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Doppler ultrasound of the umbilical artery: clinical application

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DOPPLER ULTRASOUND OF THE UMBILICAL ARTERY: CLINICAL APPLICATION

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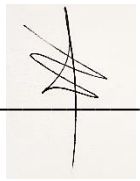

Dedicatória

À minha família.

Aos meus amigos - a minha segunda família, na Invicta.

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Resumo

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

Métodos A pesquisa bibliográfica foi realizada no 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 Índices Doppler aumentados ou formas de onda Doppler da UA anormais apontam para a existência de disfunção placentar, sofrimento fetal e aumento do risco de desfechos adversos. Até ao momento, o uso desta técnica como método de vigilância de rotina só está recomendado para gravidezes de alto risco com disfunção placentar. É consensual que os valores dos índices Doppler da UA decrescem com o avanço da idade gestacional. No entanto, há ainda muita incerteza quanto aos valores de referência.

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

Palavras-chave: Doppler, placenta, artéria umbilical, vigilância fetal, insuficiência placentar

Title: Doppler ultrasound of the umbilical artery: clinical application.

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Running head: Doppler ultrasound of the umbilical artery.

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Abbreviations

AEDV – Absent End-Diastolic Velocity

AREDV – Absent and Reversed End-Diastolic Velocities

CPR – Cerebroplacental Ratio

DC – Dichorionic

EDV – End-Diastolic Velocity

EFW – Estimated Fetal Weight

E-IUGR – Early-onset Intrauterine Growth Restriction

FVW – Flow Velocity Waveform

IUGR – Intrauterine Growth Restriction

L-IUGR – Late-onset Intrauterine Growth Restriction

MC – Monochorionic

PEDV – Positive End-Diastolic Velocity

PI – Pulsatility Index

PSV – Peak Systolic Velocity

REDV – Reversed End-Diastolic Flow Velocity

RI – Resistance Index

S/D – Systolic/Diastolic Ratio

SGA – Small for Gestational Age

UA – Umbilical Artery

US – Ultrasound

UtA – Uterine Artery

Abstract

Objective To provide a survey of relevant literature upon UA Doppler US use in clinical practice, technical considerations and limitations, and future perspectives.

Method Literature searches were conducted in PubMed and Medline with a limitation of articles written in English. Additionally, the references of all analysed studies were searched to obtain necessary information.

Results Increased Doppler indices or abnormal FVW signal placental dysfunction, fetal distress and increased risk for adverse outcomes. So far, the use of this technique as a routine surveillance method is only recommended for high-risk pregnancies with impaired placentation. It is agreed that UA Doppler indices values decrease with advancing gestational age, however a lack of consensus upon reference ranges prevails.

Conclusion Important clinical decisions are based on the information obtained with the UA Doppler US. Future investments in research are imperative to attempt to overcome the current limitations of the technique.

Keywords: Doppler, placenta, umbilical artery, fetal surveillance, placental insufficiency

Introduction

The umbilical arteries (UA) play a key role in the regulation of the fetoplacental circulation. In the UA, the nerve regulation is absent and its tonus depends uniquely on locally released or circulating vasoactive substances, as well as on ions such as Ca^{2+} and 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 a normal intrauterine growth, there are some conditions that must be met: normal umbilical cord architecture and function; adequate placental perfusion; an healthy fetus and a favourable 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 an intrauterine growth restriction (IUGR), with its inherent increased risk of perinatal mortality and morbidity in short and long-term.[1, 9-14]

The main cause of IUGR is the 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 haemodynamic changes.[9, 15, 16] The onset of IUGR can be anytime during pregnancy and strict fetal condition surveillance is required after the diagnosis in order to determine when does staying in the womb takes greater risk of adverse perinatal outcome than being born.[10, 17-20]

The 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 Dopper US use has allowed a decrease in the risk of perinatal death by approximately 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 and received of 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]

