

Understanding the uterine artery Doppler Waveform and its relationship to spiral artery remodelling

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Abstract:

Analysis of the uterine artery (UtA) Doppler waveform is frequently used in high-risk pregnancies to assess the likelihood of adverse pregnancy outcomes, including preeclampsia and fetal growth restriction. Whilst abnormal UtA waveforms at 18-20 weeks are associated with adverse outcomes, the underlying cause of these waveform changes remains unknown. Current evidence suggests the long-held dogma that the UtA waveform is merely a reflection of trophoblast-induced spiral artery remodelling is incorrect. Hence, the origins of the waveform changes must be reassessed. Recent data from human and animal models suggests that the arcuate arteries, placental bed arterio-venous anastomoses and, most notably, the radial arteries may be more important in determining the UtA waveform profile than previously appreciated. Furthermore, there is increasing evidence implicating the maternal cardiovascular system in the pathophysiology of the complications predicted by the waveform changes, particularly preeclampsia, and therefore its underlying association with the UtA waveform warrants further investigation.

Introduction

Since the first introduction of Doppler ultrasound to obstetrics [1], analysis of the uterine artery (UtA) waveform has been used to assess the risk of adverse pregnancy outcomes [2,3]. Whilst an abnormal UtA waveform has been associated with pre-eclampsia and fetal growth restriction (FGR) [4–6], the underlying mechanism for the changes in the waveform remains unknown.

Preeclampsia affects 3-5% of UK pregnancies and accounts for an estimated 13% of all maternal deaths worldwide [7]. FGR affects 3-10% of pregnancies, with 4-8 times higher perinatal mortality rates and health impacts lasting long into adulthood [8,9]. No treatment is yet available for either condition, but early prediction allows enhanced surveillance and timely delivery, thereby preventing some stillbirths. A greater understanding of the UtA Doppler waveform should enhance our knowledge regarding the pathological mechanisms involved, potentially leading to improved prevention and targeted therapies.

In this review, we examine the colour-flow Doppler waveform produced by interrogating the UtAs during pregnancy. We consider how individual sections of the vasculature, the maternal cardiovascular phenotype and systemic influences all contribute to the waveform, and how together they may predict pathology.

Uterine Vasculature

The UtAs are branches of the internal iliac artery and provide the main blood supply to the uterus (Figure 1). They branch into the arcuate arteries that run circumferentially around the uterus in the superficial myometrium. The radial arteries branch off the arcuate arteries and pass inwards, giving rise to the basal arteries and terminating as the spiral arteries (SpAs) that supply the intervillous space (IVS) of the placenta during pregnancy. Coordinated remodelling of segments of this uteroplacental vasculature occurs at different times during pregnancy. This remodelling underlies the decrease in vascular resistance, facilitating a rise in uterine blood flow from ~45 ml/min in the non-pregnant state to ~750 ml/min at term to meet the increasing demands of the feto-placental unit [10].

Uterine Artery Doppler Waveform

At 18 to 20 weeks, the site of insonation is the point at which the UtA crosses the internal iliac artery [11]. This is easily located and consistent. The angle at which the artery is insonated affects the absolute velocity recorded. Therefore, dimensionless indices are used to quantify the waveform (Figure 2). Commonly used indices include the pulsatility index (PI) and resistance index (RI), and have been shown to be robust and reproducible [5]. Remodelling of the uteroplacental vasculature results in changes in blood flow. Doppler indices are used to predict which women have an increased risk of adverse pregnancy outcomes,

particularly preeclampsia. Furthermore, several distinctive qualitative features of the waveform such as the presence of a 'notch' are also used for prediction of pregnancy outcome (Table 1).

Historically, the changes seen in the UtA waveform have been attributed to trophoblast-induced remodelling of the SpAs altering the 'downstream' vascular resistance. Support for this hypothesis came from the observed correlation between morphological evidence of deficient trophoblast-induced remodelling of the SpAs and high resistance UtA indices [4,12]. This relationship is observed in the shallow placentation associated with many of the obstetric disorders the UtA waveform is used to predict [13]. The supposition was also supported by mathematical models that incorrectly grouped the entire uteroplacental vasculature as a single load impedance [4]. However, accumulating evidence suggests this explanation is overly simplistic, and that the observed relationship is most likely correlative rather than causative [14]. The UtA waveform has been observed to change without trophoblast invasion, including during the menstrual cycle [15–17], with pharmacological agents [18,19] and intrauterine contraceptive devices [20,21], and in extra-uterine pregnancies [22]. Furthermore, if UtA flow is directly dependent on SpA flow then there should be a linear relationship between flow and the progressive canalization of the SpA trophoblast plugs; this has not been observed [23]. Instead, there is a significant increase in flux at 13 weeks, currently attributed to increases in radial artery lumen diameters [23,24].

Many of the models supporting the UtA waveform as a reflection of SpA remodelling omit the arterio-venous (A-V) anastomoses in the myometrium of the placental bed. The anastomoses were described in 1956, and their existence demonstrated by injection of coloured resins into the arterial and venous circulations [25]. More recent data were provided using 3D and 2D Doppler analysis and anatomical studies (hysterectomy specimens and a vascular cast) [26], confirming the presence of a rich anastomotic intra-myometrial vascular network under the placenta. Furthermore, the functional nature of the network was demonstrated by the presence of a significant oxygen gradient between the uterine venous blood and the intervillous space, the latter being significantly more desaturated. Subsequently, more models have included these anastomoses and in doing so found convincing evidence against the SpA dogma [4,14,26]. New models (Figure 3) demonstrate that the IVS is functionally connected in parallel with the uterine circulation, an arrangement that maintains a low resistance UtA waveform both during and after pregnancy.

