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Simulating the Placenta in a Hemodynamic Model of the Pregnant Woman

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1 Abstract

Introduction. The placenta is the organ that exchanges nutrients between mother and child. This means that when the placenta develops or functions poorly, it results in malnourishment of the fetus and complications during pregnancy. As the placenta plays a crucial role in these complications, it is important to get a better understanding of the (mal-)functioning of the placenta. **Methods.** By using an existing hemodynamic model from Radboudumc and defining values of resistances, elastances and initial and unstressed volumes, the pressures, and flows of the uterine arteries, spiral arteries, intervillous space and uterine veins could be examined. The values were defined for the first and second trimester of a healthy pregnancy and for the second trimester of gestational hypertension (GH), early-onset preeclampsia (PE), placenta accreta syndrome (PAS) and fetal growth restriction (FGR). **Results.** The simulation of the uncomplicated first and second trimester were according expectation, based on knowledge gained by literature. Adjustments made for PE, FGR and PAS resulted in a representative hemodynamic pathological profile. However, adjustments made to simulate GH did not result in hypertension. **Discussion.** The volume distribution within the model does not resemble reality, due to the closed-loop system. Furthermore, the model is a simplified version of reality, solely displaying pressures and flows based on compliances lumped via resistances.

***Keywords**: hemodynamic model, pregnancy, placenta, first trimester, second trimester, gestational hypertension, early-onset preeclampsia, placenta accreta syndrome, fetal growth restriction.*

Contents

2 Introduction

The placenta is the organ responsible for the nutrient exchange between mother and child. Poor development or functioning of the placenta thus results in a decreased reception of nutrients from the mother by the child and is therefore associated with complications during pregnancy [1]. Because of this crucial role, understanding the functioning of the placenta is important.

In addition to the function of a healthy placenta, the placental dysfunction in complicated pregnancies needs to be better understood. 5.2-8.2% of pregnancies are complicated by hypertension, often with an unknown cause [2]. This high blood pressure may lead to health problems in both the pregnant woman and the fetus. Excessive blood pressure can damage vessel walls, causing a reduced elasticity and thus lower blood flow [3]. In the pregnant body, a low blood flow affects not only the maternal organs, but also placental functioning. This in turn results in a reduced exchange of oxygen and nutrients, leading to serious consequences for the growth and development of the fetus [4].

The underlying cause of hypertension often remains unknown, because in clinical settings only the blood pressure is measured. Several theories suggest that the development and dysfunction of the placenta and its vascularization are central to hypertension [5, 6]. By modelling the hemodynamics of the cardiovascular system of the pregnant body, an explanation of these physiological changes can be obtained. In this model, patient characteristics can be incorporated to create an individual image of hemodynamics that include pressures, flows, volumes, elastances and resistances of the various vessels in the pregnant body.

The hemodynamic model of the pregnant woman already exists, made by Radboudumc. However, the placental components need to be further explored, because of the many changes that occur during pregnancy. This report focusses on the first and second trimester of pregnancy, since most vascular changes in the placenta take place in this period [7]. This report will also focus on gestational hypertension type 1, early-onset preeclampsia, placenta accreta syndrome and early-onset fetal growth restriction.

2.1 Research question

To get better insight into the hemodynamics of the placenta, the following research question will be focussed on:
What is the hemodynamic behaviour of the placenta, represented by flows and pressures, simulated with the lumped compartment model, in complicated and uncomplicated pregnancies?

To this end, the following sub-questions will be answered:

- What is the underlying theory of the computational hemodynamic model?
- Which vascular elements of the placenta are important to implement in the hemodynamic model?
- What are the values of elastance, resistance, and initial and unstressed volumes of the implemented compartments of the placenta in uncomplicated pregnancies?
- What are the values of elastance, resistance and initial and unstressed volumes of the implemented compartments of the placenta in gestational hypertension type 1, early-onset preeclampsia, placenta accreta syndrome and early-onset fetal growth restriction?

3 Background Research

3.1 Anatomy

The human placenta is a discoid organ that forms during pregnancy to supply the fetus with oxygen and nutrients. It is formed by cells of the nested blastocyst, interacting with the cells of the lining of the uterus, the endometrium [8]. As a result of this interaction, the endometrium undergoes vascular changes, supplying a higher blood flow to the fetus. After these changes, the altered endometrium is called the decidua [9].

The circulation of the mother and fetus are separated by a placental membrane, forming a maternal and a fetal part [7, 10]. The fetal part, the chorionic plate, is covered by the amnion and the amniotic mesenchyme. The maternal part, or basal plate, comprises the endometrium with its vascularisation. The basal plate can be divided into 10–40 lobs, each consisting of 1–4 lobules. These lobules are also called cotyledons, although the term 'placentones' would be more correct in human placentae, as the lobules are not fully separated from each other [11, 12]. There are about 30-60 placentones in a placenta at term. Every placentone forms a maternal-fetal exchange unit and comprises one or more spiral arteries, one villous tree and the intervillous space that surrounds the latter [10, 11]. These terms will be explained below in section 3.1.1.

The development of the placenta occurs in phases, which are as follows:

- The pre-implantation phase (day 6): the blastocyst begins to differentiate, resulting in a trophoblastic outer layer that forms the basis of further differentiation to other cell types. This forms the placenta, as presented below in figure 1 [13].
- The pre-lacunar phase (day 7-8): the trophoblast develops into two primitive cell lineages: the syncytium and the cytotrophoblast [13]. The cytotrophoblast then again differentiates into two cell lineages: the syncytiotrophoblasts and the extravillous trophoblasts (EVTs). The differentiation of the trophoblast and its derivatives are made visible in figure 2. The syncytiotrophoblasts invade the epithelium of the uterus and are responsible for the implantation of the blastocyst [10].
- The lacunar phase (day 9): nine days after conception, the lacunae are formed by merging of the vacuoles in the syncytiotrophoblasts. In this phase, the three layers of the placenta become more distinct. The precursor of the chorionic plate, the lacunar system and the trabeculae form the intervillous space and the villous tree. Furthermore, the EVTs differentiate to two cell lineages, namely the interstitial and the endovascular EVTs. The interstitial EVTs invade the decidua. The endovascular EVTs invade the spiral arteries and remodel them, which forms the basis of the uteroplacental perfusion [10].
- The villous phase: thirteen days after conception, the primary villi develop from a layer of syncytiotrophoblasts with a core of cytotrophoblasts that fold into the lacunar space. The secondary villi are formed by a core of embryonic mesoderm in the primary villi. At day 21, the tertiary villi develop by the formation of vessels in the embryonic membrane that merge with the vessels that will vascularise the umbilical cord and the fetus. One layer of trophoblasts is kept intact, to separate the embryonic circulation and the maternal decidua [10, 14].

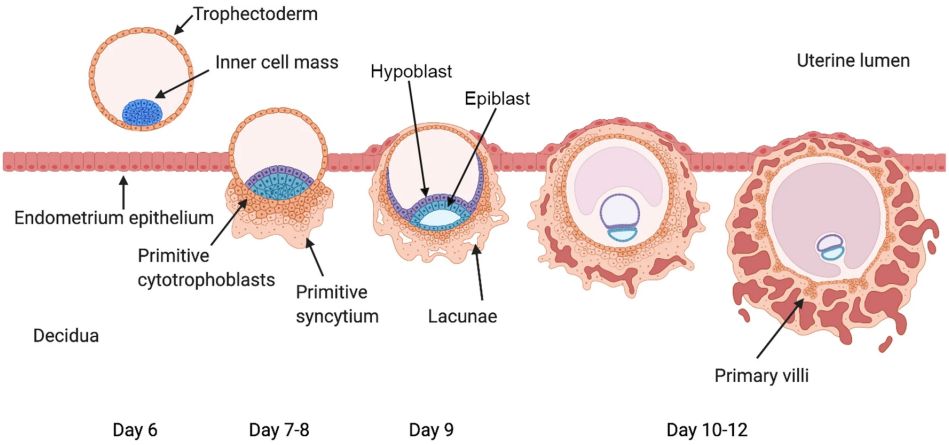


Figure 1: The implantation of the blastocyst in the endometrium, with the associated development of the placenta from the trophoblasts. Figure obtained from [13].

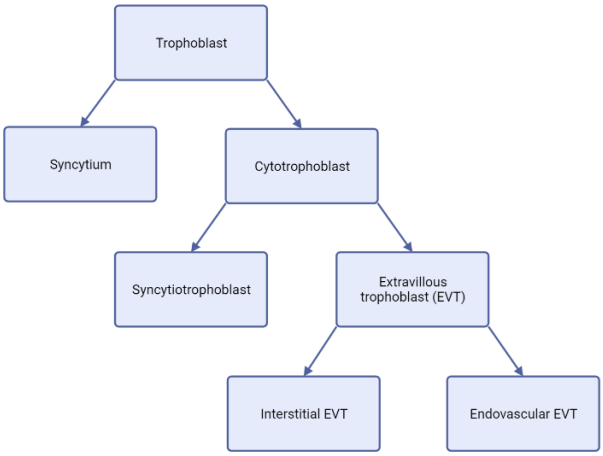


Figure 2: Flowchart describing the differentiation of trophoblasts.

3.1.1 Vascularisation

The uterine artery is the largest artery in the vascularisation of the uterus. The uterine arteries give off branches called the arcuate arteries, which flow to the myometrium. They flow parallel to the uterine artery, as can be seen in figure 3. The arcuate arteries are orientated circularly and give off perpendicular branches, named radial arteries. The radial arteries run deeper through the myometrium to the endometrium. Where the myometrium meets the endometrium, the radial arteries each split into one spiral artery and one or more basal arteries, that both vascularise the endometrium radially [12]. The maternal part of the placenta is supplied with blood from approximately 120 spiral arteries [7]. The spiral arteries and the distal parts of the radial arteries are together called the uteroplacental arteries, as they both undergo transformations during healthy pregnancy. These transformations can be divided into two processes: vascular growth with forming of the decidua and vascular reorganisation as a result of the invading EVTs [12].

The maternal blood flows through the spiral arteries into the intervillous space (IVS), a cavity filled with maternal blood that flows freely, as can be seen in figure 4. Since the IVS surrounds the villous trees of the fetal part of the placenta, this is where the exchange of nutrients and waste products takes place. Via the endometrial veins and uterine vein, the blood flows back to the iliac vein. The maternal blood flow in the placenta is completely dependent on hormonal and structural factors, since the placenta is not innervated [10, 14].

