Diplomarbeit

Cardiovascular Regulation and Vascular Function in Pregnancy and Pre-eclampsia: An Update of existing Literature

eingereicht von

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unter der Anleitung von

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Graz,19.03.2015

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Graz, am 19.03.2015 *Kaltrina Kutllovci eh.*

ACKNOWLEDGEMENTS

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ZUSAMMENFASSUNG

Während der Schwangerschaft frauen Körper erfährt viele körperliche Veränderungen,die notwending sind in die Entwicklung des Fötus zu helfen und für den Geburt vorbereitet werden.Morphologische und funktionale Anpassung der maternalen Herzkreisleufsystem is Teil dieser Änderungen. Diese Diplomarbeit beschreibt die physiologischen Grundlagen der Herz-Kreislauf-Regelung mit der primären Frage, wie das Herz-Kreislauf-System durch Präeklampsie beeinflusst wird. Die vergangene und aktuelle Literatur wurde aus Pubmed,Web of Since Datenbank recherchiert und darüber hinaus diese Arbeit richtet sich an die aktuellen Wissen über die Blutdruckregulation, was passiert mit dem Herz-Kreislauf-System in einer normalen Schwangerschaft sowie Effekte von Präeklampsie auf das kardiovaskulären System. Als Präeklampsie kann lebensbedrohlich sein, die pharmakologischen Optionen, die derzeit für die Präeklampsie zur Verfügung stehen, sind dargelegt und diskutiert.

Diese Arbeit hat Anwendung in den Bereichen der Schwangerenvorsorge und zukünftige Ärzte, die Interesse an einer Zusammenarbeit im Bereich der Gynäkologie und Geburtshilfe haben.

ABSTRACT

During the pregnancy, the women's body undergoes in many physical changes which are necessary to help fetal development and be prepared for delivery. Morphological and functional adaption of maternal cardiovascular system is part of these changes. This Diploma work explores the physiological basis of cardiovascular regulation with the primary question how cardiovascular system is affected by pre-eclampsia. The past and current literature from Pubmed, Web of Since database were researched and furthermore this work focuses on the current knowledge regarding blood pressure regulation, what happens to the cardiovascular system in normal pregnancy as well as effects of pre-eclampsia on the cardiovascular system. As pre-eclampsia can be life threatening, the pharmacological options that are presently available for pre-eclampsia, are outlined and discussed.

This work has application in the areas of antenatal care and future medical practitioners who have interest in working in the area of Obstetrics and Gynecology.

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ABBREVIATIONS

CO	Cardiac output
HR	Heart rate
SV	Stroke volume
SA node	Sinus atrial node
ANV	Autonomic nerve system
NTS	Nucleus tractus solitaries
AV node	Atria ventricular node
NE	Nor epinephrine
MAP	Mean arterial pressure
BP	Blood pressure
R	Resistance
TPR	Total peripheral resistance
SVR	Systemic vascular resistance
RAAS	Renin-angiotensin-aldosterone system
ANP	Atrial natriuretic peptid
ACOG	American College of Obstetricians and Gynecologist
DIC	Disseminated intravascular coagulation
HELLP syndrome	Hemolysis, elevated liver enzymes, low platelet count
IUGR	Intrauterine growth restriction
Ca^{+2}	Calcium ions
PV	Plasma volume
GRF	Glomerular filtrations rate
LV	Left ventricle
2DE	Tow dimensional echocardiography
EF	Ejection fraction
CI	Cardiac index
PWV	Pulse wave velocity
BMI	Body mass index
OR	Odds ratio
hr-CRP	High –sensitivity C-reactive protein
sFlt-1	**S**oluble fms-like tyrosine kinase-1
PGF	Placental growth factor
sVEGF1	Soluble vascular endothelial growth factor 1
PAPP-A	Pregnancy-associated plasma protein A
DP	Diastolic pressure
VR	Vascular resistance
SP	Systolic pressure
FBF	Forearm blood flow
TF	Tissue factor
TFPI	TF pathway inhibitor
TGF-b	Transforming growth factor beta

$MgSO_4$	Magnesium sulfate
ACE-Inhibitors	Angiotensin-converting-enzyme inhibitor
SOGC	The society of obstetricians and gynecologists of Canada
RV	Right ventricle
RA	Right atrium
LA	Left atrium
Ach	Acetylcholine
NE	Nor epinephrine
EDV	End diastolic volume
ESV	End systolic volume
P.p	Post partum
G.w	Gestation week
AP	Arterial pressure
CHD	Coronary heart disease

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Introduction

1.1 Anatomy of cardiovascular system

Heart with blood vessels and blood make three essential components of the cardiovascular system (3).The primary function of the heart is pumping the blood from near 0 mmHg systemic venous pressure through RV contraction into pulmonary artery, with pressure of 20-30 mmHg and through contraction of the left ventricle into systemic arterial system with generated high pressure 100 to 140 mmHg. Blood vessels distribute body tissues with blood and provide the body cells proper function through delivering oxygen and nutrients and keep a sufficient arterial blood pressure to adequately organ perfuse (4).

1.1.2- Anatomy of the heart

The human Herat has average mass of 250-300gr for females and 300-350 grams for males. (1).Heart is muscular pumping organ, located in the middle mediastinum. The apex of the heart is turned anterior, inferior to the left side, the top of the heart known as heart base, is mostly formed from left atrium and is connected with the great blood vessels, ⅔ of the heart is located on the left side of midline and ⅓ on to right side. Heart has tree surface: anterior, posterior and inferior or diaphragm surface (2).