In a parallel vascular system, the total resistance of a network is lower than that of the lowest resistance vessel. In comparison, the total resistance within a series system is the sum of all the resistances. Hence, a series system produces a greater total resistance than a parallel one for the same individual vessel resistances. Therefore, the A-V anastomoses afford a reduced total uterine vascular resistance, and hence impedance, during pregnancy, allowing a significant increase in uterine blood-flow with advancing gestation [4]. When the uteroplacental vasculature is modelled with absent or reduced calibre anastomoses the

resistance of the uterine vasculature increases [4]. The low resistance offered by the anastomoses will also reduce vascular pressure distal to them. This effect, along with the dilation of the mouths of the SpA created through remodelling [14], will reduce the velocity and pressure with which maternal blood enters the IVS.

This parallel circulation allows the A-V anastomoses to mitigate the impact of high SpA resistance by allowing blood-flow to bypass the IVS. When A-V anastomoses are included in the model, physiological increases in SpA and/or IVS resistances do not impact the UtA waveform to any great extent [4]. Therefore, where SpA remodelling is deficient the UtA waveform would only be impacted if the A-V anastomoses were significantly compromised or absent. This ability to divert blood from downstream, high resistance vessels has been hypothesised to protect the placenta from maternal hypertensive events [4]. Additionally, the A-V anastomoses may buffer the downstream blood-flow if the radial arteries are also insufficiently remodelled. Their presence does, however, risk significant diversion of blood from the SpAs and placental hypoperfusion. Placental hypoperfusion [27] and infarction [28] have been observed in both preeclampsia and FGR.

After placental delivery, uterine contraction 'pinches off' the terminal SpAs [4]. If, the SpAs were the predominant contributor to uterine vascular resistance a dramatic increase in UtA resistance indices would be seen. This does not happen [26]. Instead, UtA PI remains low for 48 hours before gradually increasing over the following weeks to a pre-pregnancy value [26]. Mathematical modelling of the postpartum circulation with complete occlusion of the SAs sees all blood diverted via the A-V anastomoses, with no immediate, significant change to the UtA profile [4].

It is frequently stated that the SpAs contribute the most resistance to the total uteroplacental arterial resistance, and therefore must be the main determinants of the UtA waveform. However, in mice the SpAs have been shown to only make a minor contribution in late gestation [29]. Instead, the radial arteries contribute 90% of total uteroplacental resistance and are the largest determinant of the uteroplacental blood-flow. This also appears to be true in humans, as modelling of variable SpA remodelling finds no significant impact on their volume flow [14]. Therefore, gestational changes in SpA resistance may facilitate and modulate increasing blood flow, dictated by the upstream radial arteries, rather than significantly influencing the total vascular resistance and UtA waveform. In rats the greatest pressure drop occurs across the arcuate and radial arteries [29,30], with several benefits. Firstly, this may facilitate even distribution of maternal blood across implantation sites in litter-bearing species [29], or different areas of the human placenta. Secondly, the high resistance will cause a significant decrease in pressure and velocity of flow in the distal vessels. These effects protect the fragile exchange surface from mechanical damage and prevent compression of the fetal capillaries [14]. Finally, a larger pressure gradient within different parts of the vasculature will increase volumetric flow rate between the two vessels (Poiseuille's law, Table 2). Increased dilatation of the radial arteries

results in a lower pressure relative to the arcuate arteries, thereby increasing the volumetric flow rate. Together, these effects increase nutrient and oxygen supply to support growth of the fetus.

Examination of histopathological specimens and the use of contrast-enhanced ultrasound demonstrates that there is a progressive, sequential transformation of the uterine vasculature in a retrograde, distal to proximal fashion with the decidual SpAs dilating first [23,31,32]. Consequently, radial artery remodelling may be key to understanding changes in early second trimester uteroplacental flow and resistance, and hence the UtA waveform [23]. Recently, Allerkamp et al. recorded that the junctional SpAs dilated last, after retrograde remodelling of the other vessels, proposing the rapid increase in blood flow into the IVS may be due to increases in SpA dimensions as well as radial artery dimensions [24]. However, as many of these studies have been based on *ex vivo* specimens it is difficult to confirm the precise timeline of the changes and further investigation is required.

In women with preeclampsia, the radial arteries have been shown to undergo eutrophic remodelling, resulting in reduced lumen diameters and thicker walls in comparison to normal pregnancies [33]. This will affect the UtA waveform as a reduced lumen diameter will reduce the volume of radial artery flow, impacting upstream UtA flow rate and hence UtA waveform (Poiseuille's law, Table 2). Finally, the radial artery diameters observed in pre-eclampsia will produce high-resistance indices and notching in the UtA Doppler, considered indicative of a high-risk pregnancy [4].

After pregnancy, the decidual lining and decidual SpAs are lost. The myometrial vasculature, however, remains, and some of the changes induced during remodelling persist [23,31,34]. Thus, in consecutive pregnancies parts of the uterine vasculature will already exhibit some of the remodelling necessary to provide a low-resistance, high flow system. This may explain why birth weight increases in subsequent pregnancies, and complications, such as preeclampsia, are more common in a woman's first pregnancy [33].

The uterine and arcuate arteries have been largely overlooked in the literature, although both sets of vessels undergo remodelling and may therefore have a contribution warranting further investigation [23,35]. The UtAs undergo significant dilation, with their diameters doubling by mid-gestation [35]. Notching after 20 weeks' gestation is attributed to an abnormally high placental bed resistance (Table 1). However, using computational modelling Talbert demonstrated that increased arcuate and possibly uterine artery compliance is associated with the appearance of notching later in gestation. Talbert proposed gestational increases in flow cause an abnormally large transient volume to be stored within these vessels during systole. This volume then supplies the downstream vasculature, resulting in temporarily less input into the UtA and creating a notch [36].