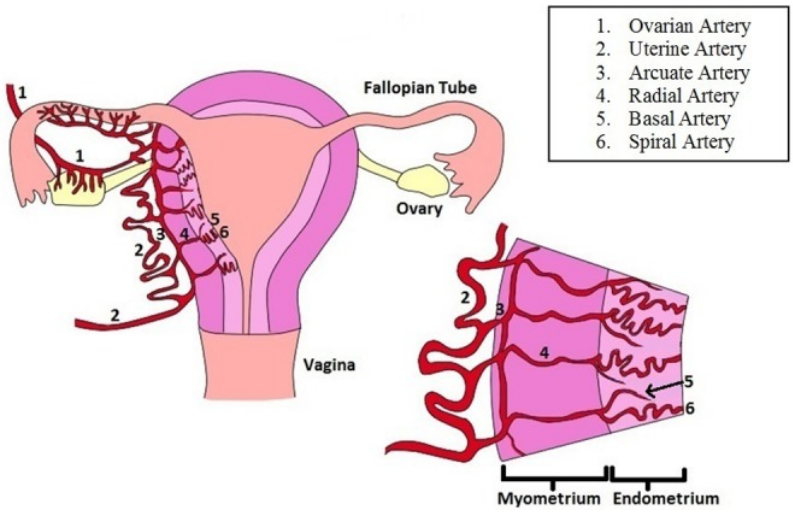


Figure 3: The vascularisation of the uterus. Figure obtained from [12].

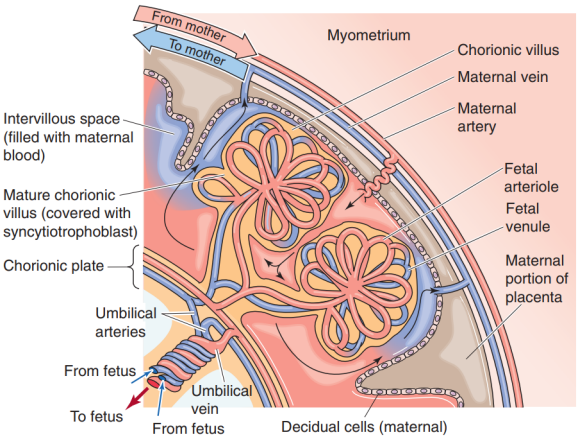


Figure 4: The placentone containing the branches of the chorionic artery and maternal blood in the intervillous space. Figure obtained from [7].

Not all blood from the uterine artery flows into the spiral arteries. There is also a flow from the uterine arteries directly to the uterine vein via arteriovenous anastomoses. These shunts ensure that no mismatch of flow rate occurs on the maternal and fetal sides and that pressure remains constant and low. Another function is to carry the uterine blood flow after labour [15]. Especially in the first trimester, these shunts are important. This is because at the beginning of pregnancy, not all the blood can flow to the IVS, since the spiral arteries are not remodelled yet [16]. This will be discussed in section 3.2.

The fetal side of the placenta is vascularised by the umbilical arteries, from which the chorionic artery arises. The chorionic artery then distally branches off multiple times, with each branch forming one villous tree [10]. The villous tree consists of villi that are classified into stem villi, intermediate villi, terminal villi and lastly mesenchymal villi. This classification is based on form and function, with stem villi being the most proximal and mesenchymal villi the most distal [11].

3.2 Physiology

In addition to the formation of the placenta, systemic changes in the maternal circulation take place throughout pregnancy. After five weeks of gestation, systemic vasodilation occurs, making the systemic vascular resistance (SVR) decrease by 30-40% throughout pregnancy [17]. Besides that, starting in the first few weeks, the total blood volume increases, especially in the second trimester. By the end of pregnancy, the total blood volume has increased by 45% [7, 17]. This increase is caused by an increase in the plasma volume and the erythrocyte volume. In addition, the heart rate will increase, making it 20-25% higher by the end of gestation [17]. Furthermore, the cardiac output (CO) rises in the first trimester with 35-40% [7]. This is a result of the increased blood volume and heart rate. Due to higher CO and the decreased SVR, the renal blood flow will increase by 40-50% and the uterine vascularisation from 1 to 15% of the total cardiac output [7, 17]. Lastly, the blood pressure varies during gestation; during a normotensive pregnancy the blood pressure will decrease in the first and second trimester and will increase again by the third, ending at the same value or lower than the pressure before fertilization [17].

Not only systemic vascular changes occur during pregnancy, but also in the spiral arteries in the endometrium, as mentioned in section 3.1.1. The reorganisation of the spiral arteries has a great influence on the vascularisation of the placenta. This process starts at the end of the first trimester. This is done by endovascular EVTs invading the wall of the spiral arteries, initiating a complex process [18]. This causes the highly contractile muscular vessels to become flaccid, dilated drainage ducts [8, 12]. Because of this, the resistance and pulsatility of the spiral arteries decrease, resulting in a constant blood flow into the IVS [12, 19]. Moreover, during the same period, plugs of EVTs in the distal parts of the spiral arteries are removed [20]. During the first trimester, these plugs serve to decrease the vascularisation of the placenta, lowering the oxygen level in the fetus [12, 20]. This is beneficial for the development because, at the beginning of pregnancy, the fetus has limited resistance against oxidative stress, which can arise due to excessive oxygen levels [19]. However, after the first trimester, it is important that the fetus receives enough oxygen through the placenta, to prevent hypoxia from happening [19, 20].

The maternal blood flow in the IVS is determined by the maternal blood pressure, intrauterine pressure and the periodical contractions of the uterus that occur throughout gestation [7]. The blood that is already present in the IVS causes the flow velocity to decrease. Then the blood spreads laterally, completely surrounding the villi. Due to the low flow, there is sufficient time for the exchange of substances between the maternal and fetal blood [7].

The fetus is supplied by the mother's blood with oxygen, carbohydrates, amino acids, proteins, lipids, vitamins and hormones, among other things. At the same time, carbon dioxide, urea, and creatinine are secreted from the fetal blood via the maternal circulation. As mentioned above, the fetal and maternal circulation are separated by the placental membrane [7]. This membrane contains transporters, making limited transport of, for example, glucose and amino acids possible. Most exchange of substances, for example, oxygen, takes place by diffusion. The amount of exchange depends on the concentration gradient between the maternal and fetal blood [7].

3.3 Pathology

During pregnancy, many changes occur in the vasculature, as described above. These changes can be affected by different pathologies. In this report, there are four common pathologies described and how they affect the vasculature on the maternal side of the placenta. There is some evidence that certain underlying pathophysiologies overlap. In particular, early-onset preeclampsia and early-onset fetal growth restriction are reasonably often associated with each other [21].

3.3.1 Gestational Hypertension Type 1

Gestational hypertension (GH) is a form of hypertension, developing after 20 weeks of gestation without signs of organ dysfunction [22]. This is clinically quantified with a systolic blood pressure above 140 mmHg and a diastolic blood pressure above 90 mmHg [23]. Following Ohm's law, hypertension in the basis can be caused by a high peripheral resistance or a high CO, or a combination. Consequently, GH knows two subtypes: one dominated by a volume overload, and one by a higher resistance. Type 1 GH is the resistance-dominated variant, meaning that from the start of week 20 on to the end of gestation, total SVR increases. Type 2 is volume-dominated, characterized by a decrease in SVR and a rising of the CO from the start of week 20 till the end of gestation [22]. This report will focus on GH type 1, as simulation of type 2 within the current model is rather complicated.

3.3.2 Early-Onset Preeclampsia

Preeclampsia (PE) is another hypertensive pregnancy disorder. In developed countries, 16% of maternal deaths are caused by PE [24]. Blood pressures in PE are equal to those in GH, however, in PE there is also a proteinuria of 0.3 g per 24 hours or higher. Even though PE cannot be diagnosed until after the 20^{th} week, there is some evidence that the physiology is already abnormal at the beginning of pregnancy [23].

Preeclampsia is subdivided into two categories. This report will only focus on the early-onset PE, as late-onset PE originates in the third trimester of gestation [22]. The exact underlying mechanism of hypertension and proteinuria is unsure. However, there are some theories involving the vasculature in the placenta [5, 6]. In PE, other than in GH, the hemodynamical dysfunction involves the venous system, due to abnormal adaption during pregnancy [22]. The venous impedance, which is the opposition of pulsatile blood flow in the vessels and which is dependent on resistance and compliance [25], is 20%-120% higher in PE than in normal pregnancies. This suggests a state of venoconstriction and a low volume capacity, leading to venous congestion [22]. This venous dysfunction results in a reduced venous return, impaired cardiac diastolic function, and decreased CO [26].

Normal placentation requires the involvement of both proinflammatory agents, produced by the embryo and the maternal decidua, as well as the build-up of immune tolerance in the maternal system for the fetus. An imbalance in favour of the proinflammatory over the protolerance mediators may damage the endothelial cells of the veins while the spiral arteries are still blocked with trophoblast plugs. Trophoblast invasion of the maternal veins and lymphatics occurs weeks before spiral artery remodelling. Abnormal agents originating from the veins may alter spiral artery remodelling, as anastomoses in the placenta allow for venoarterial communication [22, 23].

3.3.3 Placenta Accreta Syndrome

Another pathology that affects the vasculature in the placenta is placenta accreta syndrome (PAS). PAS is a pregnancy-related pathology, marked by an abnormally deep placement of the placenta into the uterine wall. In developed countries, this condition affects 1 in 500 pregnant women, which is a lot higher than it used to be in the 20^{th} century. This is due to an increase in caesarean deliveries [27]. This deep placement of the placenta results in difficulties during labour. The placenta does not separate from the uterine wall and stays in the uterus, resulting in a chance for a hysterectomy [28]. Based on the degree of invasiveness in the uterine wall, placenta accreta is divided into three categories. The least invasive category is called placenta accreta and is classified by a superficial attachment of the placenta to the myometrium. When the placenta also penetrates the myometrium, the condition is called placenta increta. In the last category, placenta percreta, the placenta is penetrated through the entire uterine wall and can even attach to other organs, for example, the bladder [27].

Although the exact underlying mechanism of PAS remains unclear, there are some theories [11]. The most convincing theory explains a defective decidualization, resulting in unusual anchoring of placental villi to the myometrium. This defective anchoring can possibly result from surgery, explaining the high prevalence in women who have had a caesarean section [27]. The decidua in the uterine wall operates as a matrix, enabling EVTs to invade the inner third of the myometrium for remodelling of the spiral arteries. In case of an absent decidua, the EVTs colonize further into the myometrium, possibly resulting in the remodelling of the arcuate and radial arteries. This would result in dilating of these vessels. Placenta increta and percreta follow a slightly different mechanism, not initially caused by the abnormal invasion of EVTs. The opening of a scar allows the presence of anchoring villi deep into the uterine wall. As a consequence, EVTs can invade deeper into the myometrium and beyond, again resulting in the remodelling of deeper arteries [28].