The heart is surrounded and protected by pericardium sac, which is divided into two membranes: a) fibroses pericardium, who covers the heart and prevents its overstretching b) the serous pericardium, which is divided into two layers: a parietal layer, consist the inner side of fibrous pericardium and a visceral layer, forms the epicardium. Between these two layers of serous pericardium is a thin lubricating serous fluid, called pericardial fluid which reduces friction between two layers of serous pericardium as the heart moves (1).

The heart walls consist tree layers: pericardium (outside layer), myocardium (middle muscle layer, responsible for its pumping action) and endocardium (inner side, thin layer of endothelium) (2).

The heart is divided into right and left side, has four chamber, tow superior receiving chamber called atria (left, right) and two inferior pumping chamber called ventricle(left, right).Between right and left atria is a dividing wall, inter-atrial septum and between ventricles inter-ventricular septum(1).

On anterior surface of the each atrium is a structure known as auricular. Inside the ventricles are papillary muscles, which are connected through chordate tendineae and cusp to the atria-ventricular valves.

Blood flows from RA to RV through tricuspid valve and from LA into LV through mitral valve. The heart pump the blood from left ventricle through aortic valve to other part of the body and collect it back from vena cava inferior and superior to RA then into RV. From RV, heart pumps the blood into pulmonary artery to the lungs where will be rich with oxygen and collect it back from left pulmonary vena to LA.

Myocardium is supplied with oxygenated blood from the coronary arteries which are branches from ascending aorta. Branches (circumflex and anterior interventricular) come from left coronary artery and branches (posterior inverventricular and marginal) makes right coronary artery (2).

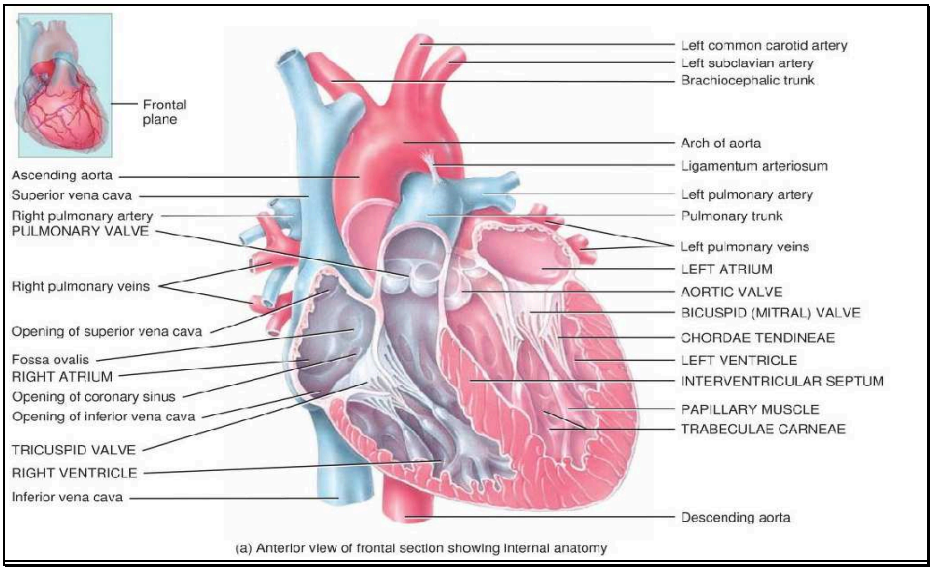


Figure.1.1 Internal anatomy of the heart, obtained from Principles of anatomy and physiology by G.Tortora, B.Derrickson (2).

1.1.3 The structure of the blood vessels

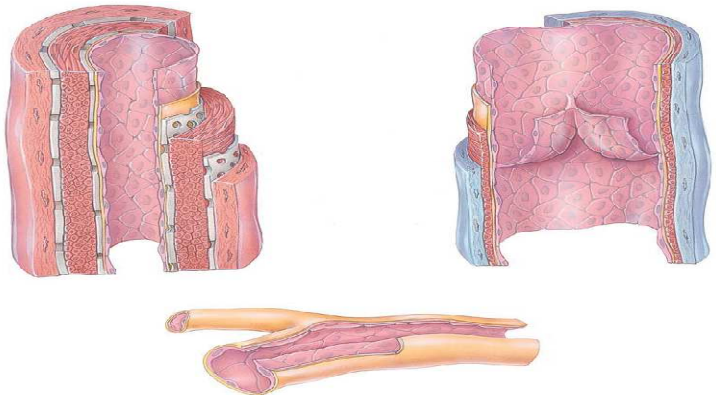
Blood vessels makes main part of circulatory system, which plays an important transporting role of the blood form heart to the periphery .Transporting nutrients, hormones, electrolytes and supporting normal cell function is a responsibility of the circulation (2).
There is systemic and pulmonary circulation. The systemic circulation is also called the greater circulation, supplies all the tissues of the body with blood flow, except the lungs. The blood flows from LV along the aorta to the next arteries and arterioles until arrives the capillary, where occurs the exchange of fluids and other substances. Venules collect non oxygenated capillary blood, than transport it to the larger veins and ends to the vena cava superior and inferior, to the right atrium and then to the right ventricle (4).