The Spectral Doppler US is a speed-time spectral recording, presenting as flow velocity waveforms (FVW)[25], which enables the quantification of the peak systolic

velocity (PSV) and the end-diastolic velocity (EDV) of blood flow within the UA with which three indices can be obtained: the pulsatility index (PI), resistance index (RI) and systolic/diastolic ratio (S/D).[26, 27] These indices are considered to be indirect measures of placental vasculature resistance to blood flow.[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 non-invasive, economical, simple, and reproducible method.[8, 12, 13, 15] However useful, this technic has some limitations, including the potential to lead to considerable anxiety in families and clinicians, further diagnostic testing and early (possibly very preterm) birth.[11] Likewise, 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 this review is to provide a survey of relevant literature upon UA Doppler US in clinical practice, technical considerations and limitations, and future perspectives.

Methods

To compose this review, thorough literature searches were conducted in PubMed and Medline with a limitation of articles written in the English language. The search terms used were Doppler, placenta, umbilical artery, fetal surveillance, and placental insufficiency. Additionally, the references of all analysed studies were searched to obtain necessary information.

Results

UA waveform analysis

Concerning the UA, the standard Spectral Doppler US FVW pattern presents as a "sawtooth" pattern, revealing a unidirectional, continuous and pulsatile flow towards the placenta (Figure 1). Its pattern can be distinguished from that of the Umbilical Vein since the umbilical vein 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 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 and thereafter it gradually decreases and becomes a low-resistance system.[8] This phenomenon occurs from the end of the second 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 is expected.[37] A deviation from the expected indices values signals an underlying placental dysfunction and an increased risk of fetal demise[31, 38-40], regardless of the Doppler technique used.[35, 41]

The UA pathological FVW have a progressive pattern, 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) (Figure 2) and can even reverse (reversed end-diastolic velocities - REDV) (Figure 3) whilst PSV is not affected.[37, 40, 42] In these cases, the PI is more indicated for the interpretation of FVW findings[35] and it starts to increase solely 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 first trimester is associated with chromosomal abnormalities, great fetal cardiovascular defects and significant mortality.[45-49] However, as stated by Bellver *et al*, the latter "is not always an ominous sign".[50]

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, though it is still unknown how to predict in which fetuses it will happen.[51] The antenatal administration of betamethasone to IUGR fetuses with 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 favourable response of the responding fetuses has not yet been understood.[52]

AREDV are frequently associated with marginal placental-end cord insertion[1, 53], which can be accurately diagnosed by Color Doppler US during the second 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 favouring vasoconstriction.[1, 54, 55] Being a vasodilator and smooth muscle relaxant[56], the administration of nitroglycerine intravenously or transdermally through patches, 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 to PEDV, AREDV fetuses have higher incidence of low birth weight, 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, 59], as well as long-term neurological impairment.[14, 60, 61] 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 mal-perfusion, delayed villous maturation and fetal vascular mal-perfusion, shortened umbilical cord, congenital cardiac anomalies, which frequently results in growth restriction and death *in utero*.[62]

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, induction of labor, as long as an acceptable gestational age is achieved, seems to be the safest option in order to attain a better perinatal outcome.[37, 58]

Furthermore, 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*.[63] A systolic notch in the UA FVW

suggests the presence of an umbilical cord abnormity 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. Notching magnitude strongly correlates to how tight the knot is and it depends on the type of FVW being measured (envelope *vs* centerline), as well as on the location downstream of the constriction where the FVW is being measured.[63]

Also worth of consideration are the results of a study conducted in 2006 by Struijk *et al*, 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, although it has no applicability in the prediction of IUGR or pregnancy-induced hypertension.[64]

UA Doppler reference ranges

There is consensus amongst the authors that UA PI decreases linearly with advancing gestational age in uncomplicated singleton pregnancies.[15, 31, 35, 65-70] (Table I and Figure 4) However, the authors did not obtain the same percentile values for each corresponding gestational age.[15, 31, 35, 65-70] The same could be inferred about UA RI.[35, 67-70] (Table II and Figure 5)