3.3.4 Early-Onset Fetal Growth Restriction

The last deficiency this report describes is fetal growth restriction (FGR), formerly named intrauterine growth restriction. FGR is diagnosed if a fetus has not reached its growth potential, caused by an insufficient placental function [4, 29]. Fetuses with FGR are at higher risk for perinatal morbidity and mortality, and, depending on the severity of the placental dysfunction, multiple homeostatic disorders, long-term impaired growth and neurodevelopmental problems [30]. Both the placental diameter and volume are smaller in pregnancies complicated with FGR in comparison with normal pregnancies.

In 20-30% of FGR diagnoses, the placental dysfunction is further complicated by inadequate remodelling of the spiral arteries in the first trimester. Leading to a decrease in uteroplacental perfusion, and therefore a decrease in a nutrient exchange between mother and fetus, including oxygen. As a result, the fetus is exposed to high levels of hypoxia. As the growth of the fetus is impaired from the first trimester on, this type of FGR is called early-onset FGR. Late-onset FGR is diagnosed after 32 weeks of gestation, when the fetus grows normally up to the third trimester, but does not gain much weight after [4]. Due to the late development of the pathology, this report will focus on early-onset FGR.

In general, the CO is lower and the SVR is higher in pregnancies complicated by FGR relative to uncomplicated pregnancies [31]. The impaired remodelling of the spiral arteries has multiple consequences for the vascularisation of the placenta. Firstly, the resistance in the uterine and spiral arteries increases, resulting in a decrease in blood flow to the IVS [21, 32]. Combined with the reduced placental volume, the volume of the IVS is reduced, compared to normal pregnancies [33]. Moreover, the blood flow into the IVS is more pulsatile and has a higher velocity, which can damage the placental membrane [32]. The pulsatility of the uterine

arteries is also increased [8, 32].

3.4 Hemodynamics

The model that will be described in this report, simplifies the anatomy and physiology of the placenta into mathematical descriptions based on hemodynamic formulas. The input parameters of the model are the resistances, elastances and the initial and unstressed volumes of the vessels. The output will show the corresponding pressures and flows. The quantities and units are also shown in appendix A, table 4.

3.4.1 Flow

The flow is a result of the cardiac output (CO). The CO is defined as the product of the heart rate (HR) and the stroke volume (SV), see equation (1) [34]

$$CO = HR * SV. \tag{1}$$

This results in a flow, defined as a volume per time, travelling through a vessel. The quantity of flow is dependent on the resistance.

3.4.2 Resistance

In a tube with a flowing liquid, the resistance depends on the pressure gradient ($\Delta P = P_1 - P_2$) and the flow (Q). These pressures and flow change through time (t). The resistance is smaller when the vessel is dilated. The following equation defines R [34]:

$$R = \frac{8l\mu}{\pi r^4} = \frac{P_1(t) - P_2(t)}{Q(t)}. \tag{2}$$

3.4.3 Volume

The volume it takes to stretch the vessel walls is called the stressed volume. The rest of the volume is unstressed. The unstressed volume (V_u) is the minimal volume in a blood vessel and does not determine the blood flow; the stressed volume does this. The greater the stressed volume, the greater the mean systemic pressure, and the greater the venous return [35, 36]. In this report, the initial volume V will mean the total starting volume in a vessel, so stressed and unstressed combined. The total volume changes over time due to the pulsatility of the blood flow.

3.4.4 Elastance

Elastance (E) is a measure of the stiffness of a blood vessel. It represents the extent to which the blood vessel returns to its original shape once the forces are removed. It is defined using the following formula:

$$E = \frac{P(t)}{V(t) - V_u}. \tag{3}$$

Here, both the pressure and the volume change through time, but the elastance and unstressed volume stay constant. Formula (3) describes the responsive change in pressure as a consequence of volume change. A high elastance indicates a stiff vessel wall and means that a low change in volume is needed for a certain change in pressure [34]. Compliance (C) is the inverse of the elastance: $C = \frac{1}{E}$. It describes the stretchability of a vessel wall [37].
Conclusively, compliance and thus elastance are important factors in determining the pressures and flows within a vessel because of their mutual connections.

4 Methods

4.1 Model Analysis

The model in this report is based on an existing model from Radboudumc. It is a lumped compartment model, with the input parameters consisting of initial volume, resistance, and elastance. From this, the output is computed and displayed in the form of flows and pressures [38]. In figure 5, the full-body hemodynamic model as used by Radboudumc can be seen.

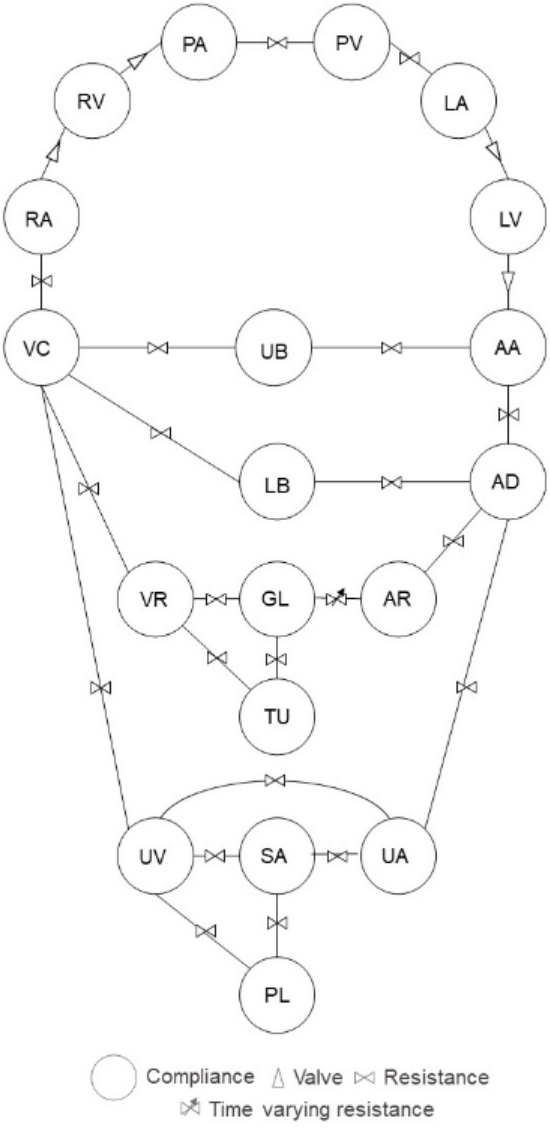


Figure 5: Hemodynamic model of the pregnant women that already existed from research at Radboudumc. The compartments are: pulmonary veins (PV), left atrium (LA), left ventricle (LV), ascending aorta (AA), descending aorta (AD), upper body (UB), lower body (LB), renal arteries (AR), glomerulus (GL), renal tubule (TU), renal veins (VR), uterine arteries (UA), spiral arteries (SA), placenta (PL), uterine veins (UV), vena cava (VC), right atrium (RA), right ventricle (RV), and pulmonary arteries (PA) [38].

In this model, the circles are called compliances and represent compartments. A compartment is a vascular volume filled with blood, with its accessory elastance and pressure. These compartments can be described using equation (3). Between these compartments, there are connectors which are described as resistances, defined by equation (2). The valves, seen in figure 5, are connectors with an infinite backward resistance, meaning that there is no back flow possible. These valves are not present in the placenta, so these will not be elaborated on in this report.

This report presents a slightly adjusted version of the hemodynamics in the uterus and maternal side of the placenta, as can be seen in figure 6. In both versions, the uterine arteries (UA) also include the arcuate and radial arteries in the uterus. The uterine veins (UV) include the endometrial veins. There are two extra connections between the compartments UA-UV and SA-UV. The connection between UA-UV represents the arteriovenous shunt, which is described in section 3.1.1. The connection between the SA-UV on the other hand, represents the blood supply to the tissue of the uterine wall. The difference between the two models is that the placenta (PL) compartment has been renamed to the intervillous space (IVS) compartment. This change is made because the placenta includes both the maternal and fetal circulation, which are not connected. This report focuses only on the maternal circulation, which is covered by the IVS.

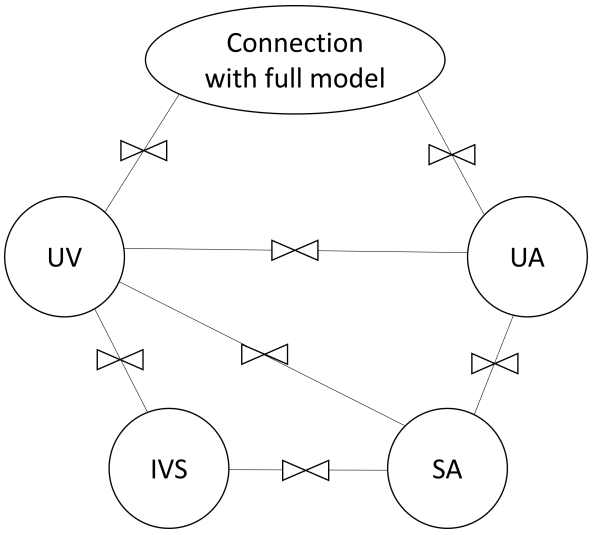


Figure 6: Adjusted model of the uterus and maternal part of the placenta. The compartments represent the uterine veins (UV), uterine arteries (UA), intervillous space (IVS), and spiral arteries (SA).

The model is a simplified version of the hemodynamic system; the model assumes a laminar blood flow and does not incorporate the blood viscosity [38]. The system is dynamic in nature. Specifically, the underlying mathematics of the model are linear and time-invariant (LTI), making the model an LTI-system [39]. The behaviour of this computational model is developed using the programming language Python in the program Jupyter.

To get a clearer view on how the pressures, flows, and volumes are simulated in the computational model, an explanation will follow using a simplified version of the lumped model. This simplified model consists of only two compartments connected by one resistance, seen in figure 7. The surrounding pressure is set to zero, making the pressures in compartments 1 (P_1) and 2 (P_2) only dependent on the parameters within the system. The example illustrated here applies to the whole model. The model can be interpreted as a complex interconnection of several of these examples placed after one another.