The blood vessels have tree major Layers (Tunica) a) interna, b) media, c) externa

a)Tunica interna: made from simple squamous epithel(endothelium) and have contact with blood. Endothelial cells are involved on vessel related activities through mediators which affects the contractile state of the vessels smooth muscle and permeability of the capillaries. The second component is basal membrane, as a physical support base for epithelial layers. In outer part of tunica interna is internal elastic lamina, which through opening like windows allows diffusion of nutrients through tunica interna to media.

b)Tunica media: contains smooth muscular cells and amount of elastic fibers .The smooth muscular cells plays an important role on regulation of the diameter of blood vessels and directly influencing the blood pressure, otherwise the elastic fibers available vessel stretching under blood pressure.

c)Tunica externa :the outer cover of the blood vessels consist elastic and collagen fibers, this layer consist nerves and blood vessels called vasa vasorum to supply the tissue of the vessels wall, which are better seem on large vessels as aorta.



a) Artery b) Vein

Figure 1.2 Comparative structure of Blood vessel: a) Artery b) Vein, obtained from Principles of anatomy and physiology by G.Tortora & B.Derrickson (2).

Main types of blood vessels are:

Arteries – the artery wall has three layers, especially thick muscular- elastic tunica media, the smooth muscle of these layers are innervated from sympathetic fibers of the autonomic nervous system, which by increasing the sympathetic, stimulates smooth muscle to contract and decrease the diameter of the lumen called vasoconstriction. In contrast by decreasing the sympathetic stimulation or present of some chemicals as nitric oxide, H+, acid lactic, the smooth muscle will relax and in this way result the increase of lumen diameter called vasodilatation.

Elastic Arteries –have the largest diameter among arteries and relatively thin vessels wall dominated by elastic fibers in tunica media. This group includes aorta, common carotid and subclavian arteries, pulmonary trunk.

Their function is to conduct the blood from heart to the muscular arteries, as the blood is ejected from the heart, the elastic arteries walls stretch and play a role as pressure reservoir, the stored energy will be convert to the kinetic energy in the vessels with influence of elastic fibers, thus, blood will continues to flow through muscular arteries even while the ventricles are relaxed.

Muscular Arteries- are medium size arteries, with smooth muscle dominated tunica media, that's why, they have greater vasoconstriction and vasodilatation capabilities, but because of reduced elastic tissue they can't help on recoil and propel the blood like the elastic arteries.

Arterioles- are microscopic vessels with thin tunica interna, distal circulatory oriented smooth muscle on tunica media forms a pre capillary sphincter which monitors the blood flow into the capillaries and tunica externa contains unmyelinated sympathetic nerves. Arterioles regulate the blood flow into the capillary networks of the body tissues by regulating the resistance, that's why known as resistance vessels.

Capillaries-are the smallest blood vessels that connect the blood flow from arterioles to the post capillary venule, this is called microcirculation of the body. They don't have tunica media and externa, they have only a single layer consist from endothelium and basal membrane. There are three types of capillaries: continuous, fenestrated and sinusoid. The main role of capillaries is to exchange the substance between blood and interstitial fluid through its single layer (2).

Number of capillaries depends on the metabolic activity of the tissue. Tissue with high metabolic activities such as brain, muscle, the liver, the kidney and the nervous system use more O_2 and nutrients and that's why they have more capillary networks, otherwise the tissues with lower metabolic activities such as ligaments have fewer capillaries. The blood flow from met arteriole to the capillary depends on contraction or relaxation of pre capillary sphincter (2, 4).

Venules-have a smaller diameter with a thin wall, which receive the blood from capillaries and transport to the veins, post capillary venules, because of theirs layers are part of microcirculation and after come the muscular venules where the nutrients exchange can no longer occur.

Veins- are composed from three layers, same as the arteries but consist very thin walls. They are distensible enough to adapt the variation on volume and pressure of blood passing through but not to resist the high pressure.

The main function is to return blood back to the heart and the most important role on this function plays heart pumping and contraction of skeletal muscle of lower limbs. Many veins, especially those in the limbs contain valves which help on blood returning by preventing the backflow of the blood.

The 65% of blood volume is stored in systemic venules and veins, which by increase of sympathetic impulse or in case of hemorrhage through vasoconstriction influence the blood flow by reducing the reserve blood in veins(2).

1.2 Physiology of cardiovascular regulation

1.2.1 Cardiac output and factors that affect its regulation

The primary function of the heart is to transport blood to the tissues and deliver oxygen, nutrients to the cells of the body, to provide their proper function and to keep a sufficient arterial blood pressure to adequately perfuse organs. The heart realizes this by contraction of its muscular walls and produces a sufficient pressure to pump blood from left ventricle into aorta. In a resting adult, cardiac output is from 5 to 6 L/min, for the women, this value is 10 to 20 per cent less (3). The volume of blood, pumped out of the heart by each heart beat is called stroke volume (SV).The cardiac output is the volume of blood ejected by the heart per minute. The units for cardiac output are milliliters /minute or liters/minute. Cardiac output is equal to product of stroke volume (SV) and the number of heart beats pro minute (heart rate, HR) (2).

