



Doppler Ultrasound of the Umbilical Artery: Clinical Application

Ultrassonografia Doppler da artéria umbilical: Aplicação clínica

Ana Sá Rocha¹ Ana Rosa Araújo Andrade² Maria Lúcia Moleiro² Luís Guedes-Martins^{1,2,3,4}

¹Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal

²Departamento da Mulher e da Medicina Reprodutiva, Centro Materno Infantil do Norte, Centro Hospitalar Universitário do Porto EPE, Porto, Portugal

³Departamento da Mulher e da Medicina Reprodutiva, Centro Materno Infantil do Norte, Unidade de Investigação e Formação, Porto, Portugal

⁴Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal

Address for correspondence Ana Sá Rocha, MD, R. Jorge de Viterbo Ferreira, 228, 4050-313, Porto, Portugal (e-mail: rochasaana@gmail.com).

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Abstract

Objective To provide a survey of relevant literature on umbilical artery Doppler ultrasound use in clinical practice, technical considerations and limitations, and future perspectives.

Methods Literature searches were conducted in PubMed and Medline, restricted to articles written in English. Additionally, the references of all analyzed studies were searched to obtain necessary information.

Results The use of this technique as a routine surveillance method is only recommended for high-risk pregnancies with impaired placentation. Meta-analyses of randomized trials have established that obstetric management guided by umbilical artery Doppler findings can improve perinatal mortality and morbidity. The values of the indices of Umbilical artery Doppler decrease with advancing gestational age; however, a lack of consensus on reference ranges prevails.

Conclusion Important clinical decisions are based on the information obtained with umbilical artery Doppler ultrasound. Future efforts in research are imperative to overcome the current limitations of the technique.

Keywords

- ▶ doppler
- ▶ placenta
- ▶ umbilical artery
- ▶ fetal surveillance
- ▶ placental insufficiency

Resumo

Palavras-chave

- ▶ doppler
- ▶ placenta
- ▶ artéria umbilical
- ▶ vigilância fetal
- ▶ insuficiência placentária

Objetivo Compilar informação relevante proveniente da literatura atual sobre a ultrassonografia Doppler das artérias umbilicais (AUs) na prática clínica, considerações e limitações técnicas e perspectivas futuras.

Métodos A pesquisa bibliográfica foi realizada nos bancos de dados PubMed e Medline e restringiu-se a artigos escritos na língua inglesa. Recorreu-se também à bibliografia dos artigos selecionados, quando necessário, para obter informação relevante.

Resultados A utilização desta técnica como método de vigilância de rotina está apenas recomendada em gravidezes de alto risco com disfunção placentar. Metanálises

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de estudos randomizados mostraram que o seguimento obstétrico baseado nos achados do Doppler da artéria umbilical pode melhorar a mortalidade e a morbidade perinatal. É consensual que os valores dos índices Doppler da AU decrescem com o avanço da idade gestacional. No entanto, há ainda muita incerteza quanto aos valores de referência.

Conclusão As informações obtidas através da AU Doppler US são a base para muitas decisões clínicas importantes. Trabalhos de investigação nesta área são essenciais para tentar colmatar atuais limitações da técnica.

Introduction

The umbilical arteries (UAs) play a key role in the regulation of the fetoplacental circulation. In the UAs, nerve regulation is absent and its tonus depends uniquely on locally released or circulating vasoactive substances, as well as on ions, such as calcium (Ca^{2+}) and potassium (K^+).¹⁻⁷ They lead the deoxygenated blood from the fetus to the placenta during systole and diastole, and together with the umbilical vein, which conducts the blood on the opposite direction, the exchange of nutrients, respiratory gases, and metabolites between the mother and the fetus, is guaranteed.⁸

To ensure normal intrauterine growth, there are some conditions that must be met: normal umbilical cord architecture and function; adequate placental perfusion; a healthy fetus and a favorable maternal condition; availability of nutrients and absence of pregnancy-related or non-related diseases.^{1,8,9} Any abnormality in any of these prerequisites can potentially lead to intrauterine growth restriction (IUGR), with its inherent increased risk of perinatal mortality and morbidity in the short and long term.^{1,9-14}

The main cause of IUGR is placental insufficiency,⁹ which is associated with an increased resistance to blood flow in the placental vasculature, restricting the blood supply to the fetus and inducing compensatory responses with hemodynamic changes.^{9,15,16} The onset of IUGR can occur anytime during pregnancy, and strict fetal surveillance is required after the diagnosis to determine when staying in the womb represents a greater risk of adverse perinatal outcomes than being born.^{10,17-20}

Doppler ultrasound (US) of the UA provides useful information regarding the blood flow features within the arteries and is a well-established surveillance method in high-risk pregnancies due to impaired placentation.^{11,20-22} In high-risk pregnancies, it is estimated that the use of Doppler US has allowed a decrease in the risk of perinatal death by ~ 29%.²⁰

The physical principle behind the Doppler US technology is named after The Doppler Effect, which is defined as the variation in the frequencies transmitted to and received from US waves between two objects when at least one is moving.^{23,24} In obstetrics, the constant object is the transducer, and the red blood cells of the uterofetoplacental circulation are the shifting reflectors that produce the returning signal echoes.²³

Spectral Doppler US is a speed-time spectral recording, presenting as flow velocity waveforms (FVWs).²⁵ It enables the quantification of the peak systolic velocity (PSV) and of the end-diastolic velocity (EDV) of blood flow within the UA, with which three indices can be obtained: the pulsatility index (PI), the resistance index (RI), and the systolic/diastolic ratio (S/D).^{26,27} These indices are considered to be indirect measures of the resistance to blood flow of the placental vasculature.^{1,11,28-30} Therefore, values not expected for the gestational age indicate placental dysfunction and fetal distress.^{15,26,28,31}

The UA Doppler US is widely used in fetal surveillance because it is a noninvasive, economical, simple, and reproducible method.^{8,12,13,15} However useful, this technic has some limitations, including the potential to cause considerable anxiety in families and clinicians, further diagnostic testing, and early (possibly very preterm) birth.¹¹ Moreover, it has been found that many studies reporting reference ranges for UA Doppler are based in methodologies with much heterogeneity.^{20,31}

The aim of the present review is to provide a survey of the relevant literature on UA Doppler US in the clinical practice, its technical considerations and limitations, and to explore future perspectives.

Methods

The present research aimed to include studies that focused on the applicability of UA Doppler US in pregnancy management. To compose the present review, thorough literature searches were conducted in the PubMed and Medline databases, restricted to articles written in the English language. The screening of articles was performed using the following terms from the Medical Subject Heading of the Index Medicus as keywords: *Doppler ultrasound* AND/OR *umbilical artery*. The list of obtained articles was revised and the ones dealing with placental evaluation, placental insufficiency, fetal/pregnancy surveillance, and IUGR were chosen for further revision. Articles found by cross-referencing that met the inclusion criteria were also included.

All identified studies were screened for these inclusion criteria: (1) published in English (2) with full-text available, (3) UA Doppler US application in pregnancy.

A selection of the articles was performed. First, articles were filtered by reviewing titles and abstracts using the same

inclusion criteria. Second, the remaining articles were accessed based on the full text. Studies that did not meet all the inclusion criteria were excluded.

Results

Umbilical Artery Waveform Analysis

Concerning the UA, the standard Spectral Doppler US FVW pattern presents as a “sawtooth” pattern, revealing a unidirectional, continuous, and pulsatile flow toward the placenta (► Fig. 1). Its pattern can be distinguished from that of the umbilical vein since the UV FVW are continuous and non-pulsatile throughout the cardiac cycle.^{32,33} In the “sawtooth” pattern of the UA, the highest point corresponds to the PSV, the lowest point corresponds to the EDV, and TAV stands for time-averaged velocity. These parameters enable the calculation of three indices: S/D Ratio: PSV/EDV; PI: (PSV - EDV)/TAV; RI: (PSV - EDV) / PSV.²³ In the clinical practice, the PI is the most commonly used.³⁴

In low-risk pregnancies, the fetoplacental circulation presents itself with a placental high resistance to flow until the 20th week; thereafter, it gradually decreases and becomes a low-resistance system.⁸ This phenomenon occurs from the end of the 2nd trimester due to the progressive placental villi maturation, greater width and wall compliance of the umbilical vessels along with greater fetal cardiac output and blood pressure.^{35,36} Consequently, an acceleration in the EDV occurs and a proportional decrease in the three indices mentioned above is expected.³⁷ A deviation from the expected indices may signal an underlying placental dysfunction, and it indi-

cates an increased risk of fetal demise,^{31,38–40} regardless of the Doppler technique used.^{35,41}

Pathological UA FVW has a progressive pattern of alterations, depending on the severity of the disorder: the EDV of the waveform becomes reduced (positive end-diastolic velocities [PEDV]), might disappear (absent end-diastolic velocities [AEDV]) (► Fig. 2), and can even reverse (reversed end-diastolic velocities [REDV]) (► Fig. 3), while PSV is not affected.^{37,40,42} In these cases, the PI is more indicated for the interpretation of FVW findings³⁵ and it starts to increase only when 40% of the placental vascular tree remains functioning.⁴³

While an AEDV flow before the 15th week is a normal physiological finding,⁴⁴ a REDV flow during the 1st trimester is associated with chromosomal abnormalities, fetal cardiovascular defects, and significant mortality.^{45–49} However, as stated by Bellver et al.,⁵⁰ the latter “is not always an ominous sign.”