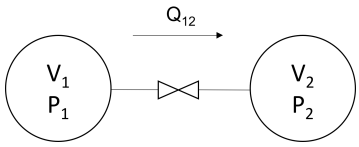


Figure 7: Simplified lumped model showing only two compartments with time dependent volumes (V_1, V_2), and pressures (P_1, P_2), and flow (Q_{12}) from compartment 1 to 2.

The compartments are connected by a resistance, which influences the pressure difference and the flow between two compartments. This flow (Q_{12}) is the volume moving from compartment 1 to 2. The total volume (V) in this closed system is distributed over compartment 1 (V_1) and compartment 2 (V_2). This distribution of volume is dependent on pressures and elastances of the compartments. These relations will be described in the following equations:

$$V = \begin{bmatrix} V_1(t) \\ V_2(t) \end{bmatrix}. \tag{4}$$

Here, V shows the dependency of $V_1(t)$ and $V_2(t)$. Due to the closed system, the total volume stays constant, but $V_1(t)$ and $V_2(t)$ change over time. Their initial value, the starting volumes, are input parameters for the model.

The pressure in a compartment follows from its volume:

$$P_1 = F_1(V_1), \tag{5}$$

$$P_2 = F_2(V_2). \tag{6}$$

Here, F_1 and F_2 represent the functions describing the relation of volume difference affecting the pressure, following equation (3).

The other output parameter, the flow, is dependent on the pressure gradient between two compartments,

$$Q_{12} = F_3(P_1, P_2). \tag{7}$$

Here, F_3 describes the relation between pressure and flow, F_3 is called resistance and follows from equation (2). The condition for this equation to be true and implementable in the model is that $P_1 > P_2$.
The volumes in the two compartment change according to the following equations:

$$V_1(t+h) = V_1(t) - hQ_{12}(t), \tag{8}$$

$$V_2(t+h) = V_2(t) + hQ_{12}(t). \tag{9}$$

Here, h is the time step. It shows that the volume at time t is dependent on the volume one time step before. Furthermore, the change in volume is dependent on the value of flow, which shows how much volume enters or leaves a compartment per time step h. Because the volume flows from compartment 1 to 2, equation (8) shows a subtraction of flow, and equation (9) an addition of flow.

Differentiation in time of this equation results in the equation describing flow, as flow is defined as the movement of volume per time.

$$V'(t) = Q(t) = \begin{bmatrix} -V_1'(t) \\ V_2'(t) \end{bmatrix} = \begin{bmatrix} -Q_{12}(t) \\ Q_{12}(t) \end{bmatrix} = \begin{bmatrix} F_3(P_1, P_2) \end{bmatrix} = \begin{bmatrix} F_4(V_1, V_2) \end{bmatrix}. \tag{10}$$

For additional explanation, the formulas explained above have been implemented in MATLAB to obtain corresponding plots, shown in Appendix B.

4.2 Parameters for Uncomplicated Pregnancy

To simulate the behaviour of the pressures, flows, and volumes of the different compartments, as explained in the example above, values for the input parameters are needed. The values for resistance, elastance, initial volume and unstressed volume were obtained from scientific literature and unpublished research by Radboudumc, calculated based on hemodynamic equations (3) and (5), or estimated based on literature or Python plots.

The gestational ages that are focussed on in this report are week 13 and week 20, corresponding to the end of the first trimester and the middle of pregnancy. This choice is made because of the dilatation of the spiral arteries starting at the end of the first trimester and the hypertensive pathologies occurring after week 20 [18, 22]. Initially, the model that was used was only suitable for a first trimester pregnancy. During research, obstacles were experienced in finding values for the first trimester. Moreover, the pathologies that this report focuses on do not show noticeable changes in the first trimester. This put together resulted in the decision to include simulations for the second trimester, serving for a better comparison between both the first trimester pregnancy and the uncomplicated second trimester pregnancy. These input parameters are based on the healthy pregnant body. To create the behaviour of the second trimester pregnancy in the full-body model, changes were made to the SVR and the heartbeat.

To find the input parameters for the placenta, the resistances between two blood compartments needed to be determined. Since these values were not available in literature, the mean pressure gradients and flows between compartments were used in equation (3) to calculate the resistances. The outcomes can be seen in table 1. The flows and pressures presented in table 1 were not implemented in the model, as the model calculates these parameters based on the resistances, initial volumes, unstressed volumes and elastances that are put into the model. They were used as averages to calculate the resistances between different compartments. As stated by research by Shen et al., the mean arterial pressure does not change noticeably between week 13 and week 20 [40]. Based on this research, the blood pressures in the different compartments are set equal in trimester one and two.

The assumption is made that the placenta is a closed-loop system, which means there is no leakage of blood. With this assumption, it can be concluded that the input flow entering the uterine arteries is similar to the output flow leaving the uterine veins. Furthermore, this assumption is used to calculate the average flow values between compartments. For example, the average flow from the spiral arteries to the uterine veins (SA-UV) is calculated by subtracting the known average flow going from the spiral arteries to the intervillous space (SA-IVS) from the known average flow entering the spiral arteries (UA-SA). This is because the flow is constant in a series circuit, but splits when in parallel, based on Kirchhoff's laws [41]. For visualisation, see figure 6.

In addition to the values of the resistances between two compartments, there are also input parameters for the compartments. These parameters are the initial volume (V), unstressed volume (V_u) and the elastance (E). All values can be seen in table 2.

For the uterine artery and the uterine vein compartments, no values were found in the literature for the volumes and elastances. Hence, values were used from unpublished research by Radboudumc. This research focussed on the third trimester, making certain values for the compartments less applicable due to the development of the placental vessels. However, the initial volumes and elastances of the uterine arteries and veins were assumed to be constant throughout pregnancy.

The average volumes of the total amount of spiral arteries and intervillous space were obtained from literature. Subsequently, these volumes were used to calculate the corresponding unstressed volumes. According to S. Magder, 25-30% of the total blood volume in the circulation is stressed volume, meaning that this volume stretches the vessel walls [36]. Consequently, it can be said that 75% of the initial volume is unstressed volume. The result of this calculation is shown in table 2.
Lastly, the elastances were calculated using equation (5), where ΔV is the unstressed volume (V_u) subtracted from the initial volume (V).

Table 1: Average pressure gradients and flows between the placental compartments used to calculate the corresponding resistances. The compartments are uterine arteries (UA), spiral arteries (SA), intervillous space (IVS), and uterine veins (UV). Also showing the flow entering the UA from the descending aorta (AD-UA).

		1^{st} Trimester	2^{nd} Trimester
AD-UA	Q	0.0051 [42, 43]	0.0086 [44]
UA-UV	ΔP	83 [45]	83 [45]
	Q	0.0023*	0.00152 [46]
	R	36086.96°	54605.26°
UA-SA	ΔP	20 [45]	20 [45]
	Q	0.0028*	0.00703°
	R	7142.86°	2844.95°
SA-UV	ΔP	63 [45, 47]	63 [45, 47]
	Q	0.0012°	0.00019°
	R	52500°	331578.95°
SA-IVS	ΔP	60 [45]	60 [45]
	Q	0.0016 [45]	0.00684 [48]
	R	37500°	8771.93°
IVS-UV	ΔP	3.0 [45, 47]	3.0 [45, 47]
	Q	0.0016 [45]	0.00684 [48]
	R	1875°	438.60°

*Units are as follows: pressure (P) in mmHg, flow (Q) in L/s and resistance (R) in mmHg*s/L. °values are based on calculations, and *values are estimations.*

Table 2: Initial volumes, unstressed volumes and elastances in the placental compartments used in the computational model. The compartments are: uterine arteries (UA), spiral arteries (SA), intervillous space (IVS), and uterine veins (UV).

		1^{st} Trimester	2^{nd} Trimester
	HR	69	88
UA	V	0.28^{+}	0.28^{+}
	V_u	0.21^{+}	0.21^{+}
	E	1143^{+}	1143^{+}
SA	V	0.0479 [49]	0.060 [49]
	V_u	0.0359°	0.045°
	E	5845.51°	4666.67°
IVS	V	0.032 [50]	0.044 [50]
	V_u	0.024°	0.033°
	E	1250°	909.09°
UV	V	0.5^{+}	0.5^{+}
	V_u	0.4^{+}	0.4^{+}
	E	64^{+}	64^{+}

Units are as follows: heart rate (HR) in bpm, initial volume (V) in L, unstressed volume (V_u) in L and elastance (E) in mmHg/L. °values are based on calculations, and $^{+}$values are based on unpublished research at Radboudumc.

4.3 Parameters for Pathologies

In addition to healthy pregnancy, this report focusses on the difference in pressures and flow due to adaptations occurring in gestational hypertension, early-onset preeclampsia, placenta accreta syndrome and early-onset fetal growth restriction. To simulate these pathologies, certain input parameters were altered to be in agreement with the pathophysiology. In table 3, the factors by which the values of a healthy second trimester were multiplied for each pathology are presented. For the exact input values per pathology, see the additional table in Appendix A, table 5. In the model, the SVR encompasses all the resistances except for the resistances in the heart and lungs (VC-RA, RA-RV, RV-PA, PA-PV, PV-LA, LA-LV, LV-AA).

4.3.1 Gestational Hypertension Type 1

As mentioned in section 3.3.1, the SVR rises in GH type 1. Research by Gyselaers et al. showed that the SVR in GH is 1.17 times higher than in a healthy second trimester [51]. To simulate this, all the resistances of the compartments included in the SVR in the second trimester were multiplied by a factor of 1.17. The rest of the input parameters were kept the same for simulating GH.

4.3.2 Early-Onset Preeclampsia

Like in GH, the SVR rises in PE. The SVR increases with a factor of 1.53 in comparison with uncomplicated second trimester pregnancies [51]. In addition, the venous compliance decreases due to the inflammation in the veins [22]. As compliance is the inverse of elastance, the elastance increases. Venous elastance was increased with the same factor of 1.53, as concrete values or factors for this parameter could not be found in literature.

PE is, as discussed, marked by insufficient remodelling of the spiral arteries [6]. However, the effect of this on the quantitive resistance was not found in the literature. Therefore, the resistances UA-SA and SA-IVS were set equal to those in the first trimester. Furthermore, the volume and unstressed volume of SA were set equal to the first trimester, since the spiral

arteries do not dilate and therefore cannot contain as much blood as in a healthy second trimester pregnancy.