Cardiac Output (CO)=Heart rate (beats/min) X stroke volume (ml/beat)

By increasing either heart rate or stroke volume increases also cardiac output. An average stroke volume for e resting person is 70 ml/beat with heart rate of 70 beats/ minute and then the cardiac output for this person is:

CO= 70 (beats/min) X 70(ml/beat) =4900 ml/min

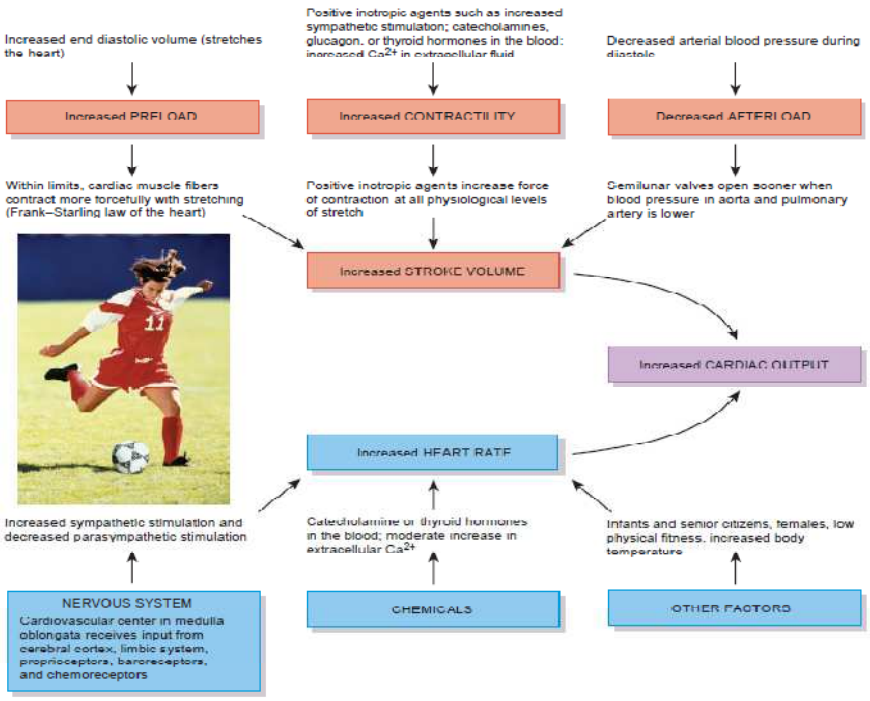


Figure 1.3 Cardiac output, obtained from Principles of anatomy and physiology by G.Tortora & B.Derrickson (2).

Heart rate: sinus atrial node is a pacemaker of the heart, generator of normal sinus rhythmus, which is innervated by sympathetic und parasympathetic nerve fibers. By the resting condition, the parasympathetic nerves through Ach slows the potential of the SA node and reduce HR, while by physical/emotional activities, the sympathetic nerve release NE, who increases the HR (2).

Stroke volume: the heart dose not fills to its max. capacity at the resting condition. The returned blood during diastole will be pumped out by a healthy heart, if more blood is returned then more blood will be ejected during next systole. The ventricles empty only 50-60% of their volume during systole, this means stroke volume is only 50% of EDV because 40 to 50% of the blood, remains in ventricle as ESV. There are three factors that regulate the stroke volume and enable that the right and left ventricle to pump equal volumes of blood:

-*Preload*-as more hearts fills with blood by diastole, so greater is the force of contraction by systole, a greater preload (stretch) on cardiac muscle fibers increase contraction force. This is known as Frank-Starling law of the heart. The preload stays proportional to EDV and by greater EDV , the next contraction is more forceful.EDV has two influence factors: the duration of ventricular diastole and venous return. When heart rate increase, there is shorter filling time during diastole and the ventricles contract before they are enough filled, this means smaller EDV. When venues return increase, increase also the EDV. The Frank-Starling law equalizes the volume of blood output from right and left ventricle, if the left side of heart pumps more blood as the right side, then the venues return increase the EDV, which cause the right ventricle to contract more forceful to bring balance for both side on the next heartbeat (2).

-*Contractility*-is contraction strength of myocardial by preload. The contractility will increase by positive inotropic agents, who helps Ca^{+2} inflows by cardiac action potential and fortify the force of next contraction. By stimulation of sympathetic nerves, hormones such as epinephrine und nor epinephrine increase Ca^{+2} level in interstitial fluid and promote positive inotropic effect, while negative inotropic agents by reducing of Ca^{+2} inflow occurs decreasing the strengths of heart beat.

-*After load*- when the pressure in ventricle overpass the pressure of pulmonary trunk (about 20mmHg) or in aorta (about 80mmHg) begins the ejection of the blood from heart, at this point, the increased pressure in the ventricle make blood to push, the semi lunar valve open and the pressure that must be overcome before the semi lunar valve open is after load. Increase in after load, decrease the stroke volume (SV) and more blood remains in ventricle. Hypertension and atherosclerosis are such condition that increase after load (2, 4).

1.2.2 Autonomic neural control of the heart and vasculature

At the rest state of the Person, the heart pumps 4 to 6 liters of blood each minute but during the exercise, the heart can adapt to pump four to seven times this amount! The base mechanism, by which the amount of volume pumped from the heart is regulated are:

1.2.2.1 Intrinsic regulation of cardiac pumping

The ability of the heart to adapt to changing inflowing blood volume is called Frank-Starling mechanisms of the heart. By greater heart stretching comes to greater contraction force and blood volume pumped into aorta.The Stretch of the right atria wall contributes on increasing of the heart rate by 10-20 per cent, this also increase the cardiac output but its contribution is lesser as that of Frank-Starling mechanism (3).