Thus, the long-held dogma that the UtA waveform is merely a direct reflection of trophoblast-induced SpA remodelling does not hold true, and the remainder of the uterine vasculature must be examined to explain the waveform changes as a purely haemodynamic phenomenon.

Systemic Influences on Vascular Tone

If the changes in the UtA waveform are not dependant on trophoblast invasion of the SpAs but instead on dilation of the radial arteries, the question remains, what is controlling the changes in the maternal uterine vascular tone?

Hormones have been shown to influence the UtA waveform. During the luteal phase of the menstrual cycle UtA impedance falls [15–17]. Women with polycystic ovarian syndrome (PCOS), who have chronically raised leutinising hormone (LH) [5], have a higher UtA impedance [37]. Furthermore, the UtA waveform exhibits a diurnal variation with higher PI in the evening, although this is greater than can be accounted for by changes in LH alone [38]. Some hormonal intrauterine contraceptive devices have been found to increase UtA impedance [20,21]. The remodelling of the vasculature from distal to proximal [23] suggests a shared, possibly diffusible, signal that may be compromised in insufficient remodelling. Increased prevalence of preeclampsia in younger mothers may therefore be a consequence of reduced vascular priming or preconditioning due to fewer menstrual cycles [39].

In a normal pregnancy eNOS activity is elevated [40], and lower levels are found in women with raised UtA impedance [5]. Sildenafil, which works via the eNOS pathway, decreases impedance in the UtA waveform [19]. Pregnancy associated vasodilation is associated with elevated oestrogens that stimulate vasodilator production, including NO [41]. Therefore, there may be a link between hormonal factors and endothelial function, both of which can influence the UtA waveform.

Pre-existing hypertension [42] is a recognised risk factor for the development of preeclampsia [43]. Elevated pressure increases vessel wall tensile stress and, particularly in hypertension, can induce arterial remodelling [44]. In small, muscular resistance arteries, such as those in the uterine vasculature, inward eutrophic remodelling or hypertrophic changes can occur in essential hypertension and some forms of secondary hypertension respectively [44]. Such remodelling normalises media stress but has additional consequences [44]; maximum vasodilation is reduced, creating a reduced ability to vasodilate, and vasomotor responses are enhanced, exaggerating the vasoconstrictive response [44]. Preeclamptic women display responses in line with this pattern, with an increased sensitivity to pressor agents and an increased ratio of thromboxane, a vasoconstrictor, to prostacyclin, a vasodilator [45].

Therefore, an overarching mechanism, such as impaired hormonal control or a pre-existing cardiovascular phenotype, may give rise to insufficient remodelling of both the SpA and the radial arteries. Evidence suggests that insufficient remodelling of the

radial arteries will produce the UtA waveforms associated with adverse pregnancy outcomes, such as FGR and preeclampsia. From here, the question remains whether it is the impaired remodelling of the radial or spiral arteries which causes the adverse outcomes or whether both merely reflect another causative pathology?

It is possible that the maternal cardiovascular system (CVS) becomes overloaded when insufficient remodelling of the uterine vasculature occurs. Such cardiovascular 'overload' would be made more likely by the pre-existence of an impaired or maladaptive maternal CVS, for which there is increasing evidence in preeclampsia [46]. There is also evidence of different haemodynamic states present at 24 weeks preceding the appearance of early- and late-onset preeclampsia in comparison with normal pregnancies [47]. Early-onset preeclampsia (EOP) appears more frequently in patients with higher total vascular resistance (TVR) and lower cardiac output (CO) [47], while late-onset preeclampsia (LOP) appears to be most associated with high BMI and exhibits cardiac features characteristic of obese individuals [47,48] associated with haemodynamic overload [48]. Thus, it is reasonable to say that, although from different origins, the CVS patterns in both EOP and LOP are maladaptive and may become overloaded by the significant additional resistance created from insufficient remodelling of the radial arteries. However, EOP is far more frequently associated with abnormal UtA than LOP, suggesting that insufficient remodelling may only be involved in a confined number of LOP patients, and most may have alternative aetiology outside of the uterine vasculature [47].

Furthermore, in the EOP cardiovascular phenotype the blood-flow to the placenta may be only just meeting fetal requirements, or already be insufficient, due to the reduced CO and elevated TVR. Additional resistance created by insufficient remodelling may not allow the necessary increase in flow, creating such a compromised nutrition and oxygen supply that FGR occurs along with preeclampsia. In support of this hypothesis, placental lesions associated with maternal underperfusion are more frequent in EOP than LOP [28] and small-for-gestational age fetuses are more frequently associated with EOP [49]. These associations may also reflect the increased incidence of acute atherotic lesions in the spiral arteries in EOP, possibly induced by turbulence arising from deficient remodelling [14], which will reduce lumen calibre and volume of flow.

Women with preeclampsia have an increased risk of cardiovascular disease death later in life, particularly following EOP [50]. Evidence suggests the increase in cardiovascular risk after preeclampsia may be due to a pre-pregnancy maladaptive phenotype, rather than an effect of preeclampsia on the maternal CVS [46,51]. If true, assessment of the maternal CVS phenotype pre-pregnancy or early in pregnancy prior to preeclampsia may have predictive value.

