Central Haemodynamics During Pregnancy

Doctoral (Ph.D.) thesis

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INTRODUCTION

Several significant physiological changes are taking place in the body during pregnancy that are necessary for the development of the fetus. These adaptational mechanisms are essential for the successful completion of pregnancy.

Cardiovascular changes appear first in the body, that support healthy development of the fetus by influencing the amount of blood flow towards the placenta, making up for proper oxygen- and nutrient provision.

Nowadays a growing number of pregnant women are diagnosed with preeclampsia, which is one of the most severe syndrome causing relatively high mortality among mothers and fetuses without treatment. The cause of the disease is yet to be clarified – a number of theories were introduced in previous decades, all of which mentioning abnormal placentation.

In the past four-five years new theories on the origin of the syndrome arose. There is no standardised terminology for the syndrome that can be divided to two main groups (based on whether it occurs at early or late gestational age of pregnancy), and differences between the two groups have been described by Hungarian and international scientific literature alike. Differences of haemodynamic parameters between early and late preeclampsia is obvious. Non-invasive haemodynamic measurements can be applied at maternity wards to distinguish between the two entities.

Considering that scientific theories on preeclampsia define two different entities, their treatment calls for more than one therapy.

Diuretics have so far been excluded from treatment of preeclampsia. In my thesis I am describing the type of cases where diuretics can be used to prolong pregnancy and provide fetus' wellbeing.

CARDIOVASCULAR CHANGES DURING PREGNANCY

Both systolic and diastolic blood-pressure readings are lower in the first trimester compared to measures before pregnancy. However, from the second trimester towards the end of pregnancy the blood-pressure slowly increases, and by the 40^{th} week it is approximately similar to the measure before pregnancy.

Growth of blood volume is also an important adaptational change. The normal amount of 4.5-5.5 litres of blood increases with approximately 40% during pregnancy, caused partly by the growth of cells (number of erythrocytes grow by 20 to 30%), and primarily by the growth of plasma volume (by 40 to 50%). A consequence of all this is physiological haemodilution, that provides for the growing blood requirements of the fetus and the developing uterus and prepares the body for blood loss during delivery.

Cardiac output (CO) starts growing in the first trimester of pregnancy and continues to increase until the 28^{th} to 32^{nd} week, when the normal level of cardiac output reaches 130-140% of pre-pregnancy level. Cardiac output hardly changes after the 32^{nd} gestational week in case of physiological pregnancy. Early changes of cardiac output are due to the increasing stroke volume, followed by increased pulse later, also influencing further growth of cardiac output.

Although cardiac output grows during pregnancy, and blood pressure decreases a bit in the beginning, heart rate does not change significantly. This is possible due to the decrease of the entire peripheral resistance and the dilated status of veins. Decrease of peripheral vein resistance contribute to the fact that cardiac output growth does not trigger significant increase in blood pressure. In arterioles, vasodilatation is strongest in uteroplacental arteries. During normal pregnancy, vasodilatation-strengthening agents are dominant within nitrogen-monoxide (NO) and prostaglandin derivatives produced by the endothelium and the placenta. Relative dominance of vasodilator substances make up for dilated veins, thus contributing to uteroplacental circulation.

BLOOD PRESSURE REGULATION

Two factors regulate systemic mean arterial pressure: cardiac output and systemic vascular resistance, which are defined by the current status of resistance arteries and flow features of vein content.

Constant growth of blood pressure is triggered by the single or coordinated growth of CO and SVR. Alongside normal blood pressure regulatory mechanisms, growth of CO leads to proportionate decrease of SVR, and decrease of CO leads to SVR growth, thus blood pressure remains approximately normal. Similarly, primary decrease of SVR leads to the secondary growth of CO, which is the basis of autoregulation.

Opposite secondary changes of SVR and CO, triggered by primary CO and SVR changes depend on a complex regulatory mechanism. Blood pressure difference is corrected by the neural baroreflex mechanism, the receptors of which are located in the carotid artery or in the aorta. Impulses of baroreceptors keep the vascular regulatory centre in the medulla oblongata under a tonic hindrance.

If blood pressure changes in accordance with similar directional changes of pressure in the juxtaglomerular area of the kidneys' afferent arterioles, then the formation of renin, followed by the formation of angiotensin II and aldosterone will be opposite to pressure changes. As part of autoregulation, this process aims normotony as well.