Gathering values obtained in three different geographical areas, Lior Drukker *et al.* 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 the inherent characteristics of its population.[67] On the other hand, Ciobanu *et al.*, 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.[66] Moreover, Widnes *et al.* considered the influence of fetal sex and proposed gestational age-dependent sex reference ranges as they found female fetuses to have more pulsatile UA from the 20th week to the 37th week and to have higher heart rates from the 26th week.[26]

In the case of fetuses with a single umbilical artery, Contro *et al.* found the UA PI to be 20% lower than in those with a normal three vessels umbilical cord. This disparity

remained constant between the 23-40th gestational weeks. Thus, lower reference values in such cases may allow a more accurate interpretation of Doppler measurements.[71]

Concerning twin pregnancies, Mulcahy *et al.* 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 to DC twins.[72] These findings are supported by Casati *et al*., who proposed uncomplicated MC-specific Doppler charts, which include UA PI values.[73] Since singleton Doppler reference ranges are not suitable for interpreting findings in twin pregnancies, further studies on both complicated and uncomplicated twin gestations and its perinatal and long-term outcomes are needed.[72, 73]

Maternal glucose loading[74] and fetal behaviour state were found not to influence UA PI value measurements if adjusted to fetal heart rate.[74, 75] Also, 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.[76]

However smoking during pregnancy is associated with an increased risk of adverse outcomes[77-79], smoking habits seem not to influence fetal Doppler parameters.[80]

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 cut-off values, which may signify important differences in clinical practice when using one cut-off 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.* 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[81] and considering the PI cut-off above the 95th percentile as recommended in current clinical guidelines.[82] This example illustrates the magnitude of the impact that heterogeneous cut-off values have on decision making in important clinical issues.[81] Another example is presented by Lior Drukker *et al*. 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 cut-off value.[67]

UA Doppler as a screening test in low-risk pregnancies

According to Alfirevic *et al.*, the methods traditionally used (symphysis-fundal height measurement, fetal movements charts and cardiotocography) in low-risk pregnancies to assess fetal well-being have no proven ability to positively impact the low incident and preventable, adverse perinatal outcomes.[11]

For that reason, 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.[83] Also, at term an abnormal UA Doppler result in these cases can only have one consequence to improve the newborn's health: intensified monitoring with possible elective delivery in the event of deteriorating fetal distress.[84] 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, 84, 85]

In contrast and according to Nkosi *et al.*, 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 at 28^{th}-32^{nd} weeks is beneficial. It allowed greater recognition of increased UA RI and AREDV patterns up to 5 to 10 times more than expected.[86] 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 an improvement in perinatal outcomes, avoiding several unexplained stillbirths.[86, 87]

Aiming to predict the perinatal outcome of low-risk pregnancies whose fetuses are suspected of IUGR, Gudmundsson *et al.* proposed a new Doppler indice: the placental pulsatility index. It combines the PI value of UA and UtA in order to evaluate the complete placental vascular impedance and the authors suggest it has greater efficiency to predict adverse perinatal outcome than UA and UtA alone.[88]

UA 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 those complicated by placental dysfunction as in IUGR or preeclampsia, as a predictive test for fetal compromise.[20, 22, 89, 90] Its applicability in other high-risk groups such as diabetes *mellitus*, post-term and uncomplicated dichorionic twin pregnancy is still uncertain.[20, 91-93]

The UA Doppler parameters are used to monitor fetal status and response to stress in preeclampsia and other hypertensive disorders related to pregnancy. However, it is the UtA PI that better predicts its future development[94, 95] and anticipates adverse outcomes related to the condition.[96]

Fetuses with estimated fetal weight (EFW) below the 10th centile are considered to be SGA and are at increased risk of fetal demise and poor perinatal outcome when compared to non-SGA.[20, 97, 98] Some of these are constitutionally small healthy fetuses whereas others are failing to reach their potential weight due to an underlying condition (IUGR).[11, 20, 99] Still, fetuses failing to reach their growth potential may or may not be SGA.[20, 100]