Alternatively, it is possible that insufficient remodelling of the SpAs creates a damaging 'jet-hose' effect. Deficient remodelling reduces the normal deceleration of blood jets emerging from the arteries, creating an inflow of blood with a high momentum that is likely damaging to the villous trees [14]. This effect may be exaggerated by aberrant remodelling of more proximal vessels

in the uterine vasculature, particularly the radial arteries [33]. Damage likely includes increased shedding of the outer syncytiotrophoblast layer. In preeclampsia, elevated amounts of unbound syncytiotrophoblast microparticles (STBMs) are observed and are believed to contribute to the increased second phase of systemic inflammatory responsiveness in these pregnancies. Furthermore, formation of these jets may impair nutrient and oxygen supply to the fetus in several ways: the sluice flow phenomenon will impair establishment of fetoplacental circulation, preventing effective diffusional exchange; damage to the placental villi will comprise the exchange surface; and the high-speed jets will transverse much of the placental lobule before decelerating sufficiently to allow effective exchange [14]. Finally, the altered haemodynamics in the SpAs may lead to the development of occlusive acute atherotic lesions that will reduce flow into the IVS [14]. Hence, it should be considered that formation of these jets due to impaired SpA remodelling may impair nutrient and gas exchange sufficiently to result in FGR. Furthermore, the impact of the hose effect may be exacerbated in mothers with higher blood pressure, due to a stronger jet hose, creating more damage and more STBMs. Thus, insufficient remodelling of the SpAs, although unlikely to affect the UtA waveform, is possibly associated with the underlying pathology.

Conclusion

The dogma that the UtA waveform changes observed during pregnancy are merely a direct reflection of SpA remodelling no longer holds true, and the radial arteries are more viable candidates for the vessels that most significantly influence the UtA waveform. Further investigation is required into why SpA remodelling correlates with pregnancy complications, such as preeclampsia and FGR, that are associated with abnormal UtA waveforms. It is possible that an over-arching mechanism, such as a hormonal influence or impaired remodelling ability, may prevent sufficient adaptation of both the radial and SpAs. In addition, the potential causal role of the radial arteries in pathologies predicted by abnormal UtA waveforms, most notably preeclampsia and preeclampsia with FGR, should be further investigated. Finally, more research should be undertaken into the potential role of the maternal CVS in pathologies associated with abnormal UtA waveforms. The maternal CVS phenotype during pregnancy may be a useful marker or predictor for pathology, particularly if a maladaptive phenotype exists pre-pregnancy.

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Figure legends

Figure 1. Diagrammatic representation of uterine and placenta vasculature (red shading = arterial; blue shading = venous) in non-pregnant, pregnant and immediate post-partum states. The uterine arteries arise from the internal iliac arteries and branch into the arcuate arteries which traverse the uterus in horizontal rings. The arcuates give rise to radial arteries that penetrate the uterine wall, ending as basal arteries supplying the basal zone of the endometrium (now decidualised) and spiral arteries that supply the functional zone of the endometrium and placenta. The spiral arteries consist of a junctional zone in the inner myometrium and a decidual segment. During pregnancy, A-V anastomoses (red and blue) form in the placental bed and persist in the immediate post-partum period. (Modified from Burton *et al.* [14]).

Figure 2. The Doppler waveform and derived indices. a) illustrates the velocity waveform and values that can be obtained from it. b) the most commonly used indices available on commercial scanners.

Figure 3. A comparison between the classical serial model of uteroplacental blood flow and the parallel model proposed by Schaaps *et al.* [26]. Red arrows represent the uterine arterial system, blue arrows represent the uterine venous system. The dashed line represents the plane of separation at the time of delivery. The persistence of the myometrial A-V shunts after delivery accounts for the lack of change in the UtA waveform observed post-partum. (Modified from Schaaps *et al.* [26]).

Table legends

Table 1. Outline of uterine artery waveform features and their clinical significance