1.2.2.2 Control of the heart rate by autonomic nervous system

HR plays an important role on regulation of CO, among many factors that contribute in regulation of HR, the most important are ANV and adrenal medulla hormones (epinephrine und nor-epinephrine). Autonomic regulation of the heart rate come from cardiovascular center in medulla oblongata, which is located in the brainstem and together with hypothalamus and the cortical regions regulate the cardiovascular function. The afferent input from peripheral sensor such as baro-chemoreceptor and sensor from the brain enter the medulla at the nucleus tractus solitaries (NTS), thereby by increased activity of the NTS will increase the vagal efferent nerve activity and decrease the sympathetic nerve activities(4,2). The heart rate can be increased by sympathetic stimulation from the normal rate 70/min up to 200/min or even more up to 250/min. By sympathetic stimulation increase the contraction force of the heart, also increase the pumped blood volume and ejection pressure. Thereby inhibition of the sympathetic nervous system decreases the heart rate and the strength of ventricular contraction.

The strong vagal stimulation can even stop for few seconds the heart beats, but then usually the heart escape and beats at a rate of 20 to 40 beats/min, this happens because the vagal fibers are speared in the atria but not much to the ventricles. This means that the vagal stimulation decrease mainly the hart rate then the strength of heart contraction, the power of the heart contraction lays on ventricles(3). The sympathetic neurons innervates from medulla oblongata ,to thoracic region of spinal cord , then through cardiac accelerator nerves innervates the SA node and AV node, then release the norepinephrine, which binds to the adrenoeceptors $\beta1,\beta2,\alpha1$ of the heart and provide inotropy, chronotropy and dromotropy increase, while prejunctional $\alpha2$ adrenoreceptros inhibit norepinephrine release through negative feedback mechanism. Parasympathetic nerve impulses reach the heart through left and right vagus nerves, release acetylcholine which binds muscarinic receptors and decrease inotropy, chronotropy and dromotropy of the heart (4).

By any given input on the right heart, the cardiac output will increase by sympathetic stimulation and will decrease by parasympathetic stimulation, thereby cardiac output result

from changes in the heart rate and changes in its contractile strength, both of these changes response to the autonomic nerve system (3).

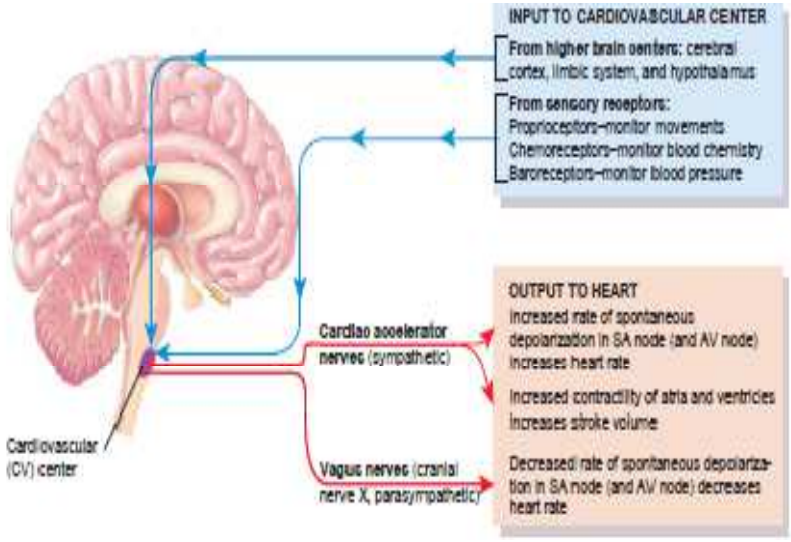


Figure 1.4 Control of the heart by autonomic nervous system, obtained from Principles of anatomy and physiology by G.Tortora & B.Derrickson (2)

By the physical activities, even before begin of these activities, limbic system monitored the situation through proprioceptors and send nerve impulse to increase frequency at the cardiovascular center. Certain chemicals have effect on physiology of cardiac muscle and heart rate, for example as hypoxie, acidose/alkalose (high pH /low pH).Sever hormones as epinephrine and nor epinephrine from adrenal medulla have major effects. These two hormones increase HR and contractility. Thyroid hormones also increase HR. Concentrations of three cations K^+, Na^+ Ca^{2+} plays an important role on cardiac function. Increased concentration of K^+, Na^+ decrease HR and contractility. A moderate high level of Ca^{2+} in interstitial and intracellular speed up the heart rate and strengthens the heartbeat. Also age, gender, physical condition, body temperature influences the heart rate, for example adult female has often higher resting heart rate as adult male(2).

In some specific organs, the efferent parasympathetic fibers innervate blood vessels and cause their vasodilatation through release of acetylcholine, which binds to the muscarinic receptors on the vascular endothelium, another method is by stimulating the nonvascular tissue to produce the vasodilatation substance as bradykinin. Parasympathetic nerves regulate the blood flow on the specific organs but do not have an important role in the regulation of systemic vascular resistance and arterial blood pressure!

Sympathetic nerve release NE which binds on the α_1-α_2-adrenoceptorat the blood vessels and directly constricts the resistance and capacity vessels, thereby increase arterial pressure

and decrease the venous pressure except in the heart and brain but binding to the β_2-adrenoceptor causes vasodilatation (4).

1.2.3 Regulation of the blood flow and blood pressure

Blood flow is blood volume at any tissue by period of time (mL/min). The blood flow deepens on CO, blood pressure and vascular resistance. Blood flows from higher pressure to the lower one and is greater by higher pressure difference, but the opposite occur for the resistance, by higher resistance the blood flow is small (2).