The criteria for diagnosing IUGR due to placental insufficiency include UA Doppler measurements.[101] There are two subtypes of IUGR, depending on whether the onset is before or after the 32nd week,[101] both of which have distinguishable Doppler patterns and postnatal outcomes.[10, 102]

The early-onset IUGR (E-IUGR) is more frequently associated with early-onset preeclampsia[103, 104] and a classical sequence of Doppler indices deterioration is present.[105-108] Firstly, 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.[105-108] The presence of an AREDV pattern or an EFW below the third centile, before the 32nd week, establishes the diagnosis of E-IUGR by itself.[101] 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 two years of age.[17, 38]

The late-onset IUGR (L-IUGR) is more prevalent and has a lower mortality rate than E-IUGR[102], however, the undetected cases constitute the major cause of unexplained stillbirth.[11, 97, 109] In this subtype of IUGR, the UA Doppler indices remain unchanged or minimally elevated, not being reliable for diagnosis.[102] 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.[102] 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 third trimester.[102, 110] Finding both normal cerebroplacental ratio (CPR) and UtA Doppler indices in fetuses presenting with an EFW above the third centile confirms the low-risk status and the managing protocol of constitutionally small fetuses is appropriate.[102] When Doppler indices suggest placental insufficiency (UA PI >95th centile or CPR<5th centile), an EFW below the 10th centile or crossing more than two quartiles on growth centiles has to be present to establish an high-risk status for late-SGA. However, an EFW below the third centile alone, after the 32nd week, is diagnostic by itself.[101]

Selective intrauterine growth restriction 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 opposition and due to the interdependent circulation, selective intrauterine growth restriction 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.[111] 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.[111, 112] Thus, twin pregnancies benefit from fetal well-being assessment with the UA Doppler US when there is growth discordance, Twin-to-twin transfusion syndrome or IUGR.[113, 114]

In pregnancies complicated by gestational diabetes[115] 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 outcome.[92, 115] Solely those complicated with vasculopathy due to diabetes could benefit from periodic UA Doppler US monitoring.[92]

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 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 that 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, 116] 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, 84, 85] Nonetheless, this assumption is based on studies conducted approximately thirty years ago. Thereby it would be paramount to replicate these investigations with more accurate methodologies, to determine whether there would be changes to 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 towards 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, 89, 90] However, during the 3rd trimester, placental insufficiency develops under normal UA Doppler indices[102], therefore, when suspected, other methods must be used to assess fetal well-being.[10, 102, 110] Regarding this issue, the TRUFFLE group is currently conducting a study (The TRUFFLE 2 study) aiming to address which monitoring methods and threshold are ideal for the delivery of L-IUGR fetuses. The role of UA Doppler US for fetal surveillance in high-risk pregnancies due to other precipitating factors requires further investigation.[20, 31, 91-93, 117]

Health improvements are not due to the application of the UA Doppler US itself but rather 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 cut-off values differ significantly.[15, 31, 35, 65-70] Studies upon the methodological quality of reports proposing reference ranges have shown major methodological and statistical bias.[31, 81] 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 influence 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.

An universal chart was recently proposed aiming to standardize UA Doppler indices globally.[67] Although it sounds promising, future studies reporting its efficacy in different populations around the globe are paramount to state a conclusion.

To summarize, 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.

Ethics Committee Approval

N/A

Peer-review

Externally peer-reviewed.

Author Contributions

Concept – A.R., L.G-M.; Design – A.R., L.G-M.; Supervision – L.G-M.; Literature Review - A.R., L.G-M.; Writer - A.R., L.G-M.; Critical Review- A.A., L.G-M.

Conflicts of Interest

We have no conflicts of interest in this review.