Once present, the AEDV can stabilize or gradually evolve to REDV.⁵¹ In a small number of cases, an AEDV can ameliorate and normalize spontaneously around the 27th week of gestation, although it is still unknown how to predict in which fetuses it will happen.⁵¹ Antenatal administration of betamethasone to IUGR fetuses with absent or reversed end-diastolic velocity (AREDV) has also been correlated with the returning of the EDV and the stabilization of the resistance in the ductus venosus. By converting the AREDV to a normal flow, the outcome greatly improves, reverting the constant hypoxemia and acidosis to a better oxygenative status.⁵² However, this positive effect of betamethasone is not seen in all cases, and the favorable response of the responding fetuses has not yet been understood.⁵²

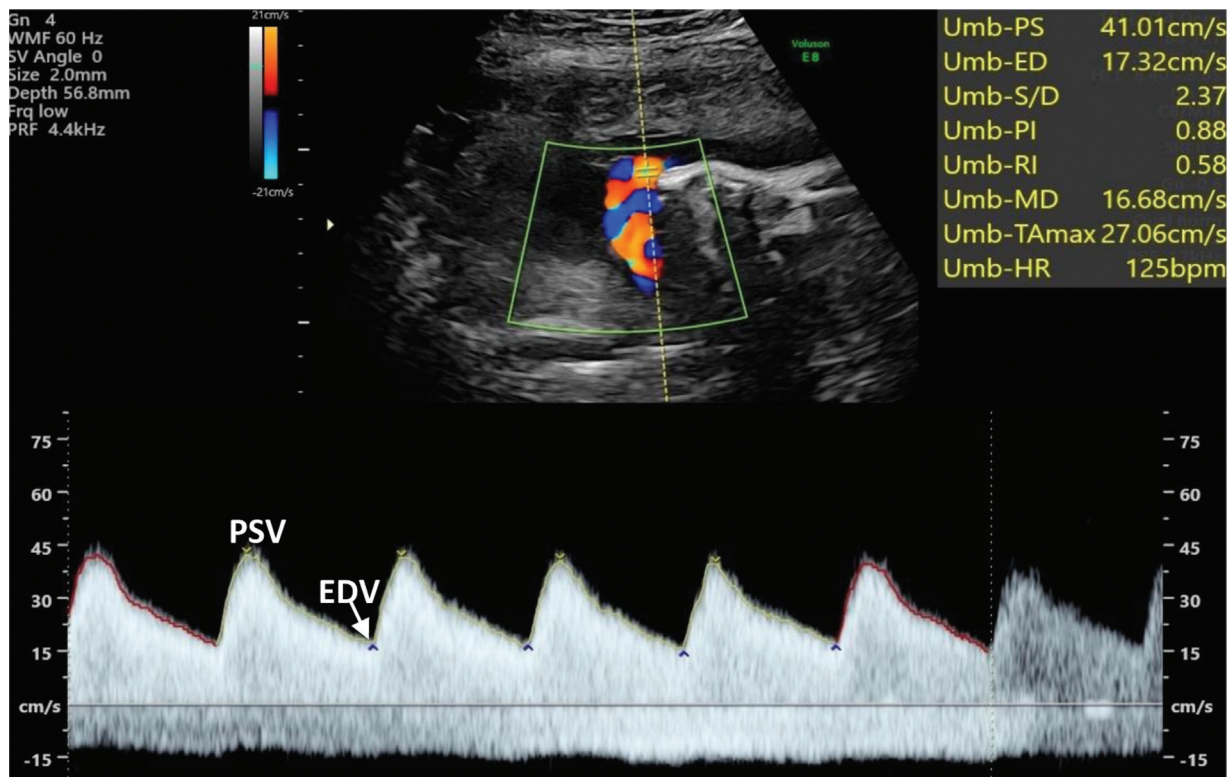


Fig. 1 Normal umbilical artery flow velocity waveform tracings obtained during the 3rd trimester. End diastolic velocities are present and are high; PSV - peak systolic velocity; EDV - end-diastolic velocity.

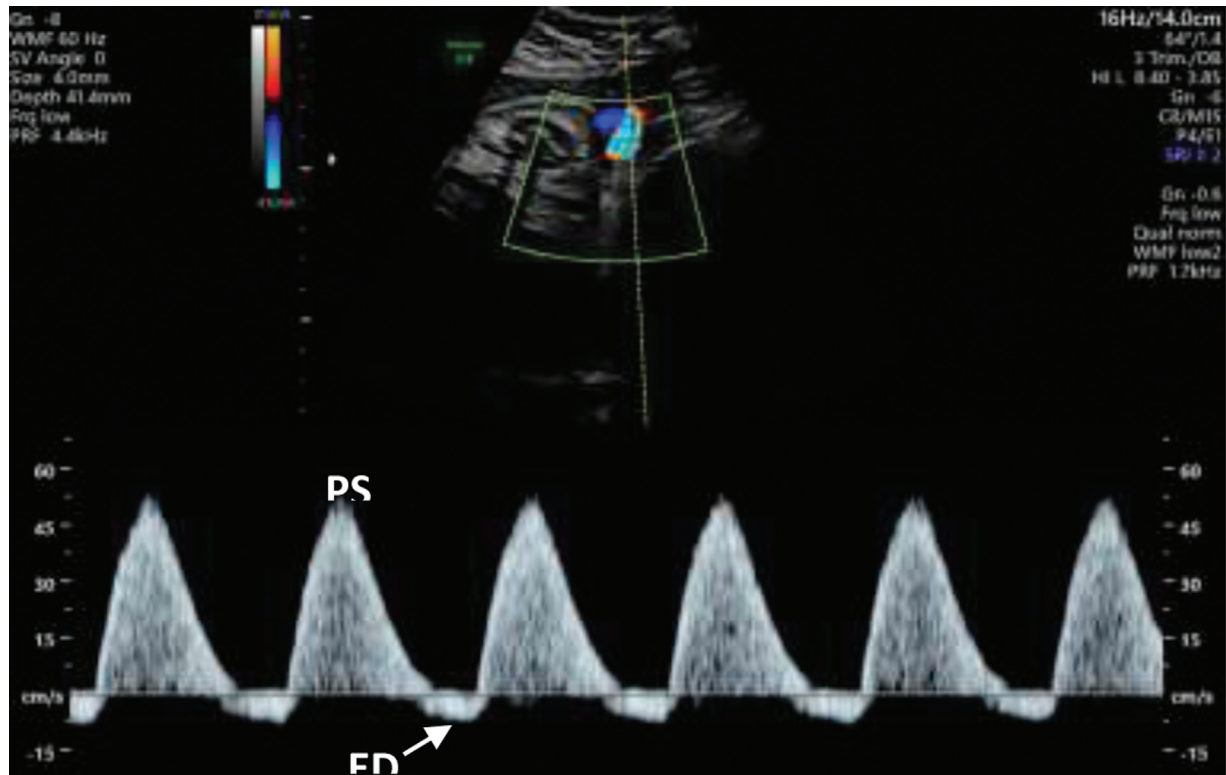


Fig. 2 Abnormal umbilical artery flow velocity waveform tracings obtained during the 2nd trimester. End diastolic velocities are absent, defining this pattern as AEDV. PSV - peak systolic velocity; EDV - end-diastolic velocity; AEDV - Absent end-diastolic velocity

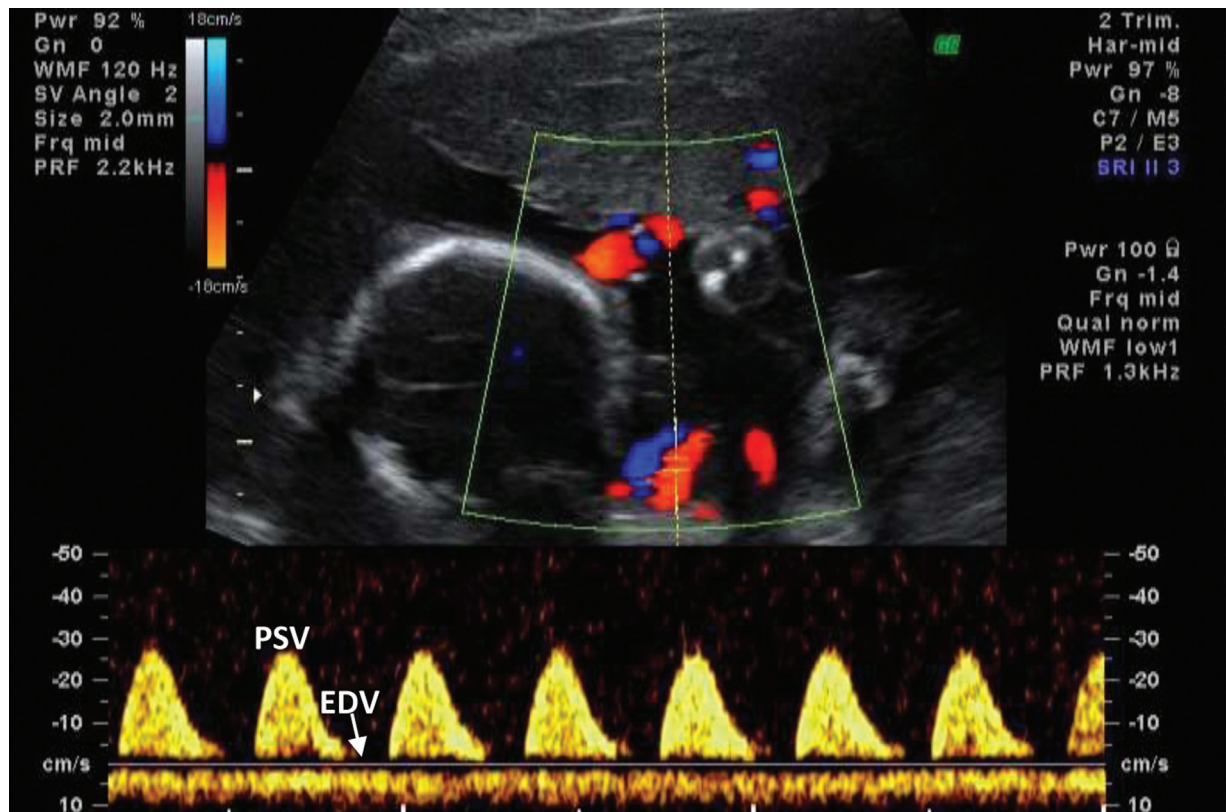


Fig. 3 Abnormal umbilical artery flow velocity waveform tracings obtained in a 3rd trimester pregnancy. End diastolic velocities are below the baseline, defining this pattern as REDV. PSV: peak systolic velocity; EDV: end-diastolic velocity; REDV: Reversed end-diastolic velocity