The slowest but most effective long-term blood pressure regulator is the pressure diuresis mechanism, which is the blood pressure dependent Na^+- and water excretion of the kidneys. Increase of perfusion pressure of blood flowing through the kidney elevates the excreted water- and Na^+ content. If the excretion function of the kidneys decline for any reason, diuresis will increase measurably only next to larger blood pressure growth, thus the salt intake growth (higher level of Na^+) will trigger larger increase of blood pressure.

PREECLAMPSIA

140/90 mmHg or above is considered high blood pressure during pregnancy, if this is measured at least twice, with more than 6 hours difference.

Various pathologic factors of pregnancy can appear due to lack of the vascular system's adaptation. Most significant is the preeclampsia, which threatens the life and health of both the mother and the fetus even by timely diagnosis and medical treatment. The severity of the disease and complications can not be presumed, and the development and course of the condition may vary largely. In case of pregnant women with hypertonia, severe complications can be expected (eclampsia, brain haemorrhage, abruptio placentae, disseminated intravascular coagulation, severe liver damage, and acute renal failure).

30% of pregnancy casualties in Hungary are in connection with high blood pressure, and fetal perinatal mortality and morbidity occurs multiple times compared to neonates of mothers with normotony. One of the most important factors in preeclampsia is the narrowing uteroplacental circulation, which is a significant difference both in terms of the development of the disease and the survival rate of the fetus. One consequence of this is the nutritive and oxidative failure of the placenta, which results in oligohydramnios, developmental retardation of the fetus, and – also in medically treated cases – fetal necrosis.

Functional changes occurring in physiological pregnancy does not happen in preeclampsia, and in some cases the change is opposite in direction.

BASIC HEMODYNAMICS

Cardiac output of the heart is the volume of blood pumped from one ventricle to a connected large vessel within one minute. Cardiac output is a standard physiological measure depending on anthropometric measures. Cardiac output of 1 m^2 body surface area is the cardiac index. Cardiac output is the product of stroke volume and cardiac frequency. Generally we measure cardiac output and calculate the stroke volume knowing the cardiac frequency. Recently, applying echocardiography or impendence cardiography we may approximately estimate stroke volume and calculate cardiac output from that.

Hemodynamic Parameters

Cardiac Output (CO) = stroke volume x pulse number

Median Arterial Pressure (MAP) = (systolic blood pressure + 2x diastolic blood pressure)/3

Cardiac Index (CI) = CO/body surface area

Its advantage compared to cardiac output is that in this measure cardiac output is independent of body measures, thus cases of single patients are comparable. In a particular case it is more important to follow the CO- or CI changes than what an absolute value is in a given moment. Normal range is 2.5-3-5 litre/minute/m^2.

Stroke volume =CO/cardiac frequency

Refers to the efficiency of cardiac mechanisms. If it is too low, the heart is bumping empty, but above normal measures also does not mean that the Frank-Starling mechanism is optimal. Normal range is 60-90 ml.

Systemic Vascular Resistance = MAP x 80/CO

Highlights the tone of the systemic circulation, and it is the main component of the left heart afterload. High SVR indicates vasoconstriction (e.g. low cardiac output, in case of catecholamine), and low SVR indicates vasodilatation (e.g. sepsis, in case of anaphylaxis).

Measuring Hemodynamic Parameters

To evaluate pumping function of the cardiac muscle and to measure hemodynamic parameters within intact circular circumstances, we can use methods that look at changes in volume, in pressure, or the connectedness of the two.

Originally invasive monitoring was required for measurement. Currently the most often used invasive measurement of cardiac output in clinical settings is the right heart catheterization (Swan-Ganz catheterization) and the thermodilution technique.

In case of certain diseases, invasive measurement techniques are not particularly favourable. In the past 40-50 years a number of noninvasive solutions were introduced that can define central hemodynamic parameters fairly precisely.

Echocardiography

Two-dimensional, M-mode and Doppler-echocardiography are the most often used methods of echocardiography in clinical practice.

Impedance Cardiography (ICG)

Developed in the 1960's, ICG is a noninvasive method that is able to measure every pressed stroke volume of each heart action, and thus constantly following the circulating cardiac output. The examination was applied as early as 1979 in pregnancy as well.

Application of the method is no burden for the patient. According to scientific literature, it can be used to measure precise stroke volume in case of physiologic or slightly deferring thoracic fluid content, primarily to follow cardiac changes. As a noninvasive technique it is a promising alternative to invasive methods of hemodynamic monitoring.