4.3.3 Placenta Accreta Syndrome

The remodelling of the arcuate and radial arteries, as happens in PAS, was simulated by changing the volume and elastance of the UA and the resistance between UA-SA. As described before, the arcuate and radial arteries are included in the compartment UA. It was assumed that all three arteries have an equal share in the total volume and elastance of the compartment UA and in the resistance of UA-SA. These total changes in quantities are less visible than would have been the case if the arcuate and radial arteries were a separate compartment from the uterine arteries. It was also assumed that the arcuate and radial arteries are remodelled to the same extent as the spiral arteries. Using the factorial changes between the healthy first and second trimester of the volume (1.25), elastance (0.8) and resistance (0.4) of the spiral arteries, the factors for the UA and UA-SA in PAS were calculated. These calculations were as follows: $\frac{1+f+f}{3}$, with f being the factorial change of the spiral arteries, so 1.25, 0.8 or 0.4. The factors presented in table 3 are therefore the mean of the remodelled arcuate and radial arteries and the unchanged uterine arteries.

4.3.4 Early-Onset Fetal Growth Restriction

For simulating early-onset FGR, the placental dysfunction was assumed to be a result of the inadequate remodelling of the spiral arteries, as described in section 3.3.4. As seen in research by D. Farsetti et al., the SVR of a patient with FGR is increased with a factor of 1.34, compared to the healthy situation in the second trimester [52]. Because the spiral arteries are less remodelled in the second trimester than in a healthy pregnancy, the resistance value of UA-SA and SA-IVS was set equal to the resistance in the first trimester. In addition, the volume of the SA was set equal to the first trimester, because the assumption was made there is no dilatation of the spiral arteries. Therefore, the volume and unstressed volume were changed with a factor of 0.80. Lastly, the volume of IVS was decreased compared to the uncomplicated second trimester. This is because it decreases with a factor of 0.71, compared to the normal volume of the IVS at term [33].

Table 3: Multiplication factors for modelling gestational hypertension (GH), preeclampsia (PE), placenta accreta syndrome (PAS) and fetal growth restriction (FGR), relative to the values of the second trimester in healthy pregnancies (HP). The compartments are: systemic vascular resistance (SVR), the uterine arteries (UA), uterine veins (UV), spiral arteries (SA), intervillous space (IVS). Quantities are: resistance (R), volume (V), unstressed volume (V_u), and elastance (E). * Veins comprises the upper body, lower body, renal veins, vena cava and pulmonary veins.

		HP	GH	PE	PAS	FGR
SVR	R	1	1.17	1.53	1	1.34
UA-UV	R	1	1.17	1.53	1	1.34
UA-SA	R	1	1.17	2.51	0.60	2.51
SA-UV	R	1	1.17	1.53	1	1.34
SA-IVS	R	1	1.17	4.27	1	4.27
IVS-UV	R	1	1.17	1.53	1	1.34
UA	V	1	1	1	1.17	1
	V_u	1	1	1	1.17	1
	E	1	1	1	0.87	1
SA	V	1	1	0.80	1	0.80
	V_u	1	1	0.80	1	0.80
	E	1	1	1	1	1
IVS	V	1	1	1	1	0.71
	V_u	1	1	1	1	0.71
	E	1	1	1	1	1
UV	V	1	1	1	1	1
	V_u	1	1	1	1	1
	E	1	1	1.53	1	1
Veins*	E	1	1	1.53	1	1

5 Results

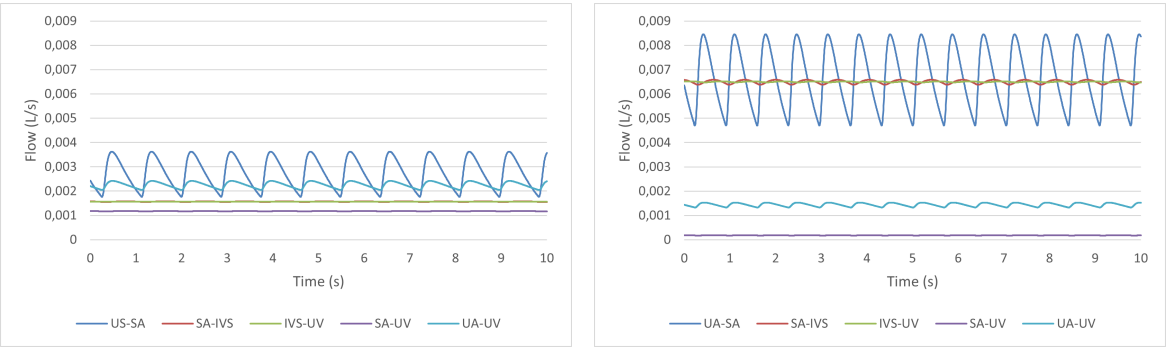
Pressures and flows of the placental compartments were plotted with the resistances from table 1 and the elastances and volumes from table 2 and table 3. From this section onward, the terms 'pressure' and 'flow' refer to the flows and pressures resulting from the plots, not the average flows and pressures from literature used to calculate resistances in section 4.2.

5.1 Uncomplicated Pregnancy

5.1.1 Flows

The flows and pressures in healthy conditions in the first and second trimester can be seen in figures 8a, 8b, 9a and 9b. The flows in the second trimester are considerably higher than in the first trimester, except for the UA-UV flow. The flow in this shunt decreases from 0.0026 L/s in the first trimester to 0.0014 L/s in the second trimester. One other aspect that stands out, is the flow from the UA to the SA and IVS. This flow has a larger increase than the other flows. Another notable thing is that the SA-IVS and IVS-UV flow are almost the same and are close to the equilibrium position of the UA-SA flow.

Additionally, the pulsatility can be deduced from figure 8a and 8b. The UA-SA flow has the highest pulsatility. Furthermore, the difference in pulsatility in this artery in the first and second trimester is conspicuous. Lastly, the intervals between the peaks are shorter in the second trimester, which corresponds to the increased heart rate.



(a) The flow in the first trimester

(b) The flow in the second trimester

Figure 8: Flows between the uterine arteries and spiral arteries (UA-SA), the spiral arteries and intervillous space (SA-IVS), the intervillous space and the uterine veins (IVS-UV), the uterine arteries and veins (UA-UV) and the spiral arteries and uterine veins (SA-UV) in the first and second trimester in healthy pregnancy.

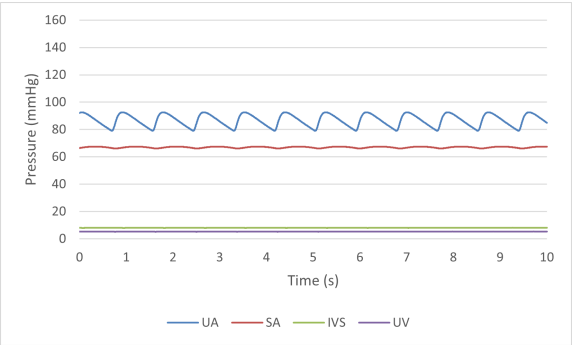
5.1.2 Pressures

It varies per compartment whether the pressure goes up or down in the second trimester, see figure 9a and 9b. For example, the pressures of the UA and the SA are lower in the second trimester than the first trimester. However, the pressures in the UV and IVS are higher in the second trimester. Additionally, the increased heart rate in the second trimester is noticeable in the plots.

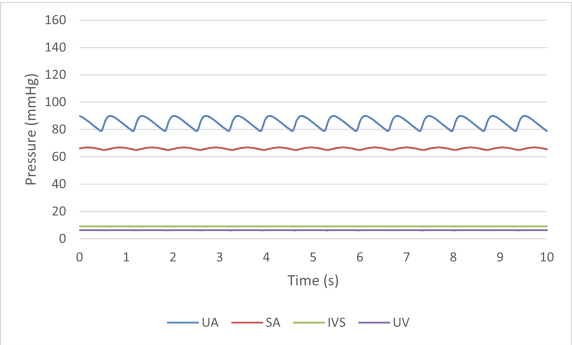
5.2 Gestational Hypertension Type 1

5.2.1 Flows

The flows in the placenta in GH can be seen in figure 10a. In comparison to uncomplicated pregnancy, all flows within the placenta between compartments decreased in GH with the same factor of circa 10%. Also, the pulsatility between UA-SA decreased, compared to the uncomplicated second trimester as seen in figure 8b.



(a) The pressures in the first trimester

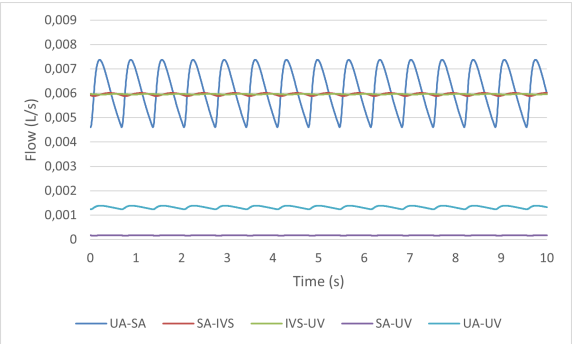


(b) The pressures in the second trimester

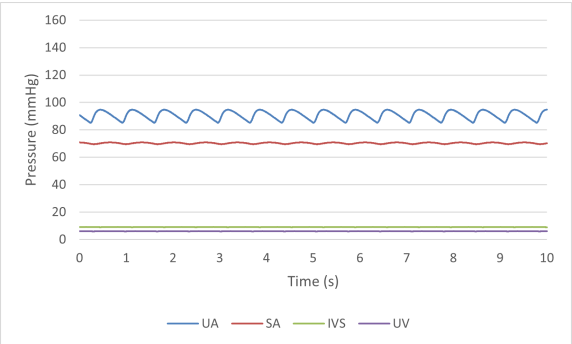
Figure 9: Pressures in the uterine arteries (UA), spiral arteries (SA), intervillous space (IVS) and uterine veins (UV) in the first and second trimester.

5.2.2 Pressures

The pressures in the placental compartments are shown in figure 10b. The pressures in the UA, SA and IVS rose. Only in the UV the pressure lowered, compared to the uncomplicated second trimester pregnancy as seen in figure 9b. As shown in figure 11, the input parameters of the simulation did not result in hypertension.



(a) The flows in gestational hypertension



(b) The pressures in gestational hypertension

Figure 10: Flows between the uterine arteries and spiral arteries (UA-SA), the spiral arteries and intervillous space (SA-IVS), the intervillous space and the uterine veins (IVS-UV), the uterine arteries and veins (UA-UV) and the spiral arteries and uterine veins (SA-UV), and pressures in the uterine arteries (UA), spiral arteries (SA), intervillous space (IVS) and uterine veins (UV) in the second trimester in gestational hypertension.