Absent or reversed end-diastolic velocity is frequently associated with marginal placental-end cord insertion,^{1,53} which can be accurately diagnosed by Color Doppler US during the 2nd trimester.¹² Furthermore, in IUGR fetuses with AREDV, there is an increased expression of estrogen receptor- β within the fetoplacental endothelium, misbalancing the vascular tonus mediators and favoring vasoconstriction.^{1,54,55} Being a vasodilator and smooth muscle relaxant,⁵⁶ the administration of intravenous or transdermal nitroglycerine causes a decrease in placental resistance to flow. This results in decreased PI, RI and S/D ratio in UA and Uterine artery (UtA) Doppler US, thus improving the outcomes.^{56,57}

When compared with PEDV, AREDV fetuses have a higher incidence of low birthweight, worse Apgar scores, and oligohydramnios; greater number of labor inductions and caesarean sections due to fetal distress; admissions to neonatal intensive care unit; fetal demise; perinatal mortality and morbidity,⁵⁸⁻⁶² as well as long-term neurological impairment.^{14,63-65} The lower the gestational age and fetal weight at birth, the more severe are the neonatal complications.⁵⁸ Specifically, fetuses with trisomy 21 have higher prevalence of AREDV, along with the presence of maternal malperfusion, delayed villous maturation and fetal vascular malperfusion, shortened umbilical cord, congenital cardiac anomalies, which frequently result in growth restriction, and death *in utero*.⁶⁶

In IUGR fetuses, when in the presence of PEDV, an expectant attitude and close monitoring with weekly UA assessment is suggested, while in the presence of AREDV, after an acceptable gestational age is achieved, pregnancy termination seems to be the safest option to attain a better perinatal outcome.^{37,58} Based on a recent meta-analysis, the 2021 International Federation of Gynecology and Obstetrics (FIGO) initiative on fetal growth suggested the application of UA Doppler findings as relative delivery criteria from 30 weeks onward for REDV and from 32 weeks onward for AEDV.^{39,67}

The analysis of FVW can alert obstetricians to other pathological entities in addition to placental disorders. A period of deceleration during a larger period of acceleration, or the opposite, is called *notching*.⁶⁸ A systolic notch in the UA FVW suggests the presence of an umbilical cord abnormality, such as an UA narrowing, an abnormal cord insertion, cord entanglement (in twin pregnancies) or a true knot. True knots, which are the major cause of notching, can impair the flow supply to the fetus and lead to adverse outcomes. The notching magnitude strongly correlates to how tight the knot is and it depends on the type of FVW being measured (envelope versus centerline), as well as on the location downstream of the constriction where the FVW is being measured.⁶⁸

Also worth of consideration are the results of a study conducted in 2006 by Struijk et al.,⁶⁹ in which the magnitude-squared coherence function between the UtA and UA FVW was found to improve the early identification of preeclampsia during the mid-trimester. However, it has no applicability in the prediction of IUGR or of pregnancy-induced hypertension.⁶⁹

Umbilical Artery Doppler Reference Ranges

There is a consensus that UA PI decreases linearly with advancing gestational age in uncomplicated singleton pregnancies.^{15,31,35,70-75} (► **Table 1**) (► **Fig. 4**).

However, the same percentile values were not obtained for each corresponding gestational age.^{15,31,35,70-75} The same could be inferred about UA RI (► **Table 2**) (► **Fig. 5**).⁷²⁻⁷⁵

Gathering values obtained in three different geographical areas, Drukker et al.⁷² proposed universal charts for UA PI. They considered that uncomplicated pregnancies in excellent health, nutritional, and environmental conditions for fetal growth have similar fetoplacental function and, consequently, similar Doppler indices regardless of the country of origin and of the inherent characteristics of its population.⁷² On the other hand, Ciobanu et al.⁷¹ suggested that the *a priori* risk related to maternal characteristics and medical history should be taken into account as maternal age, body mass index, smoking, parity, and racial origin have significant impact on UA PI. Moreover, Widnes et al.²⁶ considered the influence of fetal gender and proposed gestational age-dependent gender reference ranges, as they found that female fetuses have a more pulsatile UA from the 20th week to the 37th week, and higher heart rates from the 26th week.

In the case of fetuses with a single umbilical artery, Contro et al.⁷⁷ found the UA PI to be 20% lower than in those with a normal 3-vessel umbilical cord. This disparity remained constant between the 23rd and 40th gestational weeks. Thus, lower reference values in such cases may allow a more accurate interpretation of Doppler measurements.⁷⁷

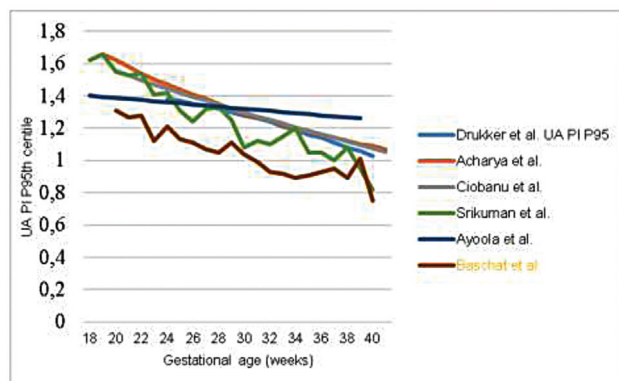
Concerning twin pregnancies, Mulcahy et al.⁷⁸ described the UA PI and RI to be consistently higher, from early pregnancy, in both monochorionic (MC) and dichorionic (DC) twins in comparison with singletons. Also among twin pregnancies, MC twins tend to demonstrate slightly higher values of UA PI and RI compared with DC twins.⁷⁸ These findings are supported by Casati et al.,⁷⁹ who proposed uncomplicated MC-specific Doppler charts, which include UA PI values. Since singleton Doppler reference ranges are not suitable for interpreting findings in twin pregnancies, further studies on both complicated and uncomplicated twin gestations and their perinatal and long-term outcomes are needed.^{78,79}

Maternal glucose loading⁸⁰ and fetal behavior state were found not to influence UA PI value measurements if adjusted to the fetal heart rate.^{80,81} Although smoking during pregnancy is associated with an increased risk of adverse outcomes,⁸²⁻⁸⁴ smoking habits seem not to influence fetal Doppler parameters.⁸⁵ A curious finding is that the left UA appears to have higher impedance to flow and as few as 2% of the pregnancies have both arteries with similar Doppler indices.⁸⁶

There is currently a wide variety of reference charts on UA Doppler indices, which could be explained, at least in part, by the heterogeneity in the methodological quality of the reports. Major methodological and statistical bias, found in some reports aiming to establish UA Doppler reference values, must be considered when examining this subject.³¹ Even the studies with the highest methodological quality have significant discrepancy in cutoff values, which may signify important differences in clinical practice when using

Table 1 Values of the 95th centile for umbilical artery pulsatility index in studies reporting reference ranges

Gestational age (weeks)	Drukker et al. ⁷²	Acharya et al. ⁷³	Ciobanu et al. ⁷¹	Srikumar et al. ⁷⁵	Ayoola et al. ⁷⁴	Baschat et al. ⁷⁶
18				1.62	1.402	
19		1.66		1.66	1.395	
20		1.62	1.553	1.55	1.388	1.31
21		1.58	1.526	1.53	1.381	1.27
22		1.54	1.499	1.54	1.375	1.28
23		1.5	1.472	1.41	1.368	1.12
24	1.38	1.47	1.446	1.42	1.361	1.21
25	1.37	1.44	1.42	1.31	1.354	1.13
26	1.35	1.41	1.395	1.24	1.348	1.11
27	1.34	1.38	1.371	1.32	1.341	1.07
28	1.32	1.35	1.346	1.33	1.334	1.05
29	1.3	1.32	1.322	1.25	1.327	1.11
30	1.28	1.29	1.299	1.08	1.321	1.04
31	1.26	1.27	1.275	1.12	1.314	0.99
32	1.24	1.25	1.252	1.1	1.307	0.93
33	1.21	1.22	1.229	1.15	1.3	0.92
34	1.19	1.2	1.207	1.2	1.294	0.89
35	1.16	1.18	1.184	1.05	1.287	0.91
36	1.14	1.16	1.162	1.05	1.28	0.93
37	1.11	1.14	1.14	1	1.273	0.95
38	1.08	1.12	1.118	1.08	1.267	0.89
39	1.06	1.1	1.097	0.95	1.26	1.01
40	1.03	1.09	1.075	0.82		0.75
41		1.07	1.053			

**Fig. 4** Comparison of the 95th percentile of the umbilical artery pulsatility index in studies reporting reference ranges. UA: Umbilical artery; PI: Pulsatility index

one cutoff value in preference to another.³¹ When evaluating the potential impact of such variability on the clinical management of small for gestational age (SGA) fetuses, Ruiz-Martinez et al.⁸⁷ found the rate of labor inductions to vary from 2.1 to 33.7%, depending on which reference chart of the UA PI was used and considering the PI cutoff > 95th