ICG measures impedance changes of thoracic organs and tissues compared to the biologically inert flow. Amount, distribution and flow of thoracic blood volume influences thoracic impedance the most. Apart from impedance measurement, ECG and phonocardiography can be used to explore relevant reference points of the heart cycle, thus cardiac frequency – amount of blood pressed out by a single heart contraction – can be calculated, and from that we can deduct cardiac output applying the following equation:

$$\mathbf{SV = \rho \times (l^2 \times Z_0^{-2}) \times dZ/\, dt_{max}^{-2} \times LVET}$$

In this equation ρ is a constant referring to the blood viscidity, l is the cm distance between measuring electrodes, Z_0 is the basis impedance, LVET is the left ventricle's ejection time in seconds, $dZ/\, dt_{max}^{-2}$ is the maximum of the time-based first derivative of the impedance cardiogram.

Based on the Kubicek-equation, stroke volume thus depends on the distance between electrodes, the base impedance (Z_0), ejection time of the ventricle (LVET) and the derived maximum of the ICG (dZ/dt_{max}), which is proportionate to the left ventricular emission during systole and may change dynamically by each heartbeat. During measurement, 1 is a constant at a given patient, Z_0 can be considered a constant during measurement, thus short-term changes of the stroke volume are defined by the LVET.

Relevant primary hemodynamic parameters that can be measured by ICG are heart rate (HR), cardiac index (CI), stroke volume (SV), stroke volume index (SVI), and peripheral resistance (SVR).

Impedance cardiograph is the single noninvasive hemodynamic measurement system applicable also without specialised personnel, which, by defining pulse volume, cardiac output, peripheral resistance, systolic time intervals and central blood volume, enables us to follow the changes of all important and calculated cardiac parameter.

During measurement, ICG considers the thoracic cage to be electrically homogenous; during pregnancy, results are influenced (even if only minimally) by changes of the shape of the thoracic cage, placement of heart and extracellular liquid.

For this reason, ICG is applicable for comparison in similar pregnancy phases, instead of using in follow-up studies.

APPLYING ICG IN PREGNANCY

Applying ICG in Physiological Pregnancy

With the aim of following changes in cardiac parameters during pregnancy, hemodynamic parameters were measured by 70 healthy pregnant women in various gestational phases at the Clinic of Obstetrics and Gynaecology of University of Pécs already in 1996. Five groups were created based on gestational age of pregnancy.

Compared to the first group, levels of SV, SVI, CO and CI were markedly higher in the second group, and decrease of SVR was significant. Hemodynamic parameters gradually decreased in groups 3 to 5, the level similar to early pregnancy levels, despite scientific literature reporting that SV and CO levels constantly grow during pregnancy. A reason behind this paradox can be that the thoracic region is considered electrically homogenous during impedance cardiography. However, anatomic features change also during pregnancy that influences haemoperfusion of thoracic organs, which leads to the decline in our measurements as pregnancy proceeds. Mean values were defined for each group, which were later compared to the values measured by pregnant women with hypertension.

ICG applied in case of gestational hypertension

Next to physiological pregnancy, impedance cardiography was carried out in case of 39 pregnant woman observed due to hypertension at our Clinic. Similarly to the previously mentioned practice, participants were divided into 5 groups based on phase of pregnancy. Comparing these results with those of healthy pregnant women, it turned out that the level of SV did not significantly differ in case of hypertension and normal pregnancy values. However, peripheral resistance was significantly higher in case of pregnant women with hypertension.

After these measurements we compared weight of neonates born from two groups of pregnancies. We corrected birth weight using the known equation: ***Corrected birth weight = (fetal birth weight + z) / gestational age***

In this equation, depending on the week of pregnancy, value of z decreases as the pregnancy proceeds, and its value is 0 between gestational week 37 and 40.

Higher measured stroke volume paired with higher birth weight by healthy pregnant women. In case of pregnant women with hypertension, higher birth weight was connected with increased CO levels.

Comparison of groups in the third trimester showed significant straight correlation between SV, SVI and CO–, while SVR showed significant but inverse correlation with corrected fetal birth weight.

Our examination of healthy pregnant participants also proved that in non-hypertensional cases also the fetus' weight depends on the mother's hemodynamics: we can predict higher birth weight if CO is higher and SVR is lower. In case of hypertension the SVR increases, and thus the fetus' birth weight is also lower. Furthermore, our study showed that fetal birth weight is not particularly dependent on the mother's blood pressure, but is rather in connection with the placental perfusion. When CO is higher, more blood can access the placenta in a given time – if the SVR is also low, this will increase the volume of blood reaching the placenta, which enables fetal wellbeing and development.