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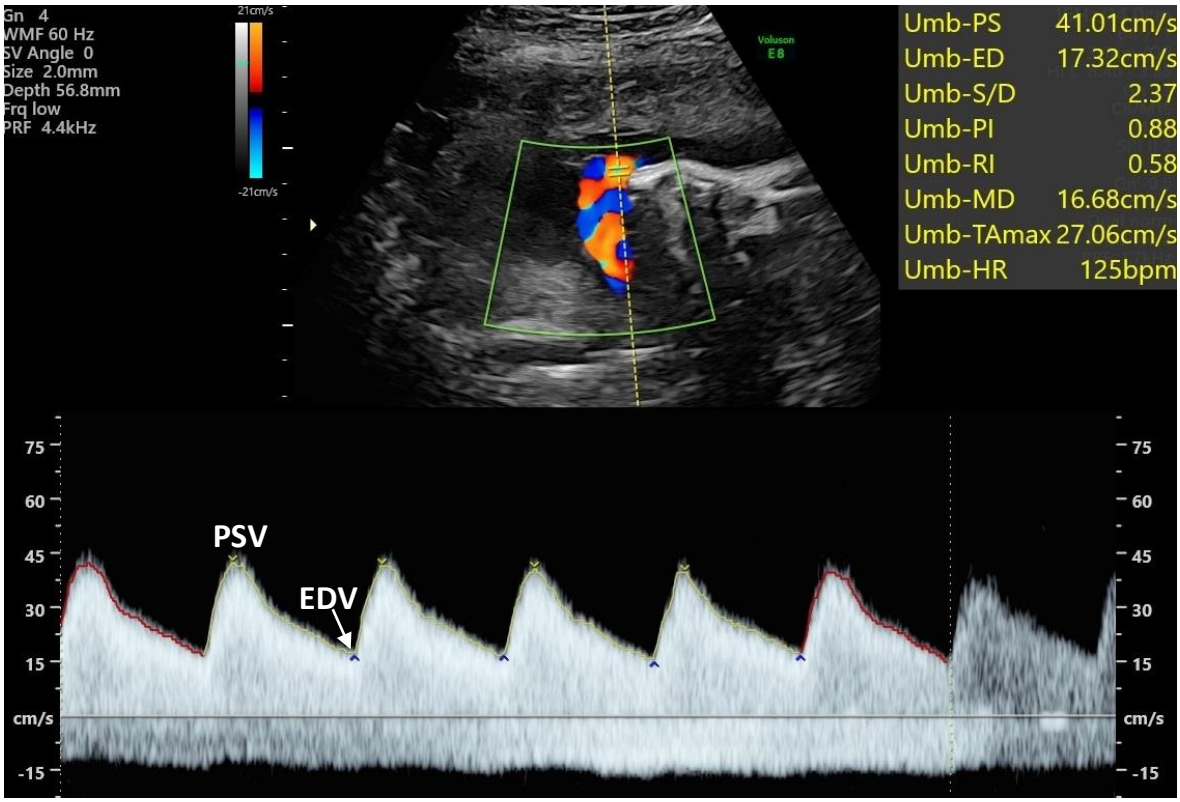

Figure 1 - Normal umbilical artery flow velocity waveform tracings obtained during the 3rd trimester. End diastolic velocities are present and are high. PSV: peak systolic velocity; EDV: end-diastolic velocity.