Table 2. Key equations relating to blood flow

References

- [1] D.E. FitzGerald, J.E. Drumm, Non-invasive measurement of human fetal circulation using ultrasound: a new method, *Br Med J.* 2 (1977) 1450–1451. <https://doi.org/10.1136/bmj.2.6100.1450>.
- [2] The Shrewsbury and Telford Hospital, Antenatal Clinical Risk Assessment, Version 11, (2015). <https://www.networks.nhs.uk/nhs-networks/staffordshire-shropshire-and-black-country-newborn/documents/documents/shrewsbury-mlu-guidelines> (accessed June 4, 2020).
- [3] Antenatal care for uncomplicated pregnancies NICE, (n.d.). <https://www.nice.org.uk/guidance/cg62> (accessed January 21, 2020).
- [4] A.R. Clark, J.L. James, G.N. Stevenson, S.L. Collins, Understanding abnormal uterine artery Doppler waveforms: A novel computational model to explore potential causes within the utero-placental vasculature, *Placenta.* 66 (2018) 74–81. <https://doi.org/10.1016/j.placenta.2018.05.001>.
- [5] T.R. Everett, C.C. Lees, Beyond the placental bed: Placental and systemic determinants of the uterine artery Doppler waveform, *Placenta.* 33 (2012) 893–901. <https://doi.org/10.1016/j.placenta.2012.07.011>.
- [6] J.S. Cnossen, R.K. Morris, G. ter Riet, B.W.J. Mol, J.A.M. van der Post, A. Coomarasamy, A.H. Zwinderman, S.C. Robson, P.J.E. Bindels, J. Kleijnen, K.S. Khan, Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: a systematic review and bivariable meta-analysis, *CMAJ.* 178 (2008) 701–711. <https://doi.org/10.1503/cmaj.070430>.
- [7] Preeclampsia Foundation Website, About Preeclampsia, Preeclampsia Foundation Official Site. (2019). <https://www.preeclampsia.org/health-information/about-preeclampsia> (accessed February 6, 2020).
- [8] Intrauterine Growth Retardation, (2004). https://www.ucsfbenioffchildrens.org/pdf/manuals/21_IUG.pdf (accessed February 6, 2020).
- [9] D.J.P. Barker, Adult consequences of fetal growth restriction, *Clin Obstet Gynecol.* 49 (2006) 270–283. <https://doi.org/10.1097/00003081-200606000-00009>.
- [10] H.J. Kliman, Uteroplacental blood flow. The story of decidualization, menstruation, and trophoblast invasion, *Am. J. Pathol.* 157 (2000) 1759–1768. [https://doi.org/10.1016/S0002-9440\(10\)64813-4](https://doi.org/10.1016/S0002-9440(10)64813-4).
- [11] ISUOG Practice Guidelines: use of Doppler ultrasonography in obstetrics: ISUOG Guidelines, *Ultrasound Obstet Gynecol.* 41 (2013) 233–239. <https://doi.org/10.1002/uog.12371>.
- [12] R. Pijnenborg, L. Vercruyse, M. Hanssens, The Uterine Spiral Arteries In Human Pregnancy: Facts and Controversies, *Placenta.* 27 (2006) 939–958. <https://doi.org/10.1016/j.placenta.2005.12.006>.
- [13] I. Brosens, R. Pijnenborg, L. Vercruyse, R. Romero, The “Great Obstetrical Syndromes” are associated with disorders of deep placentation, *Am. J. Obstet. Gynecol.* 204 (2011) 193–201. <https://doi.org/10.1016/j.ajog.2010.08.009>.
- [14] G.J. Burton, A.W. Woods, E. Jauniaux, J.C.P. Kingdom, Rheological and Physiological Consequences of Conversion of the Maternal Spiral Arteries for Uteroplacental Blood Flow during Human Pregnancy, *Placenta.* 30 (2009) 473–482. <https://doi.org/10.1016/j.placenta.2009.02.009>.
- [15] C.V. Steer, S. Campbell, J.S. Pampiglione, C.R. Kingsland, B.A. Mason, W.P. Collins, Transvaginal colour flow imaging of the uterine arteries during the ovarian and menstrual cycles, *Hum Reprod.* 5 (1990) 391–395. <https://doi.org/10.1093/oxfordjournals.humrep.a137109>.
- [16] S.L. Tan, J. Zaidi, S. Campbell, P. Doyle, W. Collins, Blood flow changes in the ovarian and uterine arteries during the normal menstrual cycle, *Am. J. Obstet. Gynecol.* 175 (1996) 625–631. <https://doi.org/10.1053/ob.1996.v175.a73865>.
- [17] M.C. Scholtes, J.W. Wladimiroff, H.J. van Rijen, W.C. Hop, Uterine and ovarian flow velocity waveforms in the normal menstrual cycle: a transvaginal Doppler study, *Fertil. Steril.* 52 (1989) 981–985. [https://doi.org/10.1016/s0015-0282\(16\)53162-8](https://doi.org/10.1016/s0015-0282(16)53162-8).
- [18] I. Järvelä, A. Tekay, P. Jouppila, The effect of diclofenac on uterine artery blood flow resistance during menstruation in patients with and without a copper intrauterine device, *Hum. Reprod.* 13 (1998) 2480–2483. <https://doi.org/10.1093/humrep/13.9.2480>.
- [19] S.A. Hale, C.W. Jones, G. Osol, A. Schonberg, G.J. Badger, I.M. Bernstein, Sildenafil Increases Uterine Blood Flow in Nonpregnant Nulliparous Women, *Reprod Sci.* 17 (2010) 358–365. <https://doi.org/10.1177/1933719109354648>.
- [20] I. Jarvela, A. Tekay, P. Jouppila, The effect of a levonorgestrel-releasing intrauterine system on uterine artery blood flow, hormone concentrations and ovarian cyst formation in fertile women, *Human Reproduction.* 13 (1998) 3379–3383. <https://doi.org/10.1093/humrep/13.12.3379>.