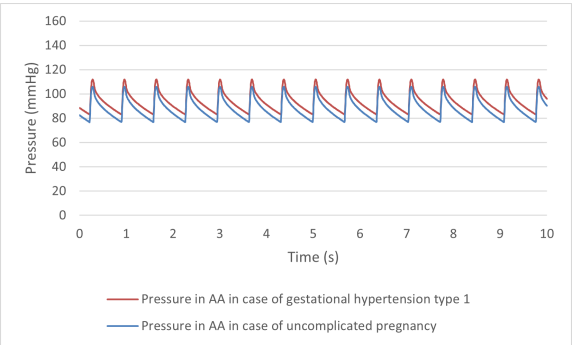


Figure 11: Pressures in the ascending aorta (AA) in uncomplicated pregnancy and in gestational hypertension type 1 in the second trimester.

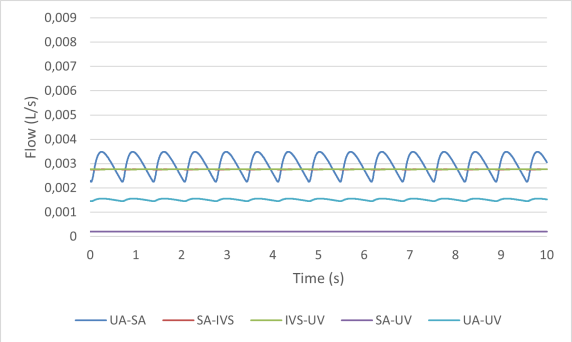
5.3 Early-Onset Preeclampsia

5.3.1 Flows

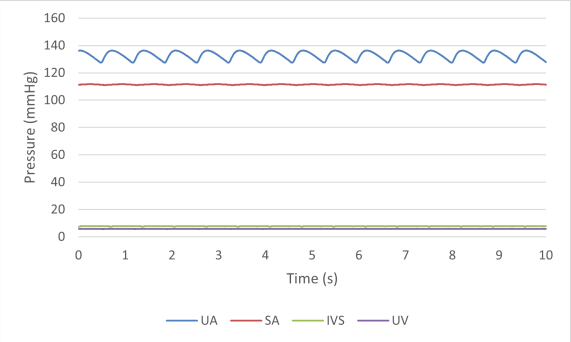
The SA-IVS and IVS-UV flows oscillate around the same equilibrium as the UA-SA flow, as shown in figure 12a. Compared to the situation in healthy pregnancy in the second trimester, which is shown in figure 8b, this is identical. Only the amplitude of the flow in the UA-SA is less, and the oscillation in the SA-IVS and IVS-UV flow is almost non-existent. Furthermore, the flows of UA-SA, SA-IVS and IVS-UV are reduced relative to the healthy first trimester. The flows of UA-UV and SA-UV, on the other hand, increased.

5.3.2 Pressures

The pressure in the UA oscillates between 136-127 mmHg. The pressures in SA, IVS and UV almost show no oscillation. The pressure in SA is almost 111 mmHg and the pressures in IVS and UV are below 10 mmHg. This can be seen in figure 12b. Comparing these pressures to the pressures in the healthy situation in the second trimester, shown in figure 9b, the pressures of the UA and SA are increased. The UA pressure increases by 51.6% and the SA pressure even increases by 67.1%. On the contrary, the pressures in the IVS and the UV decrease. Especially, the pressure in the IVS reduced by 14.8%.



(a) The flows in early-onset preeclampsia



(b) The pressures in early-onset preeclampsia

Figure 12: Flows between the uterine arteries and spiral arteries (UA-SA), the spiral arteries and intervillous space (SA-IVS), the intervillous space and the uterine veins (IVS-UV), the uterine arteries and veins (UA-UV) and the spiral arteries and uterine veins (SA-UV), and pressures in the uterine arteries (UA), spiral arteries (SA), intervillous space (IVS) and uterine veins (UV) in the second trimester in early-onset preeclampsia.

The blood pressure in the ascending aorta (AA) was compared with the healthy blood pressure in the AA, to see if hypertension was indeed simulated. The pressure in the AA is shown in figure 13. The pressure in AA is 160/124 mmHg in PE, as opposed to the AA pressure of 106/77 mmHg in healthy conditions.

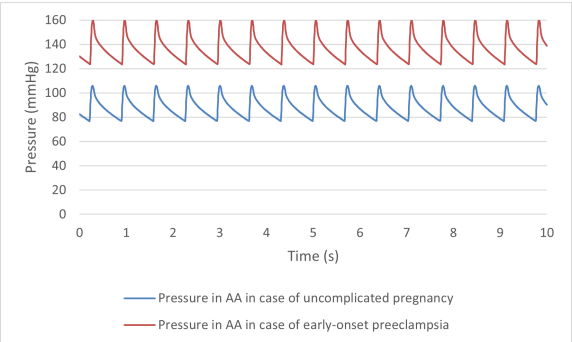


Figure 13: Pressures in the ascending aorta (AA) in uncomplicated pregnancy and in early-onset preeclampsia in the second trimester.

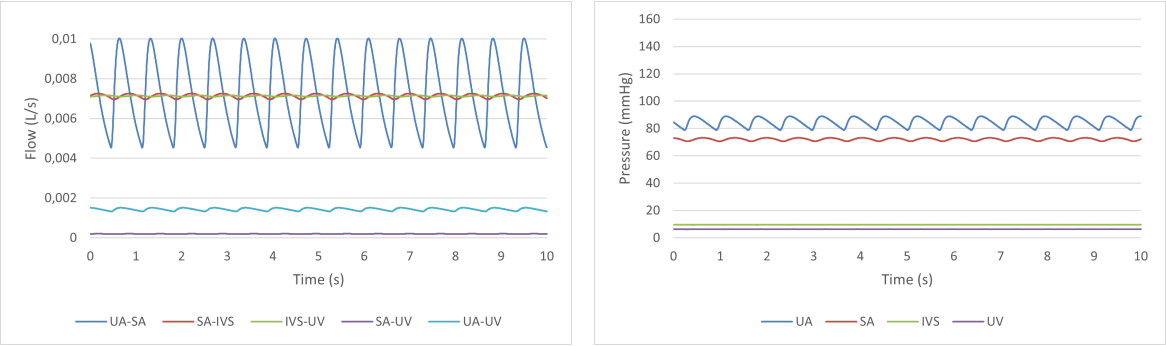
5.4 Placenta Accreta Syndrome

5.4.1 Flows

The flows of the PAS simulation are shown in figure 14a. Compared to the uncomplicated second trimester shown in figure 8b, all flows have increased, except for the UA-UV flow, which decreased. Looking at the percentage difference, the SA-IVS flow changed the most, with a 9.8% increase from 0.00650 L/s to 0.00714 L/s. The IVS-UV flow increased by 9.7% and the UA-SA flow by 8.9%. On the contrary, the UA-UV flow decreased by 0.79%. Furthermore, the amplitude of the UA-SA flow has increased in comparison with the uncomplicated second trimester.

5.4.2 Pressures

Figure 14b shows the blood pressures in the second trimester in a patient with PAS. The SA, IVS and UV pressures have increased and the UA pressure has decreased, compared to the blood pressures in the uncomplicated second trimester, shown in figure 9b. Looking at the percentage difference between the maximal pressures during PAS and uncomplicated second trimester, the maximal pressures in the SA, IVS and UV increased by 9.5%, 5.2% and 3.2%, respectively, while the maximal pressure in the UA decreased by 1.8%.



(a) The flows in placenta accreta syndrome

(b) The pressures in placenta accreta syndrome

Figure 14: Flows between the uterine arteries and spiral arteries (UA-SA), the spiral arteries and intervillous space (SA-IVS), the intervillous space and the uterine veins (IVS-UV), the uterine arteries and veins (UA-UV) and the spiral arteries and uterine veins (SA-UV), and pressures in the uterine arteries (UA), spiral arteries (SA), intervillous space (IVS) and uterine veins (UV) in the second trimester in placenta accreta syndrome.

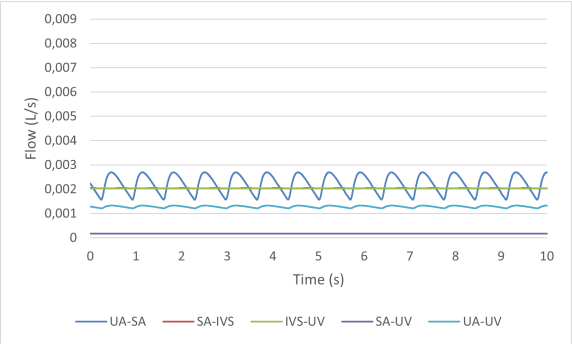
5.5 Early-Onset Fetal Growth Restricion

5.5.1 Flows

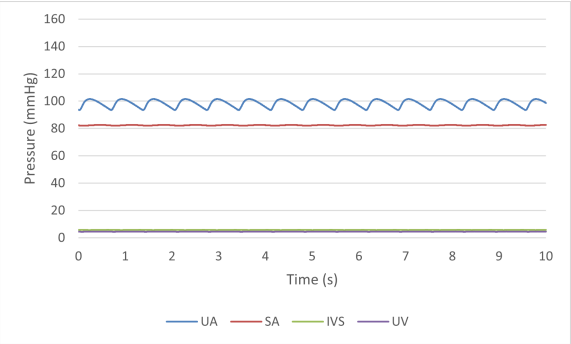
Figure 15a illustrates the flows with the input parameters described in table 3 to approach the hemodynamic behaviour of FGR. Compared to the flows of an uncomplicated second trimester, as shown in figure 8b, all flows in FGR underwent a reduction. The flows between the UA-SA, SA-IVS and IVS-UV fell by approximately 66%, whereas the flows between the UA-UV and SA-UV only by approximately 10%, compared to the uncomplicated situation.

5.5.2 Pressures

Compared to the pressures in figure 9b, showing the situation in an uncomplicated second trimester, the pressures in UA and SA in FGR are elevated, while on the other hand, the pressures in the IVS and UV are reduced. Figure 15b illustrates this behaviour. The pressure in the AA in the case of FGR is higher than in the case of uncomplicated pregnancy in the second trimester, see figure 16. By contrast, the pressure is not as high as it would be with hypertension.



(a) The flows in fetal growth restriction



(b) The pressures in fetal growth restriction

Figure 15: Flows between the uterine arteries and spiral arteries (UA-SA), the spiral arteries and intervillous space (SA-IVS), the intervillous space and the uterine veins (IVS-UV), the uterine arteries and veins (UA-UV) and the spiral arteries and uterine veins (SA-UV), and pressures in the uterine arteries (UA), spiral arteries (SA), intervillous space (IVS) and uterine veins (UV) in the second trimester in fetal growth restriction.