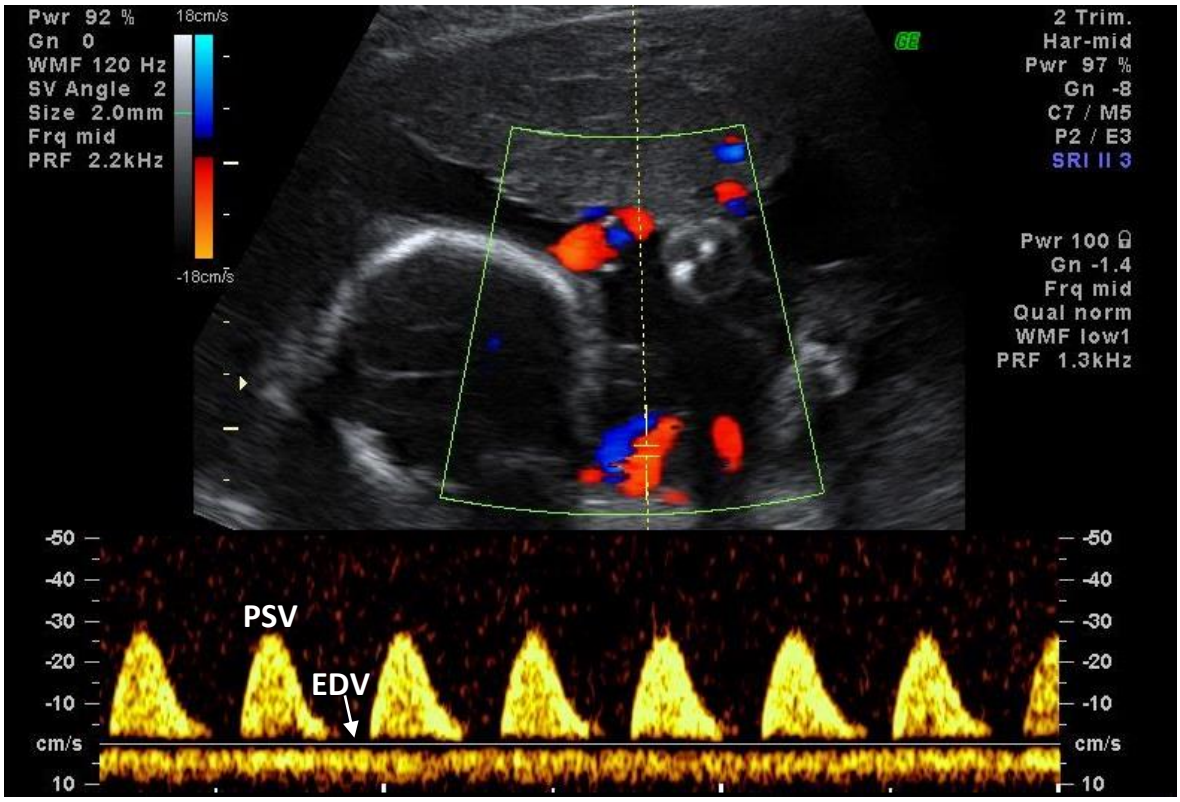

Figure 2 - Abnormal umbilical artery flow velocity waveform tracings obtained during the 2nd trimester. End diastolic velocities are absent, defining this pattern as AEDV. PSV: peak systolic velocity; EDV: end-diastolic velocity; AEDV: Absent end-diastolic velocity.