- [21] M. Jiménez, E. Arbo, F. de Freitas, J. Cunha-Filho, The effect of the levonorgestrel-releasing intrauterine system and the copper intrauterine device on subendometrial microvascularization and uterine artery blood flow., *Fertil Steril.* 90 (2008) 1574–1578. <https://doi.org/10.1016/j.fertnstert.2007.10.004>.
- [22] S.L. Collins, D. Grant, R.S. Black, M. Vellayan, L. Impey, Abdominal pregnancy: A perfusion confusion?, *Placenta.* 32 (2011) 793–795. <https://doi.org/10.1016/j.placenta.2011.07.032>.
- [23] V.H.J. Roberts, T.K. Morgan, P. Bednarek, M. Morita, G.J. Burton, J.O. Lo, A.E. Frias, Early first trimester uteroplacental flow and the progressive disintegration of spiral artery plugs: new insights from contrast-enhanced ultrasound and tissue histopathology, *Human Reproduction.* 32 (2017) 2382–2393. <https://doi.org/10.1093/humrep/dex301>.
- [24] H.H. Allerkamp, A.R. Clark, T.C. Lee, T.K. Morgan, G.J. Burton, J.L. James, Something old, something new: digital quantification of uterine vascular remodelling and trophoblast plugging in historical collections provides new insight into adaptation of the utero-placental circulation, *Human Reproduction.* (2020). <https://doi.org/10.1093/humrep/deaa303>.
- [25] G.P. Heckel, C.E. Tobin, Arteriovenous shunts in the myometrium, *American Journal of Obstetrics and Gynecology.* 71 (1956) 199–205. [https://doi.org/10.1016/0002-9378\(56\)90695-0](https://doi.org/10.1016/0002-9378(56)90695-0).
- [26] J. Schaaps, V. Tsatsaris, F. Goffin, J.F. Brichant, K. Delbecq, M. Tebache, L. Collignon, M.C. Retz, J.M. Foidart, Shunting the intervillous space: New concepts in human uteroplacental vascularization., *Am J Obstet Gynecol.* (2005) 323–32.
- [27] P. Gathiram, J. Moodley, Pre-eclampsia: its pathogenesis and pathophysiology, *Cardiovasc J Afr.* 27 (2016) 71–78. <https://doi.org/10.5830/CVJA-2016-009>.
- [28] G. Ogge, T. Chaiworapongsa, R. Romero, Y. Hussein, J.P. Kusanovic, L. Yeo, C.J. Kim, S.S. Hassan, Placental lesions associated with maternal underperfusion are more frequent in early-onset than in late-onset preeclampsia, *J Perinat Med.* 39 (2011) 641–652. <https://doi.org/10.1515/jpm.2011.098>.
- [29] M.Y. Rennie, K.J. Whiteley, S.L. Adamson, J.G. Sled, Quantification of Gestational Changes in the Uteroplacental Vascular Tree Reveals Vessel Specific Hemodynamic Roles During Pregnancy in Mice, *Biology of Reproduction.* 95 (2016) 43–43. <https://doi.org/10.1095/biolreprod.116.140681>.
- [30] W. Moll, W. Künzel, The blood pressure in arteries entering the placentae of guinea pigs, rats, rabbits, and sheep. - PubMed - NCBI, *Pflugers Arch.* (1973) 125–31. <https://doi.org/10.1007/bf00592748>.
- [31] J.W.S. Harris, E.M. Ramsey, The morphology of human uteroplacental vasculature, *Carnegie Institution of Washington*, 1966.
- [32] R. Pijnenborg, G. Dixon, W.B. Robertson, I. Brosens, Trophoblastic invasion of human decidua from 8 to 18 weeks of pregnancy, *Placenta.* 1 (1980) 3–19. [https://doi.org/10.1016/s0143-4004\(80\)80012-9](https://doi.org/10.1016/s0143-4004(80)80012-9).
- [33] S.S. Ong, P.N. Baker, T.M. Mayhew, W.R. Dunn, Remodeling of myometrial radial arteries in preeclampsia, *American Journal of Obstetrics and Gynecology.* 192 (2005) 572–579. <https://doi.org/10.1016/j.ajog.2004.08.015>.
- [34] R.C. Burchell, Arterial blood flow into the human intervillous space, *American Journal of Obstetrics and Gynecology.* 98 (1967) 303–311. [https://doi.org/10.1016/0002-9378\(67\)90149-4](https://doi.org/10.1016/0002-9378(67)90149-4).
- [35] G. Osol, M. Mandala, Maternal uterine vascular remodeling during pregnancy, *Physiology (Bethesda).* 24 (2009) 58–71. <https://doi.org/10.1152/physiol.00033.2008>.
- [36] D.G. Talbert, Uterine flow velocity waveform shape as an indicator of maternal and placental development failure mechanisms: a model-based synthesizing approach, *Ultrasound in Obstetrics & Gynecology.* 6 (1995) 261–271. <https://doi.org/10.1046/j.1469-0705.1995.06040261.x>.
- [37] S. Özkan, B. Vural, E. Çalışkan, H. Bodur, E. Türköz, F. Vural, Color doppler sonographic analysis of uterine and ovarian artery blood flow in women with polycystic ovary syndrome, *Journal of Clinical Ultrasound.* 35 (2007) 305–313. <https://doi.org/10.1002/jcu.20358>.
- [38] J. Zaidi, D. Jurkovic, S. Campbell, E. Okokon, S.L. Tan, Circadian variation in uterine artery blood flow indices during the follicular phase of the menstrual cycle, *Ultrasound in Obstetrics & Gynecology.* 5 (1995) 406–410. <https://doi.org/10.1046/j.1469-0705.1995.05060406.x>.
- [39] J.J. Brosens, M.G. Parker, A. McIndoe, R. Pijnenborg, I.A. Brosens, A role for menstruation in preconditioning the uterus for successful pregnancy, *American Journal of Obstetrics and Gynecology.* 200 (2009) 615.e1–615.e6. <https://doi.org/10.1016/j.ajog.2008.11.037>.
- [40] S.H. Nelson, O.S. Steinsland, Y. Wang, C. Yallampalli, Y.L. Dong, J.M. Sanchez, Increased nitric oxide synthase activity and expression in the human uterine artery during pregnancy, *Circ. Res.* 87 (2000) 406–411. <https://doi.org/10.1161/01.res.87.5.406>.