Correlation of Hemodynamic Parameters and Fetal Status in Physiological Pregnancy

Our team assessed central hemodynamic parameters of healthy pregnant women between the 36-39th gestational weeks, while fetal status was registered with NST examination. Our aim was to analyse the amount of changes the central hemodynamic parameters have on fetal oxygenation depending on the position of the body.

It is a well-known fact that if the mother lays on her side, significantly more acceleration can be detected on the fetal NST than if the mother is laying on her back. In the latter case the uterus will press the iliac vein, thus preload will decrease and consequently less blood will flow through the heart and less blood will be oxygenated in the lungs, while the amount of blood that reaches the placenta in one heart cycle and also oxygen saturation will be lower. This fact is also the origin of the well-known inferior vena cava syndrome.

100 healthy pregnant women between the 36-39th gestational weeks, applying for NST were examined at our Clinic. Student's t-test and correlation analysis was applied to analyse data. NST was carried out while the mother was lying on her back and on her left side, then hemodynamic tests were taken in the same positions. We should highlight from the results that the number of accelerations were 25% higher during the left-sided position, while stroke volume was 12% higher, pulse rate was 10% lower, and CO did not change significantly. Based on this difference researchers claimed that the haemoperfusion of the placenta significantly influences fetal oxygenation, possibly depending on the differing hemodynamic parameters. The examination also showed that heart frequency increases if stroke volume decreases.

Correlation Between Fetal Birth Weight and Maternal Cardiac Output

Physiological hemodilution is a basic requirement for carrying out a successful pregnancy and haemoperfusion of the fetus through the placenta is also based on this phenomenon. Lack of hemodilution is strongly connected to intrauterine growth retardation and preeclampsia.

International scientific literature describes the connection between maternal hemodynamic parameters and expected birth weight of the fetus usually in case of pathological pregnancies. In case of intrauterine retardation along moderate preeclampsia, both the maternal stroke volume and the cardiac output are significantly lower compared to fetuses with average weight. A number of international researchers claim that in case of pregnant women with hypertension, decrease of the fetal weight is smaller if maternal peripheral resistance grows.

We also examined significant correlation at our Institution. Fetal weight grows if the heart is more active. A lower fetal weight should be expected in case of pregnancies with hypertension and increased peripheral vascular resistance. If growing blood pressure was not matched with growing peripheral vascular resistance, we found no difference in fetal weight compared to pregnancies without hypertension.

Origins of preeclampsia are still not completely understood. A number of factors influence its development, but research of the pathomechanism is still

ongoing. Some researchers mention low level of cardiac output, increased vascular resistance and lower fetal weight, while several others mention higher cardiac output, lower vascular resistance and higher fetal weight in connection with preeclampsia.

The examination carried out in 2003 at our Clinic highlighted that fetal weight is in connection with maternal hemodynamic parameters, maternal weight, and BMI. Growing maternal CO next to decreased vascular resistance results in higher maternal and fetal weight, and significant decrease of CO is connected to increased vascular resistance and significantly lower birth weight. In case of differing central hemodynamic parameters the proteinuria detected at the pregnant woman also differed. Preeclampsia appearing early in pregnancy was connected to lower CO and high amount of proteinuria. Cases appearing further in to pregnancy (after 34-35th gestational weeks) showed higher CO and lower amount of proteinuria. Similarly to international research practice, we do not consider preeclampsia a homogenous clinical picture, and various principles are followed in its treatment depending on hemodynamic parameters.

Correlation Between Fetal Status and Maternal Hemodynamics

Relevant scientific literature highlights that likelihood of both above or below average birth weight is growing in case of preeclampsia, which also indicates that preeclampsia is probably not a homogenous clinical picture. A relevant retrospective study was carried out at our Clinic, where pregnant women hospitalised with hypertension, after the 32nd gestational week were examined. In their cases, blood pressure started to grow after the 20th week of pregnancy and a significant proteinuria was detected. Cases were grouped according to fetal birth weight: one group contained cases with birth weight considered to be average or higher by scientific literature, and the other contained cases with fetal birth rate below the average. We collected data on age, time when high blood pressure occurred, amount of proteinuria, maximum of median arterial pressure, central hemodynamic parameters, maternal weight at giving birth, BMI, gestational age, weight gain during pregnancy, and occurring pathological conditions of the fetus (abnormal CTG, flowmetry, oligohydramnios).