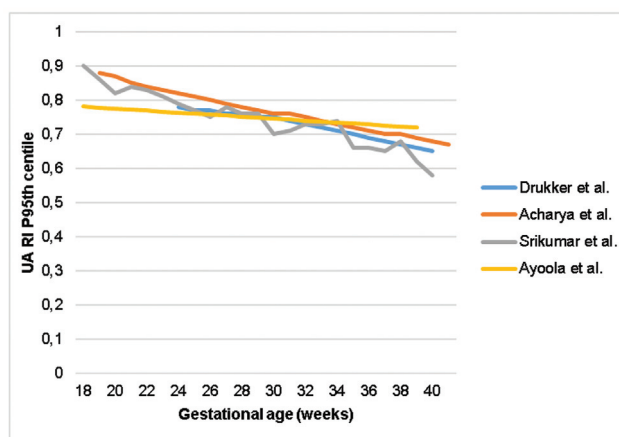
percentile, as recommended in current clinical guidelines.⁸⁸ This example illustrates the magnitude of the impact that heterogeneous cutoff values have on decision-making in important clinical issues.⁸⁷ Another example is presented by Drukker et al.,⁷² who found the 95th percentile values of UA PI to range between 1.28 and 1.48 at 32 weeks and between 1.03 and 1.40 at 39 weeks of pregnancy in different studies, illustrating a considerable uncertainty about what is a normal and expected cutoff value.⁷²

Umbilical Artery Doppler as a Screening Test in Low-Risk Pregnancies

According to Alfirevic et al.,¹¹ the methods traditionally used in low-risk pregnancies to assess fetal well-being (symphysis-fundal height measurement, fetal movements charts, and cardiotocography) have no proven ability to positively impact the low incidence and preventable adverse perinatal outcomes. Therefore, UA Doppler US was tested as a routine screening tool in low-risk pregnancies. In such pregnancies, UA Doppler US demonstrated low prognostic value concerning the risk of fetal demise, neonatal acidosis or decreased Apgar score.⁸⁹ Also, at term, an abnormal UA Doppler result in these cases can only have one consequence to improve the health of the newborn: intensified monitoring

Table 2 Values of the 95th percentile for umbilical artery resistance index in studies reporting reference ranges

Gestational age (weeks)	Drukker et al. ⁷²	Acharya et al. ⁷³	Srikumar et al. ⁷⁵	Ayoola et al. ⁷⁴
18			0.9	0.781
19		0.88	0.86	0.778
20		0.87	0.82	0.775
21		0.85	0.84	0.772
22		0.84	0.83	0.769
23		0.83	0.81	0.766
24	0.78	0.82	0.79	0.763
25	0.77	0.81	0.77	0.76
26	0.77	0.8	0.75	0.758
27	0.76	0.79	0.78	0.755
28	0.76	0.78	0.76	0.752
29	0.75	0.77	0.76	0.749
30	0.75	0.76	0.7	0.746
31	0.74	0.76	0.71	0.743
32	0.73	0.75	0.73	0.74
33	0.72	0.74	0.73	0.737
34	0.71	0.73	0.74	0.734
35	0.7	0.72	0.66	0.732
36	0.69	0.71	0.66	0.729
37	0.68	0.7	0.65	0.726
38	0.67	0.7	0.68	0.723
39	0.66	0.69	0.62	0.72
40	0.65	0.68	0.58	
41		0.67		

**Fig. 5** Comparison of the 95th percentile of the umbilical artery resistance index in studies reporting reference ranges; UA: Umbilical artery; RI: Resistance index

with possible elective delivery in the event of deteriorating fetal distress.⁹⁰ Considering its low predictable value and its cost of time, money and considerable anxiety of the parents, nowadays the routine screening of low-risk pregnancies with UA Doppler US is not recommended.^{11,15,90,91}

In contrast, according to Nkosi et al.,⁹² in developing countries and small centers with less financial resources, the routine use of Umbiflow (a continuous-wave Doppler machine) to screen low-risk pregnancies from the 28th to the 32nd week is beneficial. It allowed greater recognition of increased UA RI and AREDV patterns up to 5 to 10 times more than expected.⁹² The identification of these fetuses at risk, among the until then considered low-risk pregnancies, led to an adequate and active management of those pregnancies and to an improvement in perinatal outcomes, avoiding several unexplained stillbirths.^{92,93}

Aiming to predict the perinatal outcome of low-risk pregnancies whose fetuses are suspected of IUGR, Gudmundsson et al.⁹⁴ proposed a new Doppler index: the placental pulsatility index. It combines the PI value of UA and UtA to evaluate the complete placental vascular impedance, and the authors suggest it has greater efficiency to predict adverse perinatal outcomes than UA and UtA alone.⁹⁴

Umbilical Artery Doppler as a Screening Test in High-Risk Pregnancies

In contrast to low-risk pregnancies, the UA Doppler US is recommended as a routine surveillance method to assess

fetal well-being in high-risk pregnancies. Especially in pregnancies complicated by placental dysfunction, as in IUGR or pre-eclampsia, UA Doppler US works as a predictive test for fetal compromise.^{20,22,95,96} Its applicability in other high-risk groups such as diabetes mellitus, post-term, and uncomplicated dichorionic twin pregnancy is still uncertain.^{20,97-99}

The UA Doppler parameters are used to monitor fetal status and response to stress in pre-eclampsia and other hypertensive disorders related to pregnancy. However, it is the UtA PI that better predicts its future development^{100,101} and anticipates adverse outcomes related to the condition.¹⁰²

Fetuses with estimated fetal weight (EFW) < 10th centile are considered to be small for gestational age (SGA) and are at increased risk of fetal demise and poor perinatal outcomes when compared with non-SGA fetuses.^{20,103,104} Some of these are constitutionally small healthy fetuses, whereas others are failing to reach their potential weight due to an underlying condition – IUGR fetuses.^{11,20,105} Still, fetuses failing to reach their growth potential may or may not be SGA.^{20,106}

The criteria for diagnosing IUGR due to placental insufficiency include UA Doppler measurements.¹⁰⁷ There are 2 subtypes of IUGR, depending on whether the onset is before or after the 32nd week,¹⁰⁷ both of which have distinguishable Doppler patterns and postnatal outcomes.^{10,108} The early-onset IUGR (E-IUGR) is more frequently associated with early-onset pre-eclampsia^{109,110} and a classical sequence of deterioration of Doppler indices is present.¹¹¹⁻¹¹⁴ First, the UA PI increases to abnormally high values and then the middle cerebral artery PI starts decreasing as the cardiovascular redistribution occurs. As the downstream impedance to flow keeps increasing, the EDV within the UA decreases and AREDV pattern settles down. These are followed by an abnormal ductus venosus FVW and fetal heart insufficiency.¹¹¹⁻¹¹⁴ The presence of an AREDV pattern or an EFW < 3rd centile, before the 32nd week, establishes the diagnosis of E-IUGR by itself.¹⁰⁷ In E-IUGR fetuses, the decision of labor induction based on fetal monitoring with non-stress test and ductus venosus Doppler seems to be associated with better results at 2 years of age.^{17,38}

The late-onset IUGR (L-IUGR) is more prevalent and has a lower mortality rate than E-IUGR¹⁰⁸; however, the undetected cases constitute the major cause of unexplained still-birth.^{11,103,115} In this subtype of IUGR, the UA Doppler indices remain unchanged or minimally elevated, not being reliable for diagnosis.¹⁰⁸ After the 32nd week, the combination of biometrical parameters with Doppler measurements is more reliable than either one alone when differentiating the SGA at low-risk from those at high-risk for adverse outcomes.¹⁰⁸ These Doppler measurements must include the UA, the middle cerebral artery and the UtA as a multivessel screening in all pregnancies at high risk for placental dysfunction in the 3rd trimester.^{108,116} Finding both normal cerebroplacental ratio (CPR) and UtA Doppler indices, in fetuses presenting with an EFW > 3rd centile, confirms the low-risk status and the managing protocol of constitutionally small fetuses is appropriate.¹⁰⁸ When Doppler indices suggest placental insufficiency (UA PI > 95th centile or CPR < 5th centile), an EFW < 10th centile, or crossing > 2 quartiles on growth charts, has to be present to establish a

high-risk status for late-SGA. However, an EFW < 3rd centile alone, after the 32nd week, establishes the diagnosis by itself.¹⁰⁷

Selective IUGR in DC twin pregnancies can also be monitored using UA Doppler US as it presents a flow progression pattern similar to that of IUGR in singleton pregnancies. In contrast, and due to the interdependent circulation, selective IUGR in MC twin pregnancies does not exhibit such pattern and the UA Doppler US is not a reliable tool to predict a possible deterioration of fetal status.¹¹⁷ However, in MC pregnancies, a classification system based on the presence or absence of EDV in the UA in the affected twin guides its subsequent management.^{117,118} Thus, twin pregnancies benefit from fetal well-being assessment with the UA Doppler US when there is a growth discordance, twin-to-twin transfusion syndrome, or IUGR.^{119,120}

In pregnancies complicated by gestational diabetes,¹²¹ or with pre-existing diabetes mellitus without vascular disease, the non-stress test was found to be better than the UA Doppler US at predicting adverse perinatal outcomes.^{98,121} Only those complicated with vasculopathy due to diabetes could benefit from periodic UA Doppler US monitoring.⁹⁸

Discussion

The UA Doppler US has acquired an unquestionable importance as a fetal well-being surveillance method over the years and it is widely used in the clinical practice today.

In low-risk pregnancies, the placental impedance to flow is low and enables a continuous blood flow within the UA.^{8,37} Placental insufficiency compromises this low-resistance system at the expense of the EDV. The higher the placental resistance, the lower the UA EDV, and the normal FVW “sawtooth” pattern progressively deteriorates into PEDV, AEDV, and ultimately into REDV patterns. These abnormal patterns are recognized as ominous and anticipatory signs of poor obstetric outcomes.^{37,39,40,42,58,122} Likewise, the UA Doppler indices depend on EDV, and the PI, RI, and S/D ratio values are considered indirect measures of placental vasculature resistance to blood flow.^{1,11,28-30}

Concerning low-risk pregnancies, the routine use of UA Doppler US for fetal surveillance is not recommended.^{11,90,91} Nonetheless, this assumption is based on studies conducted approximately 30 years ago. Therefore, it would be paramount to replicate these investigations with more accurate methodologies to determine whether there would be changes to the current knowledge or a corroboration of past conclusions.