Blood pressure is generated from contraction of the ventricles with systolic pressure of 110mmHg and diastolic 70 mmHg at the aorta level and large systemic arteries, as the blood flows from aorta to the systemic arteries and capillaries drops to 35 mmHg and at venous ends of capillaries drops to 16 mmHg until arrives to the right ventricle with 0 mmHg (3).MAP is the average of blood pressure in arteries and can be calculated as follows:

MAP=diastolic BP+1/3 (systolic BP-diastolic BP) or MAP=CO x R

By calculating the MAP through cardiac output, means that if cardiac output rise by increasing the heart rate or stroke volume, will also mean arterial pressure increase if the vascular resistance stays unchangeable, otherwise decrease of cardiac output will cause the decrease of mean arterial pressure if vascular resistance does not change (2).

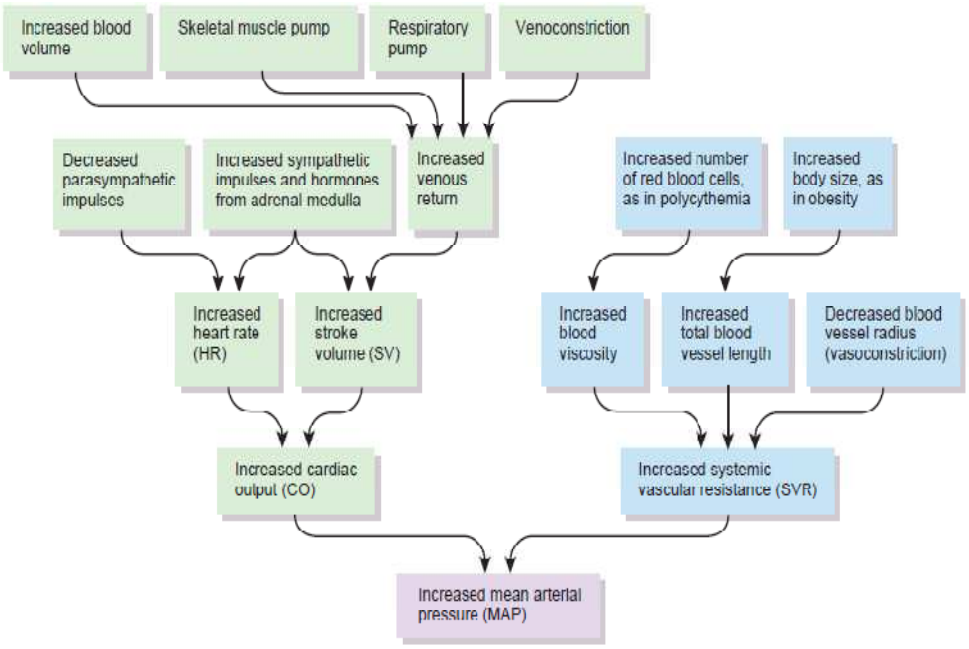


Figure 1.5 Factors that increase mean arterial pressure, obtained from Principles of anatomy and physiology by G.Tortora & B.Derrickson (2).

Vascular resistance is fraction of blood and vessels walls, it is opposition of blood flow and depends on a) size of the blood vessels, the smaller the diameter of the blood vessels ,the greater the resistance. As example when arterioles constrict, resistance will rise and also BP rises, b) blood viscosity, by higher blood viscosity increase the resistance, c) total blood vessel length, resistance is proportional to vessel length, by longer length rise the resistance.

Total peripheral resistance (TPR) represents all vascular resistance of systemic blood vessels. Diameter of arteries and veins are large that's why their vascular resistance is small and the arterioles, capillaries and venuls increase the vascular resistance. By vasodilatation or vasoconstriction of arterioles come to changes at the TPR or also known as systemic vascular resistance (SVR) (2, 4).

In medulla oblongata is located cardiovascular center that controls the neural, hormonal and local feedback system regulation of the blood flow and blood pressure. This center receives an input from higher brain region as the cerebral cortex, limbic system and hypothalamus, even before you run the limbic system sends signals to the cardiovascular center to raise the heart rate (4). Three types of sensory receptors provides an input to the cardiovascular center, proprioceptor that monitor the joints and skeletal movement, thus by physical activates increase rapidly the heart rate, baroreceptor which monitor stretching and pressure changes on blood vessels walls and chemoreceptor which monitor the concentration of chemicals on the blood. The output impulse from cardiovascular center controls the heart through sympathetic and parasympathetic neurons of ANS. This center also sends impulse via vasomotor nerves, which arrive the spinal cord, gets to the sympathetic trunk ganglia and then through sympathetic nervous innervate the blood vessels, thereby came's to vasoconstriction(2 , 4).

1.2.3.1-Short-term regulation

Short term regulation as rapid acting mechanism plays the key role on moment to moment systemic blood pressure regulation, which happens, primer via the neural pathways and targets heart and blood vessels (5).

The nervous system control the blood pressure through negative feedback systems which occurs with these types of reflex: *Baroreceptor reflex*, *Chemoreceptor reflex and Cardiopulmonary reflex* (2).

Baroreceptor reflex

High pressure arterial baroreceptors are pressure sensitive sensory receptors, located in the large arteries in neck and chest but the two most important are reflex of carotid sinus and aorta (2). As the walls of carotid sinus stretches out, the baroreceptors will be stimulated and will send an impulse through glossopharyngeal nerve to cardiovascular center, this reflex help to regulate the blood pressure on the brain and they are not stimulated by pressure between 0-50 mmHg but response to the pressure ranging from 60 to 180mmHg (3).