Data analysis showed significantly higher maternal age, CO, cardiac index, body weight, BMI, and gestational age at birth in case of mothers of neonates with higher birth weight. Also, high blood pressure occurred earlier, amount of protein in the urine was higher, and systemic vascular resistance was increased in cases with fetal birth weight below average. Abnormal umbilical flow, abnormal CTG and oligohydramnios also appeared only in this group. Birth weight correlated with maternal weight gain in the group with higher fetal weight, and it was reversely proportionate with amount of proteinuria in the lower birth weight group.

This examination thus showed that also in case of preeclampsia fetal weight is strongly connected with maternal hemodynamics, with high blood pressure occurring throughout the disease, with proteinuria, and with maternal weight. Furthermore, the research proved that the examined parameters significantly differed in case of the two groups based on fetal weight at birth.

These results also underline that preeclampsia is not a homogenous clinical picture. One type – that goes along with higher fetal weight at birth – is probably the result of hyperfusion, and goes along with hypertension in later gestational ages as well. Placental haemoperfusion is also better in these cases, thus fetal weight will be higher. The other type, resulting in higher birth weight of the fetus, develops due to hyperfusion. In this case we detected the classic symptoms that have long been examined alongside preeclampsia: decay of placental haemoperfusion, hypoperfusion of parenchymal organs, thus increasing proteinuria, fetal growth retardation, and oligohydramnios. High blood pressure also occurred in earlier gestational age in this group, but its level was not higher than that of the other group.

The two groups can not be separated based on the amount of blood pressure growth, but differences detected in other maternal parameters indicate the process. Considering that apart from maternal weight and BMI we found more significant correlation between hemodynamic parameters and fetal birth weight, we suggest this method for the basis of grouping.

Table 1. – Comparison of pregnancy parameters in case of average and above average, and below average fetal birth weight in preeclampsia

	Average or above average fetal weight (n=23)	Below average fetal weight (n = 14)	p
Occurrence of hypertension (week)	35.8 ± 0.81	31.4 ± 1.12	< 0.001
Maximum MAP (mmHg)	117.7 ± 1.82	123.5 ± 2.24	NS
Maximum proteinuria (g/day)	0.82 ± 0.124	2.47 ± 0.581	0.015
CO (l/minute)	8.5 ± 0.28	5.6 ± 0.40	< 0.001
CI (l/minute/m^2)	4.5 ± 0.28	3.0 ± 0.19	< 0.001
SVR (dyn*sec*cm^{-5})	1041.1 ± 61.55	1702.1 ± 167.68	0.002
Maternal weight (kg)	94.9 ± 2.62	76.3 ± 3.67	< 0.001
Maternal BMI (kg/m^2)	35.8 ± 1.10	29.6 ± 1.37	0.001
Oligohydramnios	0	10	-
Abnormal flow or CTG	0	7	-
Gestational age at birth (week)	38.3 ± 0.41	36.6 ± 0.64	0.035
Corrected birth weight (g/week)	95.8 ± 2.16	66.3 ± 2.75	< 0.001

FORMS OF PREECLAMPSIA

Gestational Hypervolaemic Hypertension Is Not the Same as Classic Preeclampsia

Although preeclampsia is a disease with severe complications during pregnancy, its etiology is still unclear.

Patients can be put into two groups based on the time high blood pressure occurs. We considered high blood pressure chronic when blood pressure growth occurred before the pregnancy or before the 20^{th} week of gestation, or if it is still high 12 week after giving birth. In case of the type that occurs after pregnancy (i.e. induced by pregnancy), blood pressure grows only after the 20^{th} gestational week and normotensive status returns after giving birth.

Another important difference between the two groups is that while occurrence of intrauterine growth retardation is higher among fetuses of women with chronic hypertension, perinatal mortality does not differ from non-hypertension cases.

During-pregnancy hypertension (induced by pregnancy) occurs in 2 to 7% of pregnancies. Pregnancy-induced hypertension has been divided to two groups recently, differentiating between *early-onset gestational hypertension* and *late-onset gestational hypertension*, although the names do not highlight the actual difference between the groups as it only indicates the time (gestational age) high blood pressure occurs, and other particularities of the two groups are not highlighted. It has been long known that preeclampsia is connected with increased systemic vascular resistency and anaemia. Hypoperfusion results in organ dysfunction relevant to pregnancy, consequential placental insufficiency, oligohydramnios, intrauterine growth retardation, and fetal hypoxia. However, other research papers claim increased CO and decreased SVR in case of preeclampsia, with higher fetal birth weight due to consequential hyperperfusion. As lower birth weight was detected in case of lower CO, and higher CO is connected to higher birth weight, a differentiation of two types of preeclampsia (hypo- and hyperperfusional) became necessary.