In high-risk pregnancies, the UA Doppler US allows an accurate risk assessment for adverse outcomes and helps in the decision-making toward minimization of perinatal mortality and morbidity.^{8,11,15} Current guidelines strongly recommend the routine use of this tool in high-risk pregnancies affected by placental insufficiency, such as those with IUGR and pregnancy-related hypertensive disorders.^{20,22,95,96} However, during the 3rd trimester, placental insufficiency develops under normal UA Doppler indices;¹⁰⁸ therefore, when suspected, other methods must be used to assess fetal well-being.^{10,108,116} Regarding this issue, the TRUFFLE group is currently conducting

a study (the TRUFFLE 2 study) aiming to address which monitoring methods and thresholds are ideal for determining the delivery of L-IUGR fetuses.¹²³ The role of UA Doppler US for fetal surveillance in high-risk pregnancies due to other precipitating factors requires further investigation.^{20,31,97–99,124}

Health improvements are not due to the application of the UA Doppler US itself but, rather, the result from the decision-making based on the information provided by this technology. Also, the success of Doppler measurements depends on the efficiency to spot abnormal and suspicious findings. Reference ranges are essential to establish which values of UA Doppler parameters must be considered normal and abnormal. Surprisingly, this is the point where less consensus exists. Although all studies agree that the values decrease with advancing gestational age, their proposed cutoff values differ significantly.^{15,31,35,70–75} Studies on the methodological quality of reports proposing reference ranges have shown major methodological and statistical biases.^{31,87} This may explain why so many different reference ranges have already been proposed. Another factor that may contribute to this variability is the wide range of variables that may influence UA Doppler indices. These can be fetal, maternal, or pregnancy-related variables, whose impact may be different when studied individually or in interaction. Given this and considering the potential impact of such variability on clinical decisions, the lack of consensus on reference ranges should incite scientific discussion. A universal chart was recently proposed aiming to standardize UA Doppler indices globally.⁷² Although it sounds promising, future studies reporting its efficacy in different populations around the globe are paramount to state a conclusion.

Conclusion

The UA Doppler US is an invaluable screening tool for high-risk pregnancies and on which important clinical decisions depend. Future investments in research are imperative to attempt to overcome the current limitations of the technique.

Conflict of Interests

The authors have no conflict of interests to declare.

References

- 1 Su EJ. Role of the fetoplacental endothelium in fetal growth restriction with abnormal umbilical artery Doppler velocimetry. *Am J Obstet Gynecol.* 2015;213(4, Suppl):S123–S130. Doi: 10.1016/j.ajog.2015.06.038
- 2 Lorigo M, Mariana M, Feiteiro J, Cairrao E. How is the human umbilical artery regulated? *J Obstet Gynaecol Res.* 2018;44(07): 1193–1201. Doi: 10.1111/jog.13667
- 3 Salemme S, Rebolledo A, Speroni F, Petruccioli S, Milesi V. L, P-/Q- and T-type Ca²⁺ channels in smooth muscle cells from human umbilical artery. *Cell Physiol Biochem.* 2007;20(1-4):55–64. Doi: 10.1159/000104153
- 4 Milesi V, Raingo J, Rebolledo A, Grassi de Gende AO. Potassium channels in human umbilical artery cells. *J Soc Gynecol Investig.* 2003;10(06):339–346. Doi: 10.1016/s1071-5576(03)00117-5
- 5 Reilly FD, Russell PT. Neurohistochemical evidence supporting an absence of adrenergic and cholinergic innervation in the human placenta and umbilical cord. *Anat Rec.* 1977;188(03): 277–286. Doi: 10.1002/ar.1091880302
- 6 Fox SB, Khong TY. Lack of innervation of human umbilical cord. An immunohistological and histochemical study. *Placenta.* 1990; 11(01):59–62. Doi: 10.1016/s0143-4004(05)80443-6
- 7 Poston L, McCarthy AL, Ritter JM. Control of vascular resistance in the maternal and feto-placental arterial beds. *Pharmacol Ther.* 1995;65(02):215–239. Doi: 10.1016/0163-7258(94)00064-a
- 8 Krzyżanowski A, Kwiatek M, Gęca T, Stupak A, Kwaśniewska A. Modern ultrasonography of the umbilical cord: prenatal diagnosis of umbilical cord abnormalities and assessment of fetal wellbeing. *Med Sci Monit.* 2019;25:3170–3180. Doi: 10.12659/MSM.913762
- 9 Sankaran S, Kyle PM. Aetiology and pathogenesis of IUGR. *Best Pract Res Clin Obstet Gynaecol.* 2009;23(06):765–777. Doi: 10.1016/j.bpobgyn.2009.05.003
- 10 Mureşan D, Rotar IC, Stamatian F. The usefulness of fetal Doppler evaluation in early versus late onset intrauterine growth restriction. Review of the literature. *Med Ultrason.* 2016;18(01): 103–109. Doi: 10.11152/mu.2013.2066.181.dop
- 11 Alfirevic Z, Stampalija T, Medley N. Fetal and umbilical Doppler ultrasound in normal pregnancy. *Cochrane Database Syst Rev.* 2015;(04):CD001450. Doi: 10.1002/14651858.CD001450.pub4
- 12 Sun J, Wang L, Li Y. Clinical value of color doppler ultrasound in prenatal diagnosis of umbilical cord entry abnormality. *Pak J Med Sci.* 2016;32(06):1414–1418. Doi: 10.12669/pjms.325.10518
- 13 Tanis JC, Boelen MR, Schmitz DM, Casarella L, van der Laan ME, Bos AF, et al. Correlation between Doppler flow patterns in growth-restricted fetuses and neonatal circulation. *Ultrasound Obstet Gynecol.* 2016;48(02):210–216. Doi: 10.1002/uog.15744
- 14 Baschat AA. Neurodevelopment after fetal growth restriction. *Fetal Diagn Ther.* 2014;36(02):136–142. Doi: 10.1159/000353631
- 15 Figueira CO, Surita FG, Dertkigil MS, Pereira SL, Bennini JR Jr, Morais SS, et al. Fetal Hemodynamic parameters in low risk pregnancies: Doppler velocimetry of uterine, umbilical, and middle cerebral artery. *ScientificWorldJournal.* 2016;2016:1693704. Doi: 10.1155/2016/1693704
- 16 Richardson BS, Bocking AD. Metabolic and circulatory adaptations to chronic hypoxia in the fetus. *Comp Biochem Physiol A Mol Integr Physiol.* 1998;119(03):717–723. Doi: 10.1016/s1095-6433(98)01010-1
- 17 Frusca T, Todros T, Lees C, Bilardo CMTRUFFLE Investigators. Outcome in early-onset fetal growth restriction is best combining computerized fetal heart rate analysis with ductus venosus Doppler: insights from the Trial of Umbilical and Fetal Flow in Europe. *Am J Obstet Gynecol.* 2018;218(2S, 2s):S783–S789. Doi: 10.1016/j.ajog.2017.12.226
- 18 Vollgraff Heidweiller-Schreurs CA, De Boer MA, Heymans MW, Schoondmade LJ, Bossuyt PMM, Mol BWJ, et al. Prognostic accuracy of cerebroplacental ratio and middle cerebral artery Doppler for adverse perinatal outcome: systematic review and meta-analysis. *Ultrasound Obstet Gynecol.* 2018;51(03):313–322. Doi: 10.1002/uog.18809
- 19 Bakalis S, Akolekar R, Gallo DM, Poon LC, Nicolaides KH. Umbilical and fetal middle cerebral artery Doppler at 30–34 weeks' gestation in the prediction of adverse perinatal outcome. *Ultrasound Obstet Gynecol.* 2015;45(04):409–420. Doi: 10.1002/uog.14822
- 20 Alfirevic Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. *Cochrane Database Syst Rev.* 2017;6(06):CD007529. Doi: 10.1002/14651858.CD007529.pub4
- 21 American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics and the Society for Maternal-Fetal Medicine. ACOG Practice Bulletin No. 204: fetal growth restriction. *Obstet Gynecol.* 2019;133(02):e97–e109. Doi: 10.1097/AOG.0000000000003070
- 22 Berkley E, Chauhan SP, Abuhamad A Society for Maternal-Fetal Medicine Publications Committee. Doppler assessment of the