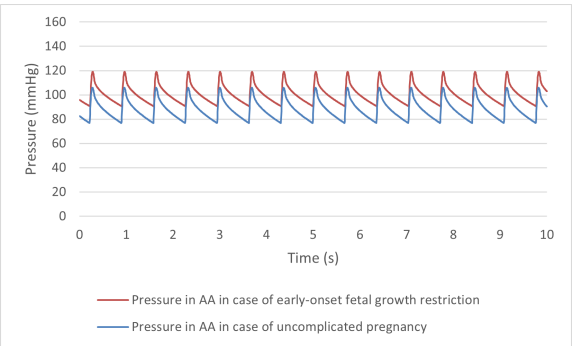


Figure 16: Pressures in the ascending aorta (AA) in uncomplicated pregnancy and in fetal growth restriction (FGR) in the second trimester.

6 Discussion

6.1 Uncomplicated Pregnancy

6.1.1 Flows

In the second trimester, the UA-SA flow rises, which is to be expected because the SA are more dilated in the second trimester than in the first trimester. The SA-IVS flow also rises in the second trimester. Hence, the UA-SA shunt flow falls, as shown in figure 8b. The SA-IVS and IVS-UV flows increased with the same value. Because of the high resistance and thus low flow between SA-UV in the second trimester, the flows of SA-IVS and IVS-UV are in the range of the equilibrium of the UA-SA flow. The SA-IVS flow can be distinguished by the pulsatility that is still present. The IVS-UV flow is reduced in pulsatility compared to the SA-IVS flow, because the elastance in the UV is lower than in the IVS, resulting in a more constant flow.

6.1.2 Pressures

All simulated pressures in the second trimester are lower than in the first trimester. The biggest difference in pressure from the first to the second trimester is 3 mmHg in the SA, which was considered as negligible. Furthermore, the frequency of oscillation is higher in the second trimester, which represents the increased heart rate.

6.2 Gestational Hypertension Type 1

The approach to simulate the resistance-dominated GH (type 1) was based on an elevation of the SVR found in literature, see section 3.3.1. However, the exact cause of GH often remains unknown. With this, the possible influence of other pathological mechanisms on developing hypertension remains unknown as well.

6.2.1 Flows

The relative change in flow, as described in section 5.2.1, is equal between all compartments. This was to be expected as the increase of the resistance between all compartments was set equal. Besides, a decreased pulsatility of the flows could be observed. This is possibly the consequence of the elevated SVR on the heart. An elevation of the SVR requires more effort from the heart to maintain a constant CO. This effort might be too much for the heart muscle to compensate, explaining the decrease in pulsatility.

6.2.2 Pressures

As seen in figure 10b, all pressures rise, except for the one in the uterine vein. This pressure even falls. This pressure fall could be explained by the same mechanism, regarding the lowered CO, as described for the flows. As CO is also a flow, a decrease in the CO leads to a decrease in circulating volume, in turn leading to a decrease in pressure.

Furthermore, when analysing the simulated pressures, there is no evidence of hypertension. Firstly, the placental arteries show no hypertension, but when evaluating this in the ascending aorta, there is still no hypertension. The blood pressures obtained with the factor of 1.17 for the SVR result in 111-82 mmHg, as can be seen in figure 11. As explained earlier in this section, this might follow from the missing underlying pathologic changes in this simulation.

6.3 Early-Onset Preeclampsia

When analysing the plots, attention should be paid to the fact that the factor of 1.53 for the change in venous elastance probably does not render reality. The venous elastance does surely increase, however, the precise factor remains unsure. The same applies to the resistances between UA-SA and SA-IVS, which were set equal to those in the first trimester in the absence of quantitive values for the resistances between these compartments. In addition, the initial volume and unstressed volume of the spiral arteries that are kept equal to the first trimester may give a less reliable simulation of the hemodynamic behaviour in PE.

6.3.1 Flows

The oscillation of the UA-SA flow is less in PE than in uncomplicated pregnancies in the second trimester. Furthermore, the equilibrium of the UA-SA flow is lower in PE. As in early-onset PE the spiral arteries do not dilate properly, the volume in SA decreases. This decrease in volume leads to a lower flow and a lower oscillation in flow. Consequently, the SA-IVS and IVS-UV flows are lower than in uncomplicated pregnancies, as this flow directly originates from the spiral arteries.

The UA-UV flow has risen, due to the trophoblast plugs in the spiral arteries that cause a higher resistance. Thereby, the blood flow through the shunt increases as the relative resistance of this way decreases.

The volume of the UA is higher, whereas that of the UV is lower. An explanation for this observation may stem from the elevated resistance between UA-SA and the decreased volume of the spiral arteries. In humans, this physiologically results in venous congestion and oedema. The model is not able to simulate oedema, and therefore the volume that otherwise would result in oedema now probably stacks in the uterine artery.

6.3.2 Pressures

Not all pressures were increased, as seen in figure 12b, even though all the resistances were increased. The UA-SA resistance was more increased than the SVR, as the undilated spiral arteries have to be taken into account as well. This increase in resistance may well explain the increase in pressure in the UA and SA, see equation (3). However, the decrease in the pressure in IVS and UV can not be explained by this argument. This decrease may be due to the reduced initial volume of the SA in PE. Equation (5) can explain why the pressure can decrease in this pathology; when the difference in initial volume and unstressed volume is less, the pressure will also be less.

PE is characterized by a blood pressure higher than 140/90 mmHg. In the placental vessels, this was not visible. Therefore, these altered values were tested by plotting the pressure in the ascending aorta (AA). As a result of both an increase in peripheral resistance between all compartments and an increase in all venous elastances, high blood pressure has come about. When only increasing the resistance, the desired result is not obtained, as seen in the simulation of GH. Only when incorporating the venous elastance, hypertension follows in the simulation. A high venous elastance lowers the ability of the veins to retain blood and expand. This leads to a higher pressure, as the same amount of blood has to travel through a less stretchable vein. The pressure shown in figure 13 is 160/122 mmHg, elevated as expected. The systolic blood pressure of 160 mmHg is realistic. The diastolic pressure, on the other hand, is on the high side.

6.4 Placenta Accreta Syndrome

To simulate PAS, changes have been made around the UA compartment. This is because of the remodelling of the arcuate and radial arteries, which are included in the UA compartment. The assumption for the weight factor being the same for the uterine, arcuate and radial arteries within the simulated compartment UA can possibly affect the outcome of the flows and pressures in PAS.

6.4.1 Flows

As discussed in section 5.4.1, all flows have increased compared to the uncomplicated second trimester, except the UA-UV flow. Considering the pathophysiology of PAS, this could be explained by the remodelled, and thus dilated, arcuate and radial arteries which are included in the UA compartment. It is easier for the blood to follow the route with the least resistance, which in this case is to the SA, instead of directly to UV via the shunts. This causes a different distribution of flow compared to a healthy situation.

Due to the remodelling and dilation of the arcuate and radial arteries, the UA volume was increased and the elastance in this compartment was decreased. It would be expected that this decrease in elastance causes a lower pulsatility in the UA-SA flow. In reality, the pulsatility of this flow has increased. This is probably caused by the fact that both the initial volume and the unstressed volume have increased by a factor of 1.17, meaning that the difference between the initial volume and unstressed volume has also increased. This greater difference means a higher pulsatility in the flow.

6.4.2 Pressures

Looking at the blood pressures resulting from the PAS simulation, all pressures in the placenta have increased, except the UA pressure, which decreased. This decrease in pressure could be a result of the decreased elastance and resistance of this compartment. A decreased elastance means a less stiff wall and, consequently, lower pressure. As a result of the increased UA volume, all following compartments have an increased pressure. In these compartments, no physiological changes have been implemented in the model, resulting in a higher pressure due to the increased blood volume.

6.5 Early-Onset Fetal Growth Restriction

As described in section 4.3, FGR was simulated by elevating the SVR and setting the values concerning the spiral arteries equal to the uncomplicated first trimester pregnancy. This includes the volume of the spiral arteries and the resistances between the compartments UA-SA and SA-IVS. According to the literature, the volume of the IVS is decreased as well, with a factor of 0.71 in placentas at term. Here, the assumption is made that this same factor is valid in the second trimester. However, because the placental volume increases still in the third trimester [53], this assumption might be inaccurate.

6.5.1 Flows

The reduced flows seen in figure 15a could be a consequence of the simulated elevation of the SVR. The relatively greater elevation of the resistance between the UA-SA and SA-IVS leads to a corresponding greater fall of flow between these compartments. A higher SVR indicates a more difficult path for the blood through the vessel, hence the same volume takes more time to travel along the same path, resulting in a reduced flow.

Additionally, it is remarkable that despite the inferior increase of SVR in FGR compared to PE, the flows in FGR are lower than those in PE. Physiologically, this may be the result

of a smaller placenta, as the placenta cannot contain as much blood as in PE and healthy pregnancy. Due to the increased SVR, the heart can not make up for this decrease in volume of the placenta, and therefore volume of the IVS, resulting in a lowered flow.

6.5.2 Pressures

The pressure in the IVS and UV are lower in the case of FGR than in the case of an uncomplicated pregnancy, which can be explained by the undilated spiral arteries that precede. On the other hand, the increased pressures in the UA and SA can be explained by the elevation of the SVR. According to the clinical manifestation, the elevation of SVR did not lead to hypertension, as shown in figure 16. However, there is some rise in blood pressure, which is no surprise regarding the elevated SVR.

6.6 Strengths and Limitations

6.6.1 Strengths

Initially, this model was only suitable for the first trimester pregnancy. This report contributed to the concept of a simulation of a second trimester pregnancy as well. This second trimester model has helped with the understanding of the pathologies.

Furthermore, the inclusion of the second trimester assisted in the possibility to simulate the pathologies and to gain insight into the underlying mechanisms. The evaluated pathologies in this report were endeavoured to simulate systemically and not only placental. Despite the placental focus of this report, the whole system was included for a better reflection of reality.

This report also provided an extra validation of the model. After research on the placental function, it was contemplated that the model with the existing compartments was sufficient for simulating the uncomplicated pregnancy. For this conclusion to be made, the contribution of placental vessels to healthy functioning was evaluated again.

Lastly, not only the results were explained, the underlying mechanism of the model was elaborated on as well. This may provide a better understanding of the hemodynamics and the simulated behaviour.

6.6.2 Limitations

Despite the strengths, this report also has limitations. In the previous sections of the discussion, the limitations specific to the outcomes of the different pathologies were mentioned. Additionally, there are some general limitations to this study.