A reason for hypertension can be increased systemic vascular resistency or higher CO as well. In case of increased SVR, hypoperfusion leads to malfunction detected in parenchyma organs, and in case of increased CO organ deviations are due to hyperperfusion.

Hemodynamics in Early Preeclampsia

Based on the collected data we can claim that maternal body's adaptation to pregnancy is not satisfactory, which can be a basis for hypoperfusional preeclampsia. This disease can be considered two-phased – abnormal placentation through the endothelial damage as the first phase can be the reason why organ dysfunction develops as the second stage. Anti-angiogenic agents (endoglin, fms-like tyrosine kinase, human interferon-inducible protein) are produced in the first phase, which will paralyze developmental factors (VEGF, PlGF, TGF-β) required for normal placentation. In the maternal blood we can detect free radicals, cytokines (TNF-α), fetal cells in an amount that is higher than normal, and also fibronectin,

thrombomodulin, vWF, which prove endothelial damage. Changes detected in vein function, hemodynamics, hemorheology and haemostasis activate thrombocytes, which, through further endothelial impairment will lead to organ deviation and consequential hypoperfusion. This process is depicted by Figure 1. below.

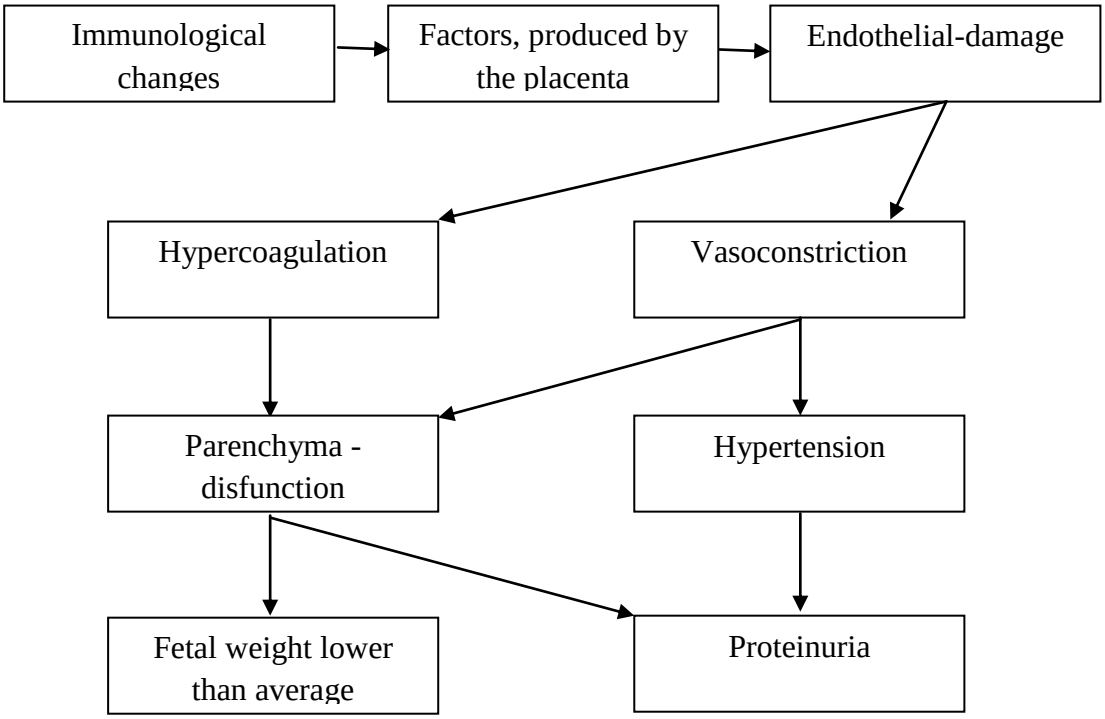

Figure 1. – Process of organ deviation development in early preeclampsia

Smooth muscle relaxation due to vasodepressors produced by intact vein endothelium is fundamental in physiological pregnancy, and it supports consequential CO-growth by increased plasma volume.