- fetus with intrauterine growth restriction. *Am J Obstet Gynecol.* 2012;206(04):300–308. Doi: 10.1016/j.ajog.2012.01.022
- 23 Oglat AA, Matjafri MZ, Suardi N, Oqlat MA, Abdelrahman MA, Oqlat AA. A review of medical Doppler ultrasonography of blood flow in general and especially in common carotid artery. *J Med Ultrasound.* 2018;26(01):3–13. Doi: 10.4103/JMU.JMU_11_17
 - 24 Moorthy RS. Doppler ultrasound. *Med J Armed Forces India.* 2002;58(01):1–2. Doi: 10.1016/S0377-1237(02)80001-6
 - 25 Wood MM, Romine LE, Lee YK, Richman KM, O'Boyle M, Paz DA, et al. Spectral Doppler signature waveforms in ultrasonography: a review of normal and abnormal waveforms. *Ultrasound Q.* 2010;26(02):83–99. Doi: 10.1097/RUQ.0b013e3181dcbf67
 - 26 Widnes C, Flo K, Wilsgaard T, Kiserud T, Acharya G. Sex differences in umbilical artery Doppler indices: a longitudinal study. *Biol Sex Differ.* 2018;9(01):16. Doi: 10.1186/s13293-018-0174-x
 - 27 Nelson TR, Pretorius DH. The Doppler signal: where does it come from and what does it mean? *AJR Am J Roentgenol.* 1988;151(03):439–447. Doi: 10.2214/ajr.151.3.439
 - 28 Mone F, McConnell B, Thompson A, Segurado R, Hepper P, Stewart MC, et al. Fetal umbilical artery Doppler pulsatility index and childhood neurocognitive outcome at 12 years. *BMJ Open.* 2016;6(06):e008916. Doi: 10.1136/bmjopen-2015-008916
 - 29 Trudinger BJ, Stevens D, Connolly A, Hales JR, Alexander G, Bradley L, et al. Umbilical artery flow velocity waveforms and placental resistance: the effects of embolization of the umbilical circulation. *Am J Obstet Gynecol.* 1987;157(06):1443–1448. Doi: 10.1016/s0002-9378(87)80241-7
 - 30 Giles WB, Trudinger BJ, Baird PJ. Fetal umbilical artery flow velocity waveforms and placental resistance: pathological correlation. *Br J Obstet Gynaecol.* 1985;92(01):31–38. Doi: 10.1111/j.1471-0528.1985.tb01045.x
 - 31 Oros D, Ruiz-Martinez S, Staines-Urias E, Conde-Aguiedo A, Villar J, Fabre E, et al. Reference ranges for Doppler indices of umbilical and fetal middle cerebral arteries and cerebroplacental ratio: systematic review. *Ultrasound Obstet Gynecol.* 2019;53(04):454–464. Doi: 10.1002/uog.20102
 - 32 Hecher K, Campbell S. Characteristics of fetal venous blood flow under normal circumstances and during fetal disease. *Ultrasound Obstet Gynecol.* 1996;7(01):68–83. Doi: 10.1046/j.1469-0705.1996.07010068.x
 - 33 Najafzadeh A, Dickinson JE. Umbilical venous blood flow and its measurement in the human fetus. *J Clin Ultrasound.* 2012;40(08):502–511. Doi: 10.1002/jcu.21970
 - 34 Bhide A, Acharya G, Bilardo CM, Brezinka C, Cafici D, Hernandez-Andrade E, et al. ISUOG practice guidelines: use of Doppler ultrasonography in obstetrics. *Ultrasound Obstet Gynecol.* 2013;41(02):233–239. Doi: 10.1002/uog.12371
 - 35 Bahlmann F, Fittschen M, Reinhard I, Wellek S, Puhl A. Blood flow velocity waveforms of the umbilical artery in a normal population: reference values from 18 weeks to 42 weeks of gestation. *Ultraschall Med.* 2012;33(07):E80–E87. Doi: 10.1055/s-0031-1299294
 - 36 Trudinger BJ, Giles WB, Cook CM, Bombardieri J, Collins L. Fetal umbilical artery flow velocity waveforms and placental resistance: clinical significance. *Br J Obstet Gynaecol.* 1985;92(01):23–30. Doi: 10.1111/j.1471-0528.1985.tb01044.x
 - 37 Todros T, Piccoli E, Rolfo A, Cardaropoli S, Guiot C, Gaglioti P, et al. Review: Feto-placental vascularization: a multifaceted approach. *Placenta.* 2011;32(Suppl 2):S165–S169. Doi: 10.1016/j.placenta.2010.12.020
 - 38 Lees C, Marlow N, Arabin B, Bilardo CM, Brezinka C, Derks JB, et al; TRUFFLE Group. 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(04):400–408. Doi: 10.1002/uog.13190
 - 39 Caradeux J, Martinez-Portilla RJ, Basuki TR, Kiserud T, Figueras F. Risk of fetal death in growth-restricted fetuses with umbilical and/or ductus venosus absent or reversed end-diastolic velocities before 34 weeks of gestation: a systematic review and meta-analysis. *Am J Obstet Gynecol.* 2018;218(2S):S774–82.e21, 782.e21. Doi: 10.1016/j.ajog.2017.11.566
 - 40 Kalache KD, Dückelmann AM. Doppler in obstetrics: beyond the umbilical artery. *Clin Obstet Gynecol.* 2012;55(01):288–295. Doi: 10.1097/GRF.0b013e3182488156
 - 41 Giles WB, Lingman G, Marsál K, Trudinger BJ. Fetal volume blood flow and umbilical artery flow velocity waveform analysis: a comparison. *Br J Obstet Gynaecol.* 1986;93(05):461–465
 - 42 Marsál K. Rational use of Doppler ultrasound in perinatal medicine. *J Perinat Med.* 1994;22(06):463–474
 - 43 Thompson RS, Trudinger BJ. Doppler waveform pulsatility index and resistance, pressure and flow in the umbilical placental circulation: an investigation using a mathematical model. *Ultrasound Med Biol.* 1990;16(05):449–458. Doi: 10.1016/0301-5629(90)90167-b
 - 44 Fisk NM, MacLachlan N, Ellis C, Tannirandorn Y, Tonge HM, Rodeck CH. Absent end-diastolic flow in first trimester umbilical artery. *Lancet.* 1988;2(8622):1256–1257. Doi: 10.1016/s0140-6736(88)90854-9
 - 45 Borrell A, Martinez JM, Farre MT, Azulay M, Cararach V, Fortuny A. Reversed end-diastolic flow in first-trimester umbilical artery: an ominous new sign for fetal outcome. *Am J Obstet Gynecol.* 2001;185(01):204–207. Doi: 10.1067/mob.2001.114872
 - 46 Borrell A, Costa D, Martinez JM, Farré MT, Palacio M, Mortera C, Fortuny A, et al. Reversed end-diastolic umbilical flow in a first-trimester fetus with congenital heart disease. *Prenat Diagn.* 1998;18(10):1001–1005. Doi: 10.1002/(sici)1097-0223(199810)18:10<1001:aid-pd395>3.0.co;2-v
 - 47 Martinez Crespo JM, Comas C, Borrell A, Puerto B, Antolin E, Ojuel J, et al. Reversed end-diastolic umbilical artery velocity in two cases of trisomy 18 at 10 weeks' gestation. *Ultrasound Obstet Gynecol.* 1996;7(06):447–449. Doi: 10.1046/j.1469-0705.1996.07060447.x
 - 48 Murta CG, Moron AF, Avila MA. Reversed diastolic umbilical artery flow in the first trimester associated with chromosomal fetal abnormalities or cardiac defects. *Obstet Gynecol.* 2000;95(6 Pt 2):1011–1013. Doi: 10.1016/s0029-7844(99)00603-1
 - 49 Comas C, Carrera M, Devesa R, Muñoz A, Torrents M, Ribas I, et al. Early detection of reversed diastolic umbilical flow: should we offer karyotyping? *Ultrasound Obstet Gynecol.* 1997;10(06):400–402. Doi: 10.1046/j.1469-0705.1997.10060400.x
 - 50 Bellver J, Lara C, Rossal LP, Remohí J, Pellicer A, Serra V. First-trimester reversed end-diastolic flow in the umbilical artery is not always an ominous sign. *Ultrasound Obstet Gynecol.* 2003;22(06):652–655. Doi: 10.1002/uog.922
 - 51 Simonazzi G, Curti A, Cattani L, Rizzo N, Pilu G. Outcome of severe placental insufficiency with abnormal umbilical artery Doppler prior to fetal viability. *BJOG.* 2013;120(06):754–757. Doi: 10.1111/1471-0528.12133
 - 52 Piazza 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(07):1179–1182. Doi: 10.3109/14767058.2011.624216
 - 53 Nordenvall M, Ullberg U, Laurin J, Lingman G, Sandstedt B, Ulmsten U. Placental morphology in relation to umbilical artery blood velocity waveforms. *Eur J Obstet Gynecol Reprod Biol.* 1991;40(03):179–190. Doi: 10.1016/0028-2243(91)90115-2
 - 54 Su EJ, Ernst L, Abdallah N, Chatterton R, Xin H, Monsivais D, et al. Estrogen receptor- β and fetoplacental endothelial prostanoid biosynthesis: a link to clinically demonstrated fetal growth restriction. *J Clin Endocrinol Metab.* 2011;96(10):E1558–E1567. Doi: 10.1210/jc.2011-1084
 - 55 Su EJ, Lin ZH, Zeine R, Yin PReierstad Innes JE, et al. Estrogen receptor-beta mediates cyclooxygenase-2 expression and vascular prostanoid levels in human placental villous endothelial cells. *Am J Obstet Gynecol.* 2009;200(04):427.e1–427.e8. Doi: 10.1016/j.ajog.2009.01.025