Firstly, the hemodynamic model, shown in figure 5, is a simplified model. Characteristics like the viscosity of the blood or the length and diameter of the vessel were not included. However, these characteristics all affect the resistance. This absence can cause an unrealistic vision of the blood circulation. For example, the viscosity of the blood and the diameter of the blood vessel can cause a turbulent flow [34, 54]. Right now, the flow is considered to be laminar, so the plotted outcomes are quite stable. However, in the IVS, the flow is turbulent when the spiral arteries remodel insufficiently [55]. If the flow is turbulent, the flows and pressures will be unstable.

Furthermore, as shown in tables 1, 2 and 3, visualising all placental input values, not all values were available in literature. Consequently, a lot of input values for the placental compartments of the model are estimates. For example, in PE there is no specific cause from which this syndrome arises, resulting in a unique portrait for each individual. This can be

an explanation for the difference between the results and expectations.

Another limiting factor is the non-vascular volume that could not be simulated. Currently, the system is a closed-loop system, but in reality, the blood circulation is a non-closed-loop system. Fluid can build up in the body as oedema, or the plasma drains into the lymphatic system. Fluid can also be drained through urination or sweating. This could potentially declare the inaccuracies in the results of PE, for example.

Lastly, the model used in this report did not adjust gradually as a real body would. For example, in PE the parameters for SVR and venous elastance are increased and the volume of the spiral arteries is decreased. Normally, the body adapts to a slow change in resistance and elastance by, for example, also gradually lowering the cardiac output. The cardiac output as obtained by the simulation is not representative, as the simulation could not mimic this physiological behaviour. In reality, the body would drain volume by sweating or urinating when CO exerts a certain threshold. To adapt this CO in the simulation, the volume of the vena cava (VC) can be lowered in future studies. In the current simulation, the change of these parameters in the model is abrupt, therewithal the system is not capable of reacting to these abrupt changes in a gradual way like a body can. That is why some outcomes are not as they would be in reality.

6.7 Future Recommendations

Other than in uncomplicated pregnancies, the role of the arcuate and radial arteries in PAS is crucial in the development of the placenta. In this report, these arteries were incorporated within the uterine artery, however, for the simulation of pathologies it should be considered to split the uterine arteries into three different compartments: the arcuate, radial, and uterine arteries.

Additionally, it could be interesting to look further into the role of contractions of the uterus. As briefly mentioned in section 3.2, the recurring contractions during pregnancy influence the blood flow in the intervillous space. It might be useful to implement this in the model, to make the model more realistic.

For the clinical application of this model, it might be useful to have the possibility to incorporate more parameters obtained from the patient, other than only hemodynamic ones. For instance, the laboratory values obtained from blood tests could be incorporated into the model. This way, the influence of molecules in blood on the hemodynamics could be simulated as well. The influence of vasoactive agents on the resistance might be valuable to consider, as well as some proinflammatory or immunosuppressive cytokines affecting the remodelling of the spiral arteries and inflammation of the endothelial wall of the veins. Appending the consequences of toxicology and pharmacology to the hemodynamics might assist in an even more accurate representation of the individual. For instance, the effect of smoking on the vessels can be simulated in the future.

The usage of this model can possibly be enhanced and made more accessible by an extension in the electronic patient dossier. This extension ideally gathers the required information directly from the electronic patient dossier and inserts them as values for the corresponding parameters in the model.

Moreover, adding the third trimester of pregnancy to the model may contribute to the insights and development of certain pathologies. In particular, for those pathologies clinically visible

in the third trimester, a third trimester simulation contributes to the comprehension of the underlying mechanism, but might also point out some clues about the origin.

7 Conclusion

This report was written to answer the following research question: What is the hemodynamic behaviour of the placenta, represented by flows and pressures, simulated with the lumped compartment model, in complicated and uncomplicated pregnancies?

Generally, the simulated flows in the placental compartments decrease when increasing the resistance and increase when raising the volume and elastance of the corresponding compartment. In contrast, the pressures rise in case of a higher resistance and drop in case of a higher volume and elastance of the corresponding compartment. This relation was found in both complicated and uncomplicated pregnancies. This was in line with the expectations and mathematical relations between resistance, pressure, and flow. However, the distribution of volume did not always respond as expected, which is probably a result of the limitations of the current model.

It can be concluded that the proposed model of the placenta, represented by the uterine arteries, spiral arteries, intervillous space and uterine veins, already comes close to the physiology, despite the absence of certain aspects of the body like the fluid drainage and blood properties. Further work can be done to create a more realistic model of the pregnant woman throughout gestation. This way, the model can be used for a better understanding of the hemodynamic changes in complicated and uncomplicated pregnancies. This will improve the care for women wanting to get pregnant, pregnant women and their children.

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A Appendix

Table 4: Overview of used quantities, abbreviations, and units.

Quantity	Abbreviation	Units
Compliance	C	L/mmHg
Cardiac Output	CO	L/s
Pressure	P	mmHg
Flow	Q	L/s
Heart rate	HR	bpm
Stroke Volume	SV	L
Volume	V	L
Unstressed Volume	V_u	L
Resistance	R	mmHg*s/L
Viscosity	μ	kg/m/s
Length of the vessel	l	m
Radius of the vessel	r	m

Table 5: Parameter values in gestational hypertension, preeclampsia, placenta accreta syndrome and fetal growth restriction in the second trimester. Adjusted parameters are printed in bold. This table includes only the placental compartments: the uterine arteries (UA), uterine veins (UV), spiral arteries (SA) and intervillous space (IVS).

		GH	PE	PAS	FGR
UA-UV	R	**63888.15**	**83546.05**	54605.26	**68256.58**
UA-SA	R	**3328.59**	**7142.86**	**1706.97**	**7142.86**
SA-UV	R	**387947.37**	**507315.79**	331578.95	**414473.69**
SA-IVS	R	**10263.16**	**37500**	8771.93	**37500**
IVS-UV	R	**513.16**	**671.06**	438.60	**548.25**
UA	V	0.28	0.28	**0.3276**	0.28
	UV	0.21	0.21	**0.2457**	0.21
	E	1143	1143	**994.41**	1143
SA	V	0.06	**0.0479**	0.06	**0.0479**
	UV	0.045	**0.0359**	0.045	**0.0359**
	E	4666.67	4666.67	4666.67	4666.67
IVS	V	0.044	0.044	0.044	**0.031**
	UV	0.033	0.033	0.033	**0.023**
	E	909.09	909.09	909.09	909.09
UV	V	0.5	0.5	0.5	0.5
	UV	0.4	0.4	0.5	0.4
	E	64	**97.92**	64	64

*Units are as follows: volume (V) in L, unstressed volume (UV) in L, elastance (E) in mmHg/L and resistance (R) in mmHg*s/L*

B Appendix

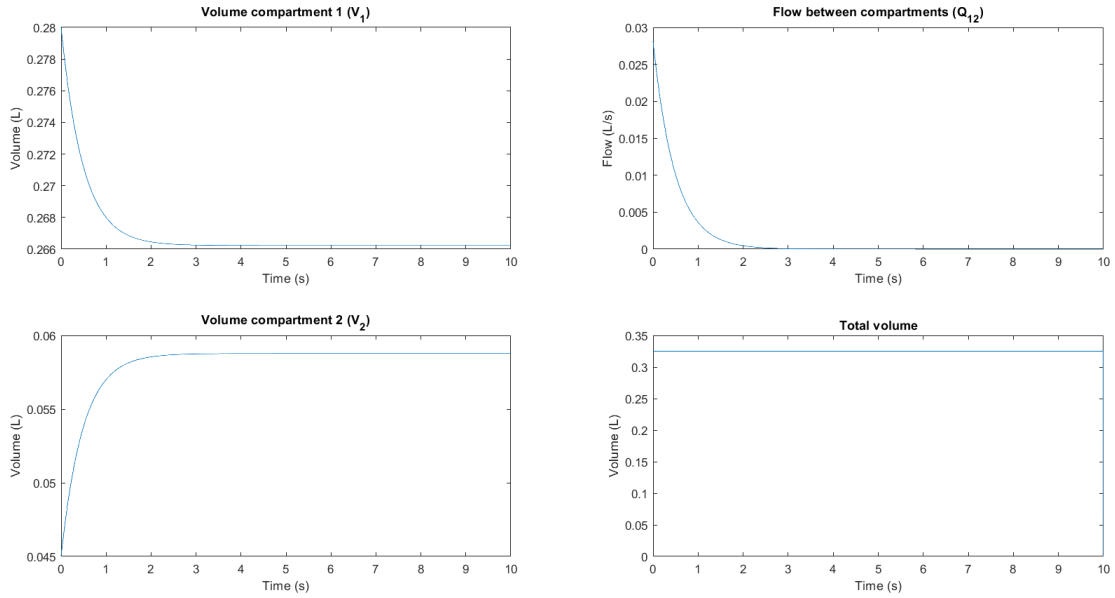

Figure 17: MATLAB plots showing the relation between volume change and flow. The formulas explained in section 4.1 have been implemented in MATLAB, resulting in these plots. Values for elastance and resistance of the uterine arteries (UA) and the spiral arteries (SA) in the second trimester were used. These values can be found in table 1 and 2. A simplified system consisting of only two compartments connected by a resistance is simulated here. As can be seen in the plot, the total volume in this system stays constant. The volume leaves compartment 1 and flows into compartment 2, both reaching an equilibrium. This equilibrium is explained by the pressures in compartment 1 and 2 reaching the same value, seen in figure 18. This results in the flow reaching 0 L/s.

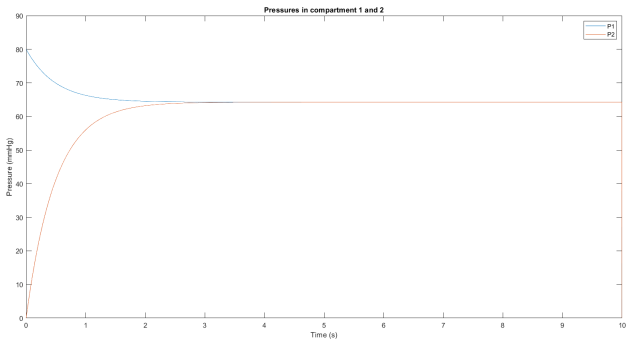

Figure 18: Pressure in compartment 1 (P_1) and compartment 2 (P_2). This shows that the pressures reach the same value, resulting in equilibria for the volumes and thus the flow reaching 0 L/s.