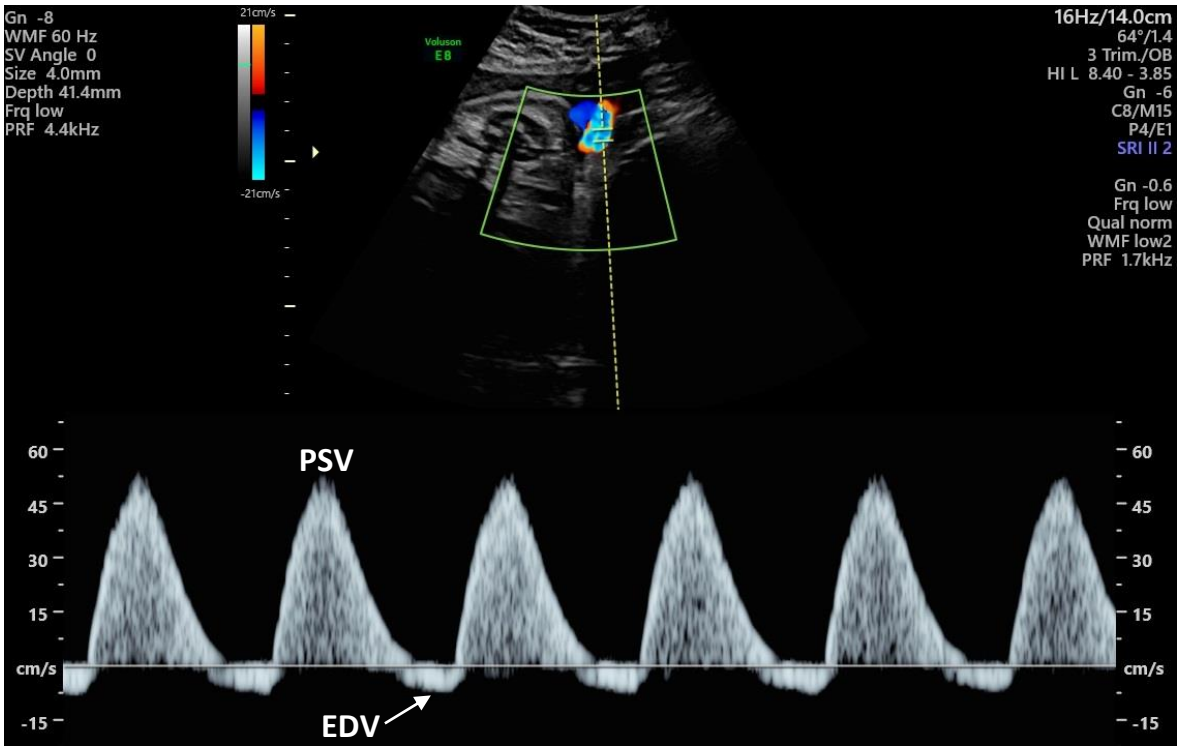

Figure 3 - Abnormal umbilical artery flow velocity waveform tracings obtained in a 3rd trimester pregnancy. End diastolic velocities are below the baseline, defining this pattern as REDV. PSV: peak systolic velocity; EDV: end-diastolic velocity; REDV: Reversed end-diastolic velocity.

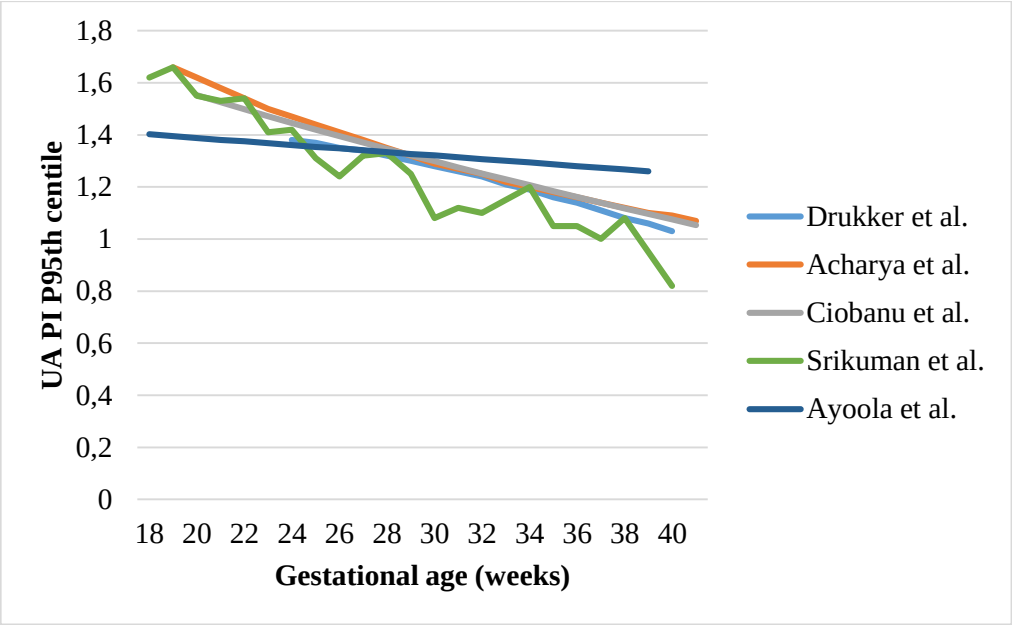

Figure 4 – Comparison of the 95th percentile of umbilical artery PI in studies reporting reference ranges.