The baroreceptor located at the walls of ascending aorta and arch of the aorta sends their impulse to cardiovascular center through vagus nerves, thereby their control the systemic blood pressure (1).

When baroreceptor stretch less as the blood pressure falls they send slowly impulse to the cardiovascular center, as a response the cardiovascular center decrease the parasympathetic and increase the sympathetic activation, resulting with increase of heart rate ,increase of the systemic vascular resistance and this produce an increase of cardiac output and blood pressure to the normal level. Conversely by increase of blood pressure, baroreceptors will send faster impulses to the cardiovascular center responding with decrease of sympathetic and increase of parasympathetic nerves activation, thereby occurs decrease of the heart rate and its contractility with decreasing of cardiac output and also through vasomotor neurons occurs vasodilatation with reduce of systemic vascular resistance (2-4).

Cardiopulmonary reflex

Cardiopulmonary receptors or low pressure baroreceptors are veno-atrial mechanoreceptor located at the atria, great veins and pulmonary arteries, which detect venous volume and pressure (5). They are innervated by myelinated vagal afferents. By increase in venous return they can be stimulated resulting with heart rate increase by activation of the sympathetic efferent of the Sino artrial node, this respond is called Bainbridge reflex. An increase in the blood volume and venous pressure activates other cardiopulmonary receptor to decrease antidiuretic hormone release by the posterior pituitary gland, which result with decrease of the blood volume and venous pressure.

Chemoreceptor reflex

These are specialized cells located as peripheral chemoreceptors at the carotid bodies and aortic bodies; they are stimulated by hypoxemia, hypercapnia and acidosis. Fall of the blood pressure leads to decrease arterial $PO_{2,}$ increase to arterial PCO_2 and H^+ thereby chemoreceptor will be stimulated and increase impulse to the vasomotor center to increase the blood pressure through increase the sympathetic activities by vasoconstriction. The central chemoreceptors are located in the medulla and are sensitive to the higher PCO_2 and

H^+ but not to the lower arterial PO_2.These receptors also provide inputs in the respiratory center in the medulla (2, 4).

1.2.3.2- Long-term regulation

Long term regulation, occurs in hours and days, meant to control the blood pressure through controlling the blood volume by involving the endocrine and renal system. There are number of hormones which interact on controlling of the blood volume (5).

Renin-angiotensin-aldosterone system RAAS

When blood pressure falls or decreases of the blood flow in the kidney, the juxtaglomerular cells of the kidney release rennin which transform angiotensinogen released from liver to the angiontensin I, then angiotensin I will be convert to angiotensin II by angiotensin converting enzyme from lungs. Angiotension II as vasoconstrictor, raises BP by increasing of SVR, in other way also stimulate secretion of Aldosteron, that raises reabsorption of Na^+ and H_2O in the kidneys, this way increases total blood volume that raises BP (2).

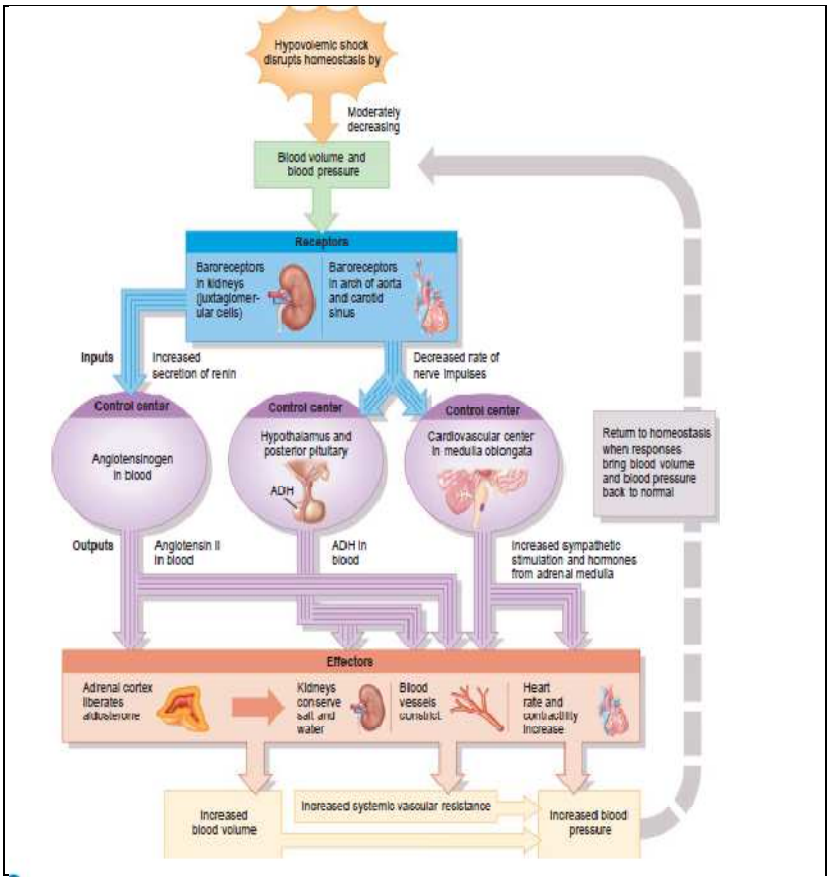


Figure 1.6 Hypovolemic shock, obtained from Principles of anatomy and physiology by G.Tortora & B.Derrickson (2).