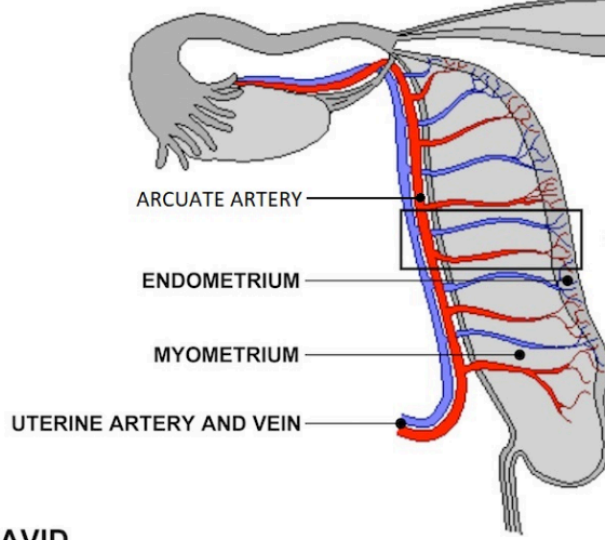
- [41] J. Bai, Q.-R. Qi, Y. Li, R. Day, J. Makhoul, R.R. Magness, D. Chen, Estrogen Receptors and Estrogen-Induced Uterine Vasodilation in Pregnancy, *Int J Mol Sci.* 21 (2020). <https://doi.org/10.3390/ijms21124349>.
- [42] C.G. Solomon, E.W. Seely, Hypertension in Pregnancy, *Endocrinology and Metabolism Clinics of North America.* 35 (2006) 157–171. <https://doi.org/10.1016/j.ecl.2005.09.003>.
- [43] Solomon C G, Graves S W, Greene M F, Seely E W, Glucose intolerance as a predictor of hypertension in pregnancy., *Hypertension.* 23 (1994) 717–721. <https://doi.org/10.1161/01.HYP.23.6.717>.
- [44] J. Mayet, A. Hughes, Cardiac and vascular pathophysiology in hypertension, *Heart.* 89 (2003) 1104–1109.
- [45] J.M. Roberts, R.N. Taylor, T.J. Musci, G.M. Rodgers, C.A. Hubel, M.K. McLaughlin, Preeclampsia: an endothelial cell disorder, *Am. J. Obstet. Gynecol.* 161 (1989) 1200–1204. [https://doi.org/10.1016/0002-9378\(89\)90665-0](https://doi.org/10.1016/0002-9378(89)90665-0).
- [46] A. Ridder, V. Giorgione, A. Khalil, B. Thilaganathan, Preeclampsia: The Relationship between Uterine Artery Blood Flow and Trophoblast Function, *Int J Mol Sci.* 20 (2019). <https://doi.org/10.3390/ijms20133263>.
- [47] H. Valensise, B. Vasapollo, G. Gagliardi, G.P. Novelli, Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease, *Hypertension.* 52 (2008) 873–880. <https://doi.org/10.1161/HYPERTENSIONAHA.108.117358>.
- [48] R.S. Vasan, Cardiac function and obesity, *Heart.* 89 (2003) 1127–1129.
- [49] T.-H. Hung, T.-T. Hsieh, S.-F. Chen, Risk of abnormal fetal growth in women with early- and late-onset preeclampsia, *Pregnancy Hypertens.* 12 (2018) 201–206. <https://doi.org/10.1016/j.preghy.2017.09.003>.
- [50] M.L. Mongraw-Chaffin, P.M. Cirillo, B.A. Cohn, Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort, *Hypertension.* 56 (2010) 166–171. <https://doi.org/10.1161/HYPERTENSIONAHA.110.150078>.
- [51] F.L. Foo, A.A. Mahendru, G. Masini, A. Fraser, S. Cacciatore, D.A. MacIntyre, C.M. McEniery, I.B. Wilkinson, P.R. Bennett, C.C. Lees, Association Between Prepregnancy Cardiovascular Function and Subsequent Preeclampsia or Fetal Growth Restriction, *Hypertension.* 72 (2018) 442–450. <https://doi.org/10.1161/HYPERTENSIONAHA.118.11092>.

Waveform Features	Definition	Changes and interpretation (according to current thinking/guidelines)	Waveform examples
Impedance [37]	<p>Combination of resistance and compliance.</p> <p>Determines the relationship between blood pressure and flow velocity.</p>	<p>Impacted by changes in resistance or compliance of the uterine vessels.</p> <p>Decreased impedance (normal decrease throughout gestation to facilitate increased blood flow to the fetoplacental unit), results in high flow that is indicated by: broader systolic peak, increased diastolic flow, decreased PI/RI.</p> <p>Increased impedance (associated with preeclampsia or FGR) results in low flow that is indicated by: sharp systolic peak, larger UtA waveform, poor diastolic flow, increased PI/RI and/or presence of an early diastolic notch.</p>	
Notching	Thought to be a result of the reflected waves that normally arise from vasculature downstream of the	<p>Presence indicates high vasculature resistance.</p> <p>Normally resistance decreases throughout pregnancy, and no reflected notches should be present after ~20 weeks gestation [4].</p>	As above

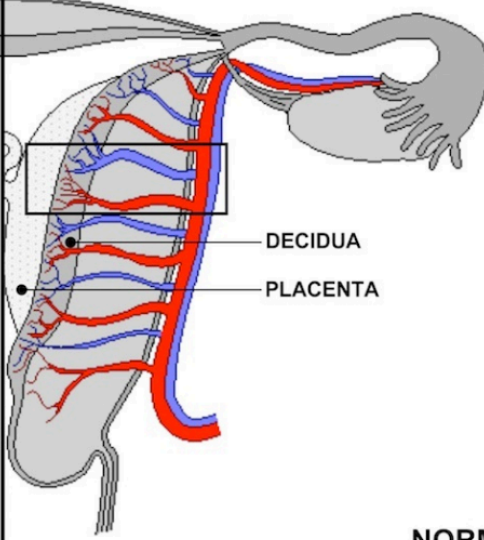
	UtA becoming significant in magnitude and delayed with respect to the incident waveform. [4]	Persistence into late second trimester is considered indicative of abnormally high placental bed resistance [5], but can occur with normal resistance values and is related to an adverse outcome.	
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<p>Poiseuille's law</p>	$q = \frac{\Delta P r^4}{8\mu L}$ <p>q = volumetric flow rate (volume of fluid flowing along the tube per unit time given by the formula)</p> <p>ΔP = change in pressure</p> <p>μ = viscosity of the fluid</p> <p>L = length</p> <p>r = radius</p>
<p>Volume flow rate</p>	$Q = \frac{V}{t}$ <p>Q= volume flow rate</p> <p>V = volume</p> <p>t = time</p>

