampsia is associated with persistent postpartum cardiovascular impairment. *Hypertension* 2011; **58**: 709–715.
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**: 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**: 496–504.
98. Stott D, Nzelu O, Nicolaides KH, Kametas NA. Maternal hemodynamics in normal pregnancy and in pregnancy affected by pre-eclampsia. *Ultrasound Obstet Gynecol* 2018; **52**: 359–364.
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**: 584–588.
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**: 110–115.
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**: 683–696.
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**: 124–133.
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* 2018; **52**: 196–204.
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**: 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**: 918–930.
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**: 1–19.
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**: 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**: 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**: 1511–1517.
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**: 478–487.
111. Foo FL, McEniery 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**: 324–331.
112. American College of Obstericians and Gynecologists. ACOG Committee Opinion No. 743: Low-dose aspirin use during pregnancy. *Obstet Gynecol* 2018; **132**: 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**: 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**: 1022–1027.
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**: 3217–3224.
117. Ayala DE, Ucieda R, Hermida RC. Chronotherapy with low-dose aspirin for prevention of complications in pregnancy. *Chronobiol Int* 2013; **30**: 260–279.
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**: 685.e1–5.
119. Ortved D, Hawkins TL, Johnson JA, Hyett J, Metcalfe A. 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. DOI: 10.1002/uog.19076.
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**: 402–414.
121. Roberge S, Demers S, Nicolaides KH, Bureau M, Cote S, Bujold E. Prevention of pre-eclampsia by low-molecular-weight heparin in addition to aspirin: a meta-analysis. *Ultrasound Obstet Gynecol* 2016; **47**: 548–553.
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**: 367–372.
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; **52**: 365–372.
124. Garcia B, Llurba E, Valle L, Gomez-Roig MD, Juan M, Perez-Matos C, Fernandez M, Garcia-Hernandez JA, Alijotas-Reig J, Higueras 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**: 680–689.
125. Wright D, Dragan I, Syngelaki A, Akolekar R, Nicolaides KH. Proposed clinical management of pregnancies after combined screening for pre-eclampsia at 30–34 weeks' gestation. *Ultrasound Obstet Gynecol* 2017; **49**: 194–200.
126. Nicolaides KH. Turning the pyramid of prenatal care. *Fetal Diagn Ther* 2011; **29**: 183–196.
127. Francisco C, Wright D, Benko Z, Syngelaki A, Nicolaides KH. Hidden high rate of pre-eclampsia in twin compared with singleton pregnancy. *Ultrasound Obstet Gynecol* 2017; **50**: 88–92.
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**: 557–561.
129. Yu CK, Papageorghiou AT, Boli A, Cacho AM, Nicolaides 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**: 535–540.
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**: 541–545.
131. Francisco C, Wright D, Benko Z, Syngelaki A, Nicolaides KH. Competing-risks model in screening for pre-eclampsia in twin pregnancy according to maternal factors and biomarkers at 11–13 weeks' gestation. *Ultrasound Obstet Gynecol* 2017; **50**: 589–595.
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**: 956–960.
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**: 663–667.
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**: 1119–1125.
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**: 465.e1–6.
136. American College of Obstericians and Gynecologists. ACOG Practice Bulletin No. 125: Chronic hypertension in pregnancy. *Obstet Gynecol* 2012; **119**: 396–407.
137. Lees C, Marlow N, Arabin B, Bilardo CM, Brezinka C, Derks JB, Duvekot J, Frusca T, Diemert A, Ferrazzi E, Ganzevoort W, Hecher K, Martinelli P, Ostermayer E, Papageorghiou AT, Schlembach D, Schneider KT, Thilaganathan B, Todros T, van Wassenaer-Leemhuis A, Valcamonico 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**: 400–408.
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**: 2089–2097.
139. Williams K. Amniotic fluid assessment. *Obstet Gynecol Surv* 1993; **48**: 795–800.
140. Moise KJ, Jr. Toward consistent terminology: assessment and reporting of amniotic fluid volume. *Semin Perinatol* 2013; **37**: 370–374.
141. Lim KI, Butt K, Naud K, Smithies M. Amniotic fluid: technical update on physiology and measurement. *J Obstet Gynaecol Can* 2017; **39**: 52–58.
142. Manning FA. Fetal biophysical profile: a critical appraisal. *Clin Obstet Gynecol* 2002; **45**: 975–985.
143. Chari RS, Friedman SA, O'Brien JM, Sibai BM. Daily antenatal testing in women with severe preeclampsia. *Am J Obstet Gynecol* 1995; **173**: 1207–1210.
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**: 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): 62–65.
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**: 1616–1622.
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**: 1111–1115.
148. Aurioles-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**: 154–161.
149. Ananth CV. Ischemic placental disease: a unifying concept for preeclampsia, intrauterine growth restriction, and placental abruption. *Semin Perinatol* 2014; **38**: 131–132.
150. Minire A, Mirton M, Imri V, Lauren M, Aferdita M. Maternal complications of preeclampsia. *Med Arch* 2013; **67**: 339–341.
151. Glantz C, Purnell L. Clinical utility of sonography in the diagnosis and treatment of placental abruption. *J Ultrasound Med* 2002; **21**: 837–840.
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)* 2017; **42**: 1062–1067.
153. Walker M, Whittle W, Keating S, Kingdom J. Sonographic diagnosis of chronic abruption. *J Obstet Gynaecol Can* 2010; **32**: 1056–1058.
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**: 566–572.
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**: 43–46.
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**: 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**: 618–626.
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**: 307–311.
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**: 233–237.
160. Mose JC. The role of maternal & fetal doppler in pre-eclampsia. *Pregnancy Hypertens* 2014; **4**: 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**: 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**: 116–122.
163. Baschat AA. Ductus venosus Doppler for fetal surveillance in high-risk pregnancies. *Clin Obstet Gynecol* 2010; **53**: 858–868.
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, TRUFFLE study group. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. *Lancet* 2015; **385**: 2162–2172.
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**: 285–290.
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**: 53–58.
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**: 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**: 322–326.
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**: 485–490.
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**: 687–692.
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**: 311–315.
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**: 688–694.
173. Thuring A, Malcus P, Marsal K. Effect of maternal betamethasone on fetal and uteroplacental blood flow velocity waveforms. *Ultrasound Obstet Gynecol* 2011; **37**: 668–672.
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**: 350–354.
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**: 344–350.
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**: 1179–1182.
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**: 123–134.
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**: 232–237.
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**: 21–25.
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. DOI: 10.1002/uog.20102.

APPENDIX 1 Levels of evidence and grades of recommendation used in ISUOG Guidelines

Classification of evidence levels	
1++	High-quality meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with low risk of bias
1–	Meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with very low risk of confounding, bias or chance and high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with low risk of confounding, bias or chance and moderate probability that the relationship is causal
2–	Case–control or cohort studies with high risk of confounding, bias or chance and significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion
Grades of recommendation	
A	At least one meta-analysis, systematic review or randomized controlled trial rated as 1++ and applicable directly to the target population; or systematic review of randomized controlled trials or a body of evidence consisting principally of studies rated as 1+ applicable directly to the target population and demonstrating overall consistency of results
B	Body of evidence including studies rated as 2++ applicable directly to the target population and demonstrating overall consistency of results; or evidence extrapolated from studies rated as 1++ or 1+
C	Body of evidence including studies rated as 2+ applicable directly to the target population and demonstrating overall consistency of results; or evidence extrapolated from studies rated as 2++
D	Evidence of level 3 or 4; or evidence extrapolated from studies rated as 2+
Good practice point	Recommended best practice based on the clinical experience of the Guideline Development Group