- 56 Gupta S, Chauhan M, Sen J, Nanda S. Effect of transdermal nitroglycerine on Doppler velocity waveforms of the uterine, umbilical and fetal middle cerebral arteries in patients with chronic placental insufficiency: a prospective RCT. *J Clin Diagn Res.* 2017;11(07):QC13–QC17. Doi: 10.7860/JCDR/2017/21438.10282
- 57 Mishra M, Sawhney R, Kumar A, Bapna KR, Kohli V, Wasir H, et al. Cardiac surgery during pregnancy: continuous fetal monitoring using umbilical artery Doppler flow velocity indices. *Ann Card Anaesth.* 2014;17(01):46–51. Doi: 10.4103/0971-9784.124141
- 58 Yildirim G, Turhan E, Aslan H, Gungorduk K, Guven H, Idem O, et al. Perinatal and neonatal outcomes of perinatal restricted fetuses with positive end diastolic and absent or reversed umbilical artery doppler waveforms. *Saudi Med J.* 2008;29(03):403–408
- 59 Karsdorp VH, van Vugt JM, van Geijn HP, Kostene PJ, Arduini D, Montenegro N, et al. Clinical significance of absent or reversed end diastolic velocity waveforms in umbilical artery. *Lancet.* 1994;344(8938):1664–1668. Doi: 10.1016/s0140-6736(94)90457-x
- 60 Al Hamayel NA, Baghlah H, Blakemore K, Crino JP, Burd I. Significance of abnormal umbilical artery Doppler studies in normally grown fetuses. *Matern Health Neonatol Perinatol.* 2020;6:1. Doi: 10.1186/s40748-020-0115-7
- 61 Tolu LB, Ararso R, Abdulkadir A, Feyissa GT, Worku Y. Perinatal outcome of growth restricted fetuses with abnormal umbilical artery Doppler waveforms compared to growth restricted fetuses with normal umbilical artery Doppler waveforms at a tertiary referral hospital in urban Ethiopia. *PLoS One.* 2020;15(06):e0234810. Doi: 10.1371/journal.pone.0234810
- 62 Byun YJ, Kim HS, Yang JI, Kim JH, Kim HY, Chang SJ. Umbilical artery Doppler study as a predictive marker of perinatal outcome in preterm small for gestational age infants. *Yonsei Med J.* 2009;50(01):39–44. Doi: 10.3349/yjmj.2009.50.1.39
- 63 Valcamonico A, Danti L, Frusca T, Soregaroli M, Zucca S, Abrami F, et al. Absent end-diastolic velocity in umbilical artery: risk of neonatal morbidity and brain damage. *Am J Obstet Gynecol.* 1994;170(03):796–801. Doi: 10.1016/s0002-9378(94)70285-3
- 64 Valcamonico A, Accorsi P, Battaglia S, Soregaroli M, Beretta D, Frusca T. Absent or reverse end-diastolic flow in the umbilical artery: intellectual development at school age. *Eur J Obstet Gynecol Reprod Biol.* 2004;114(01):23–28. Doi: 10.1016/j.ejogrb.2003.09.033
- 65 Brüttsch S, Burkhardt T, Kurmanavicius J, Bassler D, Zimmermann R, Natalucci G, et al. Neurodevelopmental outcome in very low birthweight infants with pathological umbilical artery flow. *Arch Dis Child Fetal Neonatal Ed.* 2016;101(03):F212–F216. Doi: 10.1136/archdischild-2014-307820
- 66 Corry E, Mone F, Segurado R, Downey P, McParland P, McAuliffe FM, et al. Placental disease and abnormal umbilical artery Doppler waveforms in trisomy 21 pregnancy: A case-control study. *Placenta.* 2016;47:24–28. Doi: 10.1016/j.placenta.2016.09.001
- 67 Melamed N, Baschat A, Yinon Y, Athanasiadis A, Mecacci F, Figueras F, et al. FIGO (international Federation of Gynecology and obstetrics) initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction. *Int J Gynaecol Obstet.* 2021;152(Suppl 1):3–57. Doi: 10.1002/ijgo.13522
- 68 Tejada-Martínez AE, Borberg CJ, Venugopal R, Carballo C, Moreno WA, Quintero RA. Computational fluid dynamic analysis of flow velocity waveform notching in umbilical arteries. *Am J Physiol Regul Integr Comp Physiol.* 2011;300(01):R76–R84. Doi: 10.1152/ajpregu.00864.2009
- 69 Struijk PC, Fernando KL, Mathews VJ, Steegers EAP, Wladimiroff JW, Clark EB, et al. Application of the magnitude-squared coherence function between uterine and umbilical flow velocity waveforms for predicting placental dysfunction: a preliminary study. *Ultrasound Med Biol.* 2007;33(07):1057–1063. Doi: 10.1016/j.ultrasmedbio.2007.01.012
- 70 Dias T, Abeykoon S, Mendis P, Gunawardena C, Pragasan G, Padeniya T, et al. Fetal Doppler reference values in women with a normal body mass index. *Ceylon Med J.* 2019;64(02):59–65. Doi: 10.4038/cmj.v64i2.8888
- 71 Ciobanu A, Wright A, Syngelaki A, Wright D, Akolekar R, Nicolaides KH. Fetal Medicine Foundation reference ranges for umbilical artery and middle cerebral artery pulsatility index and cerebroplacental ratio. *Ultrasound Obstet Gynecol.* 2019;53(04):465–472. Doi: 10.1002/uog.20157
- 72 Drukker L, Staines-Urias E, Villar J, Barros FC, Carvalho M, Munim S, et al. International gestational age-specific centiles for umbilical artery Doppler indices: a longitudinal prospective cohort study of the INTERGROWTH-21st Project. *Am J Obstet Gynecol.* 2020;222(06):602.e1–602.e15. Doi: 10.1016/j.ajog.2020.01.012
- 73 Acharya G, Wilsgaard T, Berntsen GK, Maltau JM, Kiserud T. Reference ranges for serial measurements of umbilical artery Doppler indices in the second half of pregnancy. *Am J Obstet Gynecol.* 2005;192(03):937–944. Doi: 10.1016/j.ajog.2004.09.019
- 74 Ayoola OO, Bulus P, Loto OM, Idowu BM. Normogram of umbilical artery Doppler indices in singleton pregnancies in south-western Nigerian women. *J Obstet Gynaecol Res.* 2016;42(12):1694–1698. Doi: 10.1111/jog.13114
- 75 Srikumar S, Debnath J, Ravikummar R, Bandhu HC, Maurya VK. Doppler indices of the umbilical and fetal middle cerebral artery at 18–40 weeks of normal gestation: A pilot study. *Med J Armed Forces India.* 2017;73(03):232–241. Doi: 10.1016/j.mjafi.2016.12.008
- 76 Baschat AA, Gembruch U. The cerebroplacental Doppler ratio revisited. *Ultrasound Obstet Gynecol.* 2003;21(02):124–127. Doi: 10.1002/uog.20
- 77 Contro E, Cataneo I, Morano D, Farina A. Reference charts for umbilical Doppler pulsatility index in fetuses with isolated two-vessel cord. *Arch Gynecol Obstet.* 2019;299(04):947–951. Doi: 10.1007/s00404-019-05086-z
- 78 Mulcahy C, McAuliffe FM, Breathnach F, Geary M, Daly S, Higgins J, et al. Umbilical and fetal middle cerebral artery Doppler reference ranges in a twin population followed longitudinally from 24 to 38 weeks' gestation. *Ultrasound Obstet Gynecol.* 2014;44(04):461–467. Doi: 10.1002/uog.13302
- 79 Casati D, Pellegrino M, Cortinovis I, Spada E, Lanna M, Faiola S, et al. Longitudinal Doppler references for monochorionic twins and comparison with singletons. *PLoS One.* 2019;14(12):e0226090. Doi: 10.1371/journal.pone.0226090
- 80 Haugen G, Bollerslev J, Henriksen T. Human umbilical and fetal cerebral blood flow velocity waveforms following maternal glucose loading: a cross-sectional observational study. *Acta Obstet Gynecol Scand.* 2016;95(06):683–689. Doi: 10.1111/aogs.12913
- 81 Mulders LG, Muijsers GJ, Jongma HW, Nijhuis JG, Hein PR. The umbilical artery blood flow velocity waveform in relation to fetal breathing movements, fetal heart rate and fetal behavioural states in normal pregnancy at 37 to 39 weeks. *Early Hum Dev.* 1986;14(3–4):283–293. Doi: 10.1016/0378-3782(86)90191-x
- 82 Soneji S, Beltrán-Sánchez H. Association of maternal cigarette smoking and smoking cessation with preterm birth. *JAMA Netw Open.* 2019;2(04):e192514. Doi: 10.1001/jamanetworkopen.2019.2514
- 83 Tikkanen M, Nuutila M, Hiilesmaa V, Paavonen J, Ylikorkala O. Prepregnancy risk factors for placental abruption. *Acta Obstet Gynecol Scand.* 2006;85(01):40–44. Doi: 10.1080/00016340500324241
- 84 Reeves S, Bernstein I. Effects of maternal tobacco-smoke exposure on fetal growth and neonatal size. *Expert Rev Obstet Gynecol.* 2008;3(06):719–730. Doi: 10.1586/17474108.3.6.719
- 85 Stalzer A, Seybold D, Hossino D, Broce M, Calhoun B. Doppler screening and predictors of adverse outcomes in high risk pregnancies affected by tobacco. *Reprod Toxicol.* 2017;67:10–14. Doi: 10.1016/j.reprotox.2016.11.006