In case of hypoperfusional preeclampsia, decrease of plasma volume and CO is caused by lack of relaxational agents and increasing concentration of vasoconstrictor materials, alongside increase of systemic vascular resistency and blood pressure. This way placental circulation will decrease and development of the fetus will lag behind normal. The relationship between birth weight and maternal CO has already been discussed in scientific literature, both in case of pregnant women with normo- and hypertension.

Hemodynamics in Late Preeclampsia

The model of hyperperfusional preeclampsia was discussed in several scientific articles in connection with preeclampsia patients with high CO and SVR. Based on the Hagen-Poisseuille equation, hypertension in these cases is not only due to higher SVR, but also to higher CO. Apart from vasodilation and higher CO the capillaries become „permeable", which leads to generalized oedema. A consequence of this can be lung- or brain oedema, and due to the increasing perfusion in the kidneys a consequential proteinuria also develops, the amount of which is proportionate to the severity of the disease.

In hyperperfusional type of preeclampsia the placental haemoperfusion is also increased, thus neonates born with average or above average weight. Vasodilation is considered to be the starting point of blood volume's increase, but it is yet unclear if the growing production of vasodepressors or the growing Na^+-reabsorption leads to consequential hypertension in the hyperperfusional type. In this group, pregnant women are usually obese, have oedema, and their weight gain during pregnancy is above average.

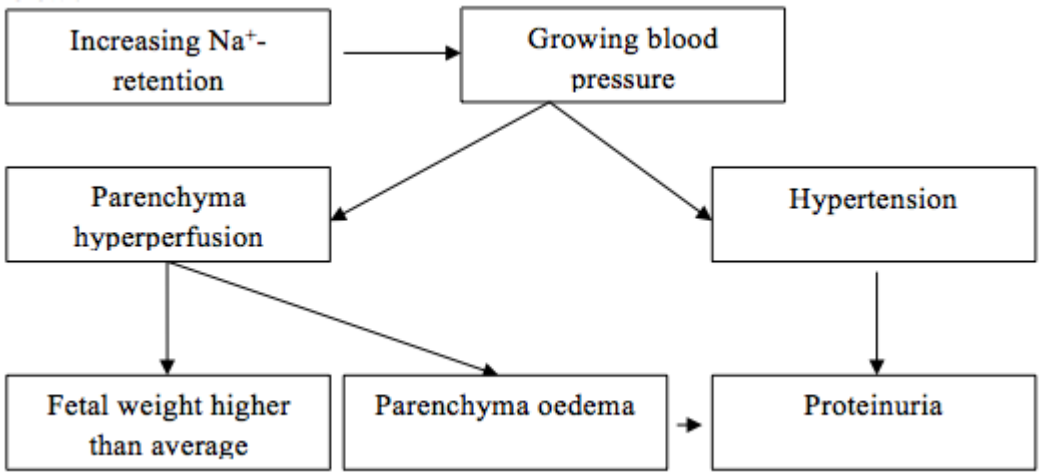

Figure 2. – Process of organ deviation development in late preeclampsia

TREATMENT OPTIONS OF PREECLAMPSIA

In light of all the above mentioned information, two types of preeclampsia requires different treatment based on the mechanism of its development.

Treatment of Early Preeclampsia

By the hypoperfusional type, the use of vasodilators (hydralazine, nifedipine) seems to be the most effective. Ca-dobesilat enables decrease of blood pressure through increasing the NO-production. Application of magnesium sulphate has a role in prevention of eclampsia, while application of corticosteroids aids fetal lung development before a possible premature birth.

Treatment of Late Preeclampsia

In treatment of hyperperfusional preeclampsia the vasodilator effect is not of primary importance, instead we expect successful blood pressure control by applying a possibly cardioselective beta blocker. It is worth considering the use of diuretics in cases that lack hemoconcentration. Premature labour (and its induction) is relatively rare in this group of patients, only early placental abruption occurs minimally more often, which is a possible consequence of extreme oedema of these cases.

Application of Furosemides in Late Preeclampsia

The reason behind high blood pressure and consequential proteinuria that develops during pregnancy can be different in various cases. At early preeclampsia the endothelial dysfunction and the decaying micro-circulation leads to the failing function of the kidney (proteinuria) and the placenta, which results in higher birth weight of the fetus. At cases of late preeclampsia the hypertension is rather considered as a disease of the mother, fetal parameters (circulation values in the umbilical cord, amount of amniotic fluid, fetal weight) are similar to those of a healthy pregnancy, and in most cases fetal weight is higher compared to normal pregnancies. We can detect differences in maternal central hemodynamic parameters between the two groups of preeclampsia. We find low CO next to vasoconstriction in early preeclampsia, and high CO with vasorelaxation in late preeclampsia.