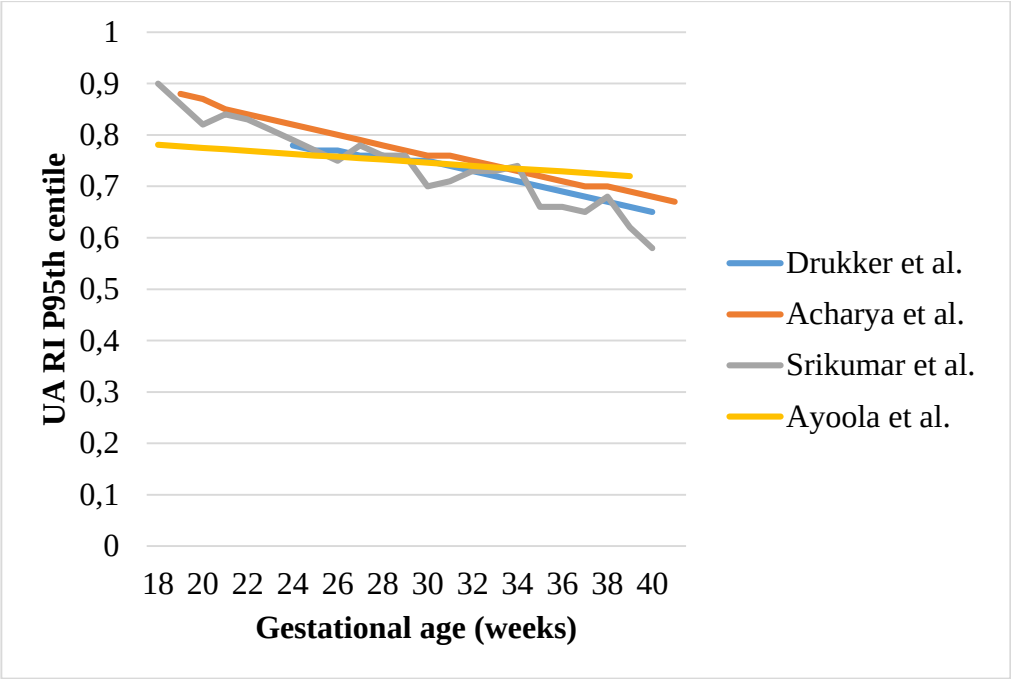

Figure 5 – Comparison of the 95th percentile of umbilical artery RI in studies reporting reference ranges.

Table I - Values of 95th centile for umbilical artery PI in studies reporting reference ranges.

Gestational age (weeks)	*Drukker et al. [67]*	*Acharya et al.[68]*	*Ciobanu et al.[66]*	*Srikumar et al.[70]*	*Ayoola et al.[69]*
18				1,62	1,402
19		1,66		1,66	1,395
20		1,62	1,553	1,55	1,388
21		1,58	1,526	1,53	1,381
22		1,54	1,499	1,54	1,375
23		1,5	1,472	1,41	1,368
24	1,38	1,47	1,446	1,42	1,361
25	1,37	1,44	1,42	1,31	1,354
26	1,35	1,41	1,395	1,24	1,348
27	1,34	1,38	1,371	1,32	1,341
28	1,32	1,35	1,346	1,33	1,334
29	1,3	1,32	1,322	1,25	1,327
30	1,28	1,29	1,299	1,08	1,321
31	1,26	1,27	1,275	1,12	1,314
32	1,24	1,25	1,252	1,1	1,307
33	1,21	1,22	1,229	1,15	1,3
34	1,19	1,2	1,207	1,2	1,294
35	1,16	1,18	1,184	1,05	1,287
36	1,14	1,16	1,162	1,05	1,28
37	1,11	1,14	1,14	1	1,273
38	1,08	1,12	1,118	1,08	1,267
39	1,06	1,1	1,097	0,95	1,26
40	1,03	1,09	1,075	0,82	
41		1,07	1,053		

Table II - Values of 95th percentile for umbilical artery RI in studies reporting reference ranges.

Gestational age (weeks)	*Drukker et al.[67]*	*Acharya et al.[68]*	*Srikumar et al.[70]*	*Ayoola et al.[69]*
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		

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