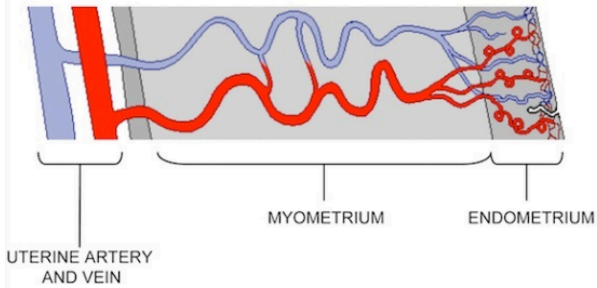
NON-PREGNANT



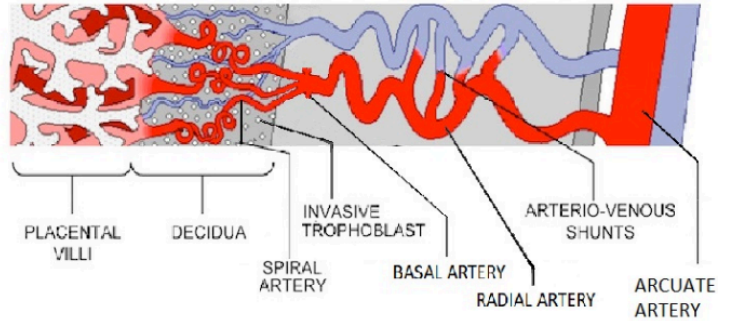
PREGNANT



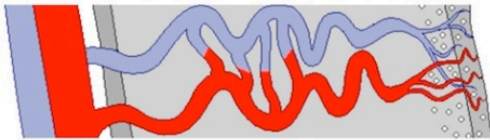
NON-GRAVID

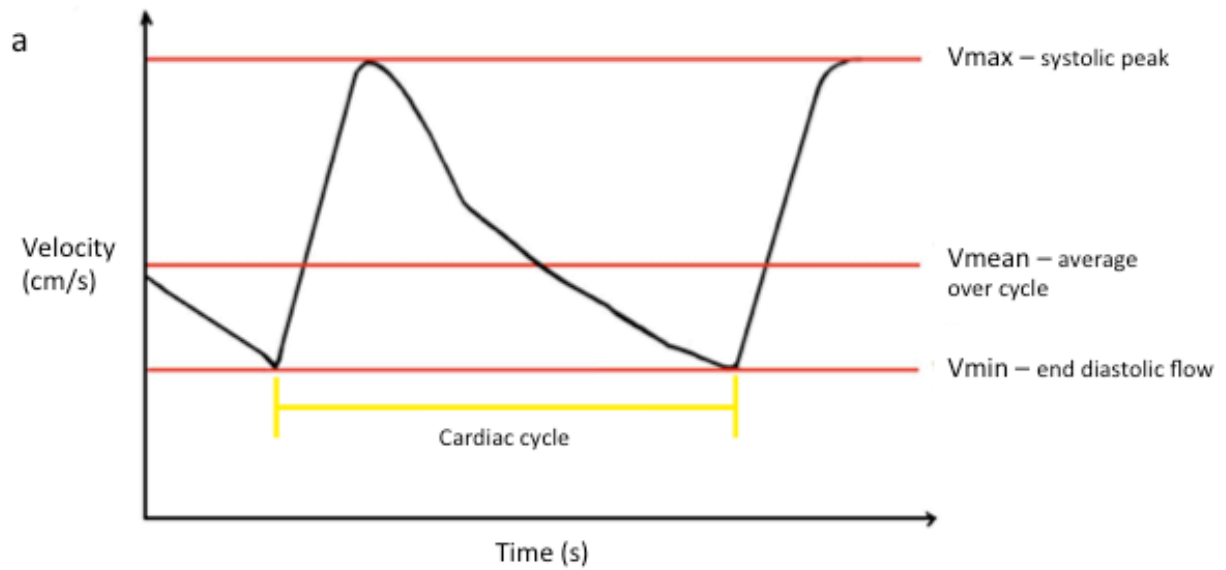


NORMAL PREGNANCY



IMMEDIATE POST-PARTUM

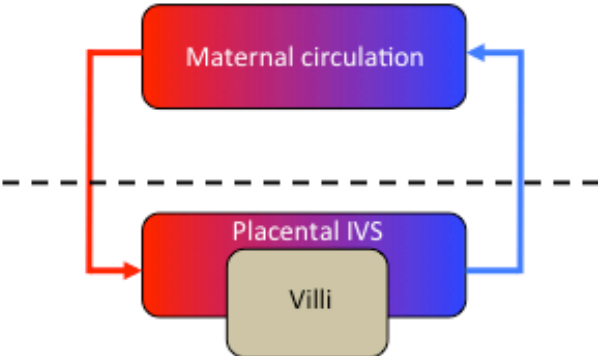




b

Doppler index	Formula
S/D ratio	$\frac{V_{max}}{V_{min}}$
Resistance index (RI)	$\frac{V_{max} - V_{min}}{V_{max}}$
Pulsatility index (PI)	$\frac{V_{max} - V_{min}}{V_{mean}}$

Series



Parallel