According to the Hagen- Poisseuille equation, CO is the proportion of blood pressure and arterial resistance, thus blood pressure grows if CO or SVR increases as well.

During our examination our aim was to decrease blood pressure in preeclampsia with CO applying diuretics.

Several international researchers have already examined the positive effects of diuretics on patients with preeclampsia. A meta-analysis with 7000 participating pregnant women highlighted that the application of diuretics increases the number of still-births and also maternal mortality. Carr et al. also examined the effect of diuretics, and registered hemodynamic parameters (SV, CO) for three weeks after applying 20 mg furosemide daily. They found that blood pressure did not decrease significantly by this dosage. Ascarelly et al. also examined the effect of 20 mg daily dosage of furosemide, and detected the medication's decreasing effect on blood pressure for 5 consecutive days after delivery.

14 pregnant women participated in the examination carried out at the Pathology of Pregnancy Ward of the Clinic of Obstetrics and Gynaecology of University of Pécs, Hungary. We examined those women admitted to the ward due to preeclampsia by whom we detected increased CO. Fetal status was examined by NST and flowmetric test in every case.

In our previous examinations, the average level of CO in normal pregnancies was 6.8 l/min in the third trimester. In the current examination we included only those pregnant women, who's CO-level was at least 10% above the average (minimum 7.48 l/min). The average CO-level at the examined participants was 8.4 l/min, which is considerably higher than in case of healthy pregnancies, possibly due to the high blood volume.

Participating pregnant women received 40 mg loop diuretics (Furosemide) and 1g KCl orally, and 60 minutes later – similarly to before taking the above mentioned medication – we carried out impedence-cardiographic hemodynamic examinations. We also carried out fetal status control in the meantime.

Our examination showed that furosemide significantly decreased the level of CO and also the systolic and diastolic blood pressure measures, although pulse rate did not change significantly. Based on the medications' mechanism, CO decrease is due to dropping blood volume.

Table 2. – Hemodynamic measures throughout the application of furosemide

	Before furosemide	After furosemide	p
Systolic blood pressure (mmHg)	150 (140-170)	140 (100-150)	0,002
Diastolic blood pressure (mmHg)	100 (90-120)	85 (60-100)	0,002
Pulse rate (n/minute)	85 (69-92)	85 (65-95)	0,875
Cardiac output (l/minute)	8,3 (7,5-9,4)	7,6 (6,9-8,6)	0,002
Vascular resistance (dyn x sec x cm^{-5})	1255 (1055-1331)	1278 (840-1388)	0,826

Our current examination showed that application of furosemide does not decrease pulse rate or total vascular resistance, thus it does not increase heart action further; it has no relevant cardiogenic effect on beta blockers, the application of which is suggested by international scientific literature. It is a well-known fact that furosemide proceeds through the placenta, and in case of correct dosage it might increase fetal urine and consequently increase the amount of amniotic fluid as well. However, we did not detect such effects – the single dosage we applied had no effects on the fetus.

Although international guidelines still don't suggest the usage of diuretics for treating preeclampsia, our results show that alongside appropriate diagnostic criteria (late preeclampsia) its application might be favourable among pregnant women with high cardiac output. Furthermore, this examination showed that excessive water retention plays an important role in the development of late preeclampsia, thus slowing the deflating oedema-development will enhance the circulatory system of pregnant women, and this placental perfusion too.

SUMMARY OF RESULTS

Our results showed that fetal weight significantly correlates with maternal cardiac output – higher cardiac output goes along with higher fetal weight.

Current fetal status is strongly influenced by maternal cardiac output: if cardiac output decreases as the mother lies on her back, the fetus will compensate this with a modest heart rate increase.

Contrary hemodynamic changes can be detected in preeclampsia.

In early preeclampsia the cardiac output is small, peripheral resistance is large; while in late preeclampsia cardiac output was above average as vascular resistance was decreasing. Intrauterine growth retardation is expected in the first case, and normal or above average fetal weight is expected in the latter case.

In late preeclampsia with high cardiac output and oedema, diuretic treatment decreases blood pressure effectively. In the background of this effect we detected the decrease of stroke volume.

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Articles related to the thesis

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