- 86 Janeczek S, Karlman R, MacMillan W. Left versus right intra-abdominal umbilical arteries: comparison of their Doppler waveforms. *J Ultrasound Med.* 2012;31(05):679–683. Doi: 10.7863/jum.2012.31.5.67
- 87 Ruiz-Martinez S, Papageorghiou AT, Staines-Urias E, Villar J, Gonzalez de Agüero R, Oros D. Clinical impact of Doppler reference charts to manage fetal growth restriction: need for standardization. *Ultrasound Obstet Gynecol.* 2020;56(02):166–172. Doi: 10.1002/uog.20380
- 88 ACOG Practice bulletin no. 134: fetal growth restriction. *Obstet Gynecol.* 2013;121(05):1122–1133. Doi: 10.1097/01.AOG.0000429658.85846.f9
- 89 Bolz N, Kalache KD, Proquitt H, Slowinski T, Hartung JP, Henrich W, et al. Value of Doppler sonography near term: can umbilical and uterine artery indices in low-risk pregnancies predict perinatal outcome? *J Perinat Med.* 2013;41(02):165–170. Doi: 10.1515/jpm-2012-0042
- 90 Doppler French Study Group. A randomised controlled trial of Doppler ultrasound velocimetry of the umbilical artery in low risk pregnancies. *Br J Obstet Gynaecol.* 1997;104(04):419–424. Doi: 10.1111/j.1471-0528.1997.tb11492.x
- 91 Goffinet F, Paris-Llado J, Nisand I, Bréart G. Umbilical artery Doppler velocimetry in unselected and low risk pregnancies: a review of randomised controlled trials. *Br J Obstet Gynaecol.* 1997;104(04):425–430. Doi: 10.1111/j.1471-0528.1997.tb11493.x
- 92 Nkosi S, Makin J, Hlongwane T, Pattinson RC. Screening and managing a low-risk pregnant population using continuous-wave Doppler ultrasound in a low-income population: A cohort analytical study. *S Afr Med J.* 2019;109(05):347–352. Doi: 10.7196/SAMJ.2019.v109i5.13611
- 93 Hugo EJ, Odendaal HJ, Grove D. Evaluation of the use of umbilical artery Doppler flow studies and outcome of pregnancies at a secondary hospital. *J Matern Fetal Neonatal Med.* 2007;20(03):233–239. Doi: 10.1080/14767050601134926
- 94 Gudmundsson S, Flo K, Ghosh G, Wilsgaard T, Acharya G. Placental pulsatility index: a new, more sensitive parameter for predicting adverse outcome in pregnancies suspected of fetal growth restriction. *Acta Obstet Gynecol Scand.* 2017;96(02):216–222. Doi: 10.1111/aogs.13060
- 95 FitzGerald DE, Drumm JE. Non-invasive measurement of human fetal circulation using ultrasound: a new method. *BMJ.* 1977;2(6100):1450–1451. Doi: 10.1136/bmj.2.6100.1450
- 96 Morris RK, Malin G, Robson SC, Kleijnen J, Zamora J, Khan KS. Fetal umbilical artery Doppler to predict compromise of fetal/neonatal wellbeing in a high-risk population: systematic review and bivariate meta-analysis. *Ultrasound Obstet Gynecol.* 2011;37(02):135–142. Doi: 10.1002/uog.7767
- 97 Vayssière C, Benoist G, Blondel B, Deruelle P, Favre R, Gallot D, et al; French College of Gynaecologists and Obstetricians. Twin pregnancies: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF). *Eur J Obstet Gynecol Reprod Biol.* 2011;156(01):12–17. Doi: 10.1016/j.ejogrb.2010.12.045
- 98 Graves CR. Antepartum fetal surveillance and timing of delivery in the pregnancy complicated by diabetes mellitus. *Clin Obstet Gynecol.* 2007;50(04):1007–1013. Doi: 10.1097/GRF.0b013e31815a63cc
- 99 de Rochambeau B, Jabbour N, Mellier G. [Umbilical Doppler velocimetry in prolonged pregnancies]. *Rev Fr Gynecol Obstet.* 1992;87(05):289–294 French.
- 100 Adekanmi AJ, Roberts A, Akinmoladun JA, Adeyinka AO. Uterine and umbilical artery doppler in women with pre-eclampsia and their pregnancy outcomes. *Niger Postgrad Med J.* 2019;26(02):106–112. Doi: 10.4103/npmj.npmj_161_18
- 101 Velauthar L, Plana MN, Kalidindi M, Zammora J, Thilaganathan B, Illanes SE, et al. First-trimester uterine artery Doppler and adverse pregnancy outcome: a meta-analysis involving 55,974 women. *Ultrasound Obstet Gynecol.* 2014;43(05):500–507. Doi: 10.1002/uog.13275
- 102 Shen G, Huang Y, Jiang L, Gu J, Wang Y, Hu B. Ultrasound prediction of abnormal infant development in hypertensive pregnant women in the second and third trimester. *Sci Rep.* 2017;7:40429. Doi: 10.1038/srep40429
- 103 Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: population based study. *BMJ.* 2013;346:f108. Doi: 10.1136/bmj.f108
- 104 Pilliod RA, Cheng YW, Snowden JM, Doss AE, Caughey AB. The risk of intrauterine fetal death in the small-for-gestational-age fetus. *Am J Obstet Gynecol.* 2012;207(04):318.e1–318.e6. Doi: 10.1016/j.ajog.2012.06.039
- 105 Figueras F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal surveillance, diagnosis, and management. *Am J Obstet Gynecol.* 2011;204(04):288–300. Doi: 10.1016/j.ajog.2010.08.055
- 106 Barden N, Whitehead CL, Tong S, Ugoni A, McDonald S, Walker SP. Placental insufficiency in fetuses that slow in growth but are born appropriate for gestational age: a prospective longitudinal study. *PLoS One.* 2016;11(01):e0142788. Doi: 10.1371/journal.pone.0142788
- 107 Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker N, et al. Consensus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet Gynecol.* 2016;48(03):333–339. Doi: 10.1002/uog.15884
- 108 Figueras F, Caradeux J, Crispi F, Eixarch E, Peguero A, Gratacos E. Diagnosis and surveillance of late-onset fetal growth restriction. *Am J Obstet Gynecol.* 2018;218(2S, 2s):S790–, 802.e1. Doi: 10.1016/j.ajog.2017.12.003
- 109 Mifsud W, Sebire NJ. Placental pathology in early-onset and late-onset fetal growth restriction. *Fetal Diagn Ther.* 2014;36(02):117–128. Doi: 10.1159/000359969
- 110 Yinon Y, Kingdom JC, Odutayo A, Moineddin R, Drewlo S, Lai V, et al. Vascular dysfunction in women with a history of pre-eclampsia and intrauterine growth restriction: insights into future vascular risk. *Circulation.* 2010;122(18):1846–1853. Doi: 10.1161/CIRCULATIONAHA.110.948455
- 111 Turan OM, Turan S, Gungor S, Berg C, Moyano D, Gembruch U, et al. Progression of Doppler abnormalities in intrauterine growth restriction. *Ultrasound Obstet Gynecol.* 2008;32(02):160–167. Doi: 10.1002/uog.5386
- 112 Baschat AA, Gembruch U, Harman CR. The sequence of changes in Doppler and biophysical parameters as severe fetal growth restriction worsens. *Ultrasound Obstet Gynecol.* 2001;18(06):571–577. Doi: 10.1046/j.0960-7692.2001.00591.x
- 113 Hecher K, Bilardo CM, Stigter RH, Ville Y, Hackelöer BJ, Kok HJ, et al. Monitoring of fetuses with intrauterine growth restriction: a longitudinal study. *Ultrasound Obstet Gynecol.* 2001;18(06):564–570. Doi: 10.1046/j.0960-7692.2001.00590.x
- 114 Ferrazzi E, Bozzo M, Rigano S, Bellotti M, Morabito A, Pardi G, et al. Temporal sequence of abnormal Doppler changes in the peripheral and central circulatory systems of the severely growth-restricted fetus. *Ultrasound Obstet Gynecol.* 2002;19(02):140–146. Doi: 10.1046/j.0960-7692.2002.00627.x
- 115 Gardosi J, Kady SM, McGeown P, Francis A, Tonks A. Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. *BMJ.* 2005;331(7525):1113–1117. Doi: 10.1136/bmj.38629.587639.7C
- 116 Geerts L, Van der Merwe E, Theron A, Rademan K. Placental insufficiency among high-risk pregnancies with a normal umbilical artery resistance index after 32weeks. *Int J Gynaecol Obstet.* 2016;135(01):38–42. Doi: 10.1016/j.ijgo.2016.03.038
- 117 Townsend R, Khalil A. Twin pregnancy complicated by selective growth restriction. *Curr Opin Obstet Gynecol.* 2016;28(06):485–491. Doi: 10.1097/GCO.0000000000000326
- 118 Gratacós E, Lewi L, Muñoz B, Acosta-Rojas R, Hernandez-Andrade E, Martinez JM, et al. A classification system for selective intrauterine growth restriction in monochorionic pregnancies according to umbilical artery Doppler flow in the smaller twin.

- Ultrasound Obstet Gynecol. 2007;30(01):28–34. Doi: 10.1002/uog.4046
- 119 Maulik D, Mundy D, Heitmann E, Maulik D. Evidence-based approach to umbilical artery Doppler fetal surveillance in high-risk pregnancies: an update. *Clin Obstet Gynecol.* 2010; 53(04):869–878. Doi: 10.1097/GRF.0b013e3181fb5f5
- 120 Morin L, Lim K. DIAGNOSTIC IMAGING COMMITTEE SPECIAL CONTRIBUTOR GENETICS COMMITTEE MATERNAL FETAL MEDICINE COMMITTEE. Ultrasound in twin pregnancies. *J Obstet Gynaecol Can.* 2011;33(06):643–656. Doi: 10.1016/S1701-2163(16)34916-7
- 121 Niromanesh S, Shirazi M, Eftekhariyazdi M, Mortazavi F. Comparison of umbilical artery Doppler and non-stress test in assessment of fetal well-being in gestational diabetes mellitus: A prospective cohort study. *Electron Physician.* 2017;9(12): 6087–6093. Doi: 10.19082/6087
- 122 Malhotra N, Chanana C, Kumar S, Roy K, Sharma JB. Comparison of perinatal outcome of growth-restricted fetuses with normal and abnormal umbilical artery Doppler waveforms. *Indian J Med Sci.* 2006;60(08):311–317. Doi: 10.4103/0019-5359.26607
- 123 Lees C. Perinatal and 2 year neurodevelopmental outcome in late preterm fetal compromise: the TRUFFLE 2 Randomised Trial [Study protocol] [Internet]. 2020 [cited 2021 Jan 12]. Available from: <https://www.fundingawards.nihr.ac.uk/award/NIHR127976>
- 124 D'Antonio F, Patel D, Chandrasekharan N, Thilaganathan B, Bhide A. Role of cerebroplacental ratio for fetal assessment in prolonged pregnancy. *Ultrasound Obstet Gynecol.* 2013;42(02): 196–200. Doi: 10.1002/uog.12357