Epinephrine and nor epinephrine

These hormones will release from adrenal medulla as response of sympathetic stimulation and provide increase of cardiac output by increase the heart rate and force of contraction. They also provide veins and arterioles vasoconstriction in the skin and abdominal organs, in other side vasodilatate arterioles of cardiac and skeletal muscle, which provides an increase of blood flow to these muscles during physical activities.

Atrial natriuretic peptid (ANP)

This hormone is released by atria cells of the heart and lowers blood pressure by reduce of blood volume in two ways, through vasodilatation and increase the loss of salt and water in the urine.

Vasopressin

As a response to a rise in osmolarity of the blood detected by osomoreceptors in hypothalamus, vasopressin will be released from supraoptic and paravetricular nuclei of hypothalamus, thus vasopressin effect the kidney to promote water retention thereby come to increase of the blood volume. Osomoreceptors can be activated also by thirst and increase water intake (2, 5).

1.3 Cardiovascular physiological adaption in the pregnancy

The women body undergoes with many changes or physiological adaption during the pregnancy, these physiological changes enable growth of fetus and placenta, also prepares the pregnant women for childbirth. The mostly changes during pregnancy begins as early as 4 week gestation and are progressive, these changes are normal and include cardiovascular system, hematology, renal, endocrine, respiratory system, musculoskeletal, immune tolerance changes, beside many changes I will be focused on cardiovascular adaption during pregnancy. The hormonal changes at the first week of the pregnancy makes women feel a body warming because of increase in the blood flow through dilatation of the blood vessels, which response with declaim of the blood pressure (6).

1.3.1 Anatomical changes of the heart

During the pregnancy changes the position of the heart in mediastinum, while uterus grows causes pressure on diaphragm and displaces the heart forward, upward to the left in more horizontal position. In the first trimester raised ventricular muscle mass and in the second or early third trimester increase end-diastolic volume (8), vasodilator effects of progesterone and nitric oxide at 5 week results with physiologic dilatation of the heart (10).Heart enlarges by increase in volume about 70-80mL as a result of increase of diastolic filling and concentric muscle hypertrophy (11).

1.3.2 Systemic vascular resistance

Changes in systemic vascular resistance make increase of hormones progesterone, nitric oxide, prostacyclin and increase capacity of the uteroplacental blood vessels. Progesterone and prostacyclin through relaxing the smooth muscle produce vasodilatation, then uteroplacental vascular system represents low vascular resistance and accommodates a large percentage of cardiac output, all these parameters decrease the SVR by about 20% at 5 gestations weeks and is lowest at 16 to 34 week (8).

	Pregnancy	Peripartum	Post partum
Blood volume	↑	↑	↓
Systolic blood pressure	↓	↑	↑
Diastolic blood pressure	↓	↑	↑
Systemic vascular resistance	↓	↑	↑
Heart rate	↑	↑	↓
Stroke volume	↑	↑	↓
Cardiac output	↑	↑	↓

Hemodynamic changes are discussed in more detail in the text.

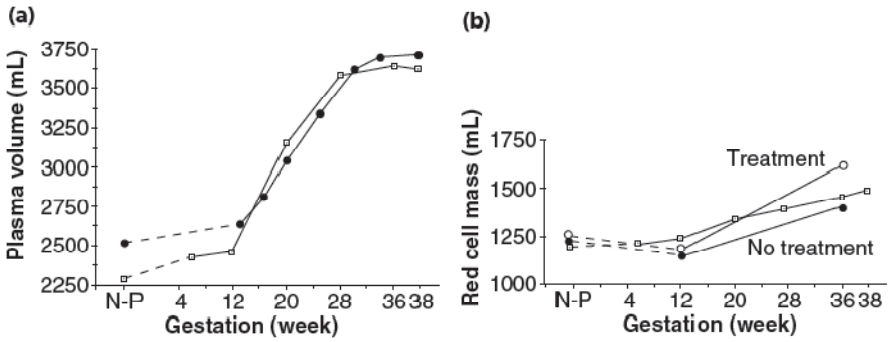


Figure 1.7 Cardiovascular adaption during normal pregnancy, obtained from Heart Disease in Pregnancy by C.K.Silverside,J.M. Colman (12).

1.3.3 Blood volume

The increase on blood volume is very important to provide sufficient blood flow to the uterus, fetus, and maternal tissues, to regulate temperature by increase cutaneous blood flow and to manage blood loss at the birth (8).

In the Figure 1.8 can be seen the difference of hemodynamic change between pregnancy, peri-postpartum period.

Blood volume increase from 8-12 gestation weeks until 36 week by about 30-40% (6), these changes in blood volume are due to increase plasma volume by about 50% and increase of red cell mass about 20-30%, these increases provide decrease of hemoglobin 12 to 16 g/dl and decrease of hematocrit 37 to 47% (8).

This is known as physiological pregnancy anemia, absence of decrease of hemoglobin can be known as first symptoms of maternal adaption disease as can be for example pre-eclampsia, if hemoglobin comes under 11g/dl than it is about Iron deficit anemia (6).

1.3.4 Cardiac output

Cardiac output as we know is a product of heart rate and stroke volume, both of them increase during pregnancy .Cardiac output increase from 30 % to 50%, the fist increase occurs early as 5 gestations week, reaches the peak in second trimester then remains unchanged till term or decrease near term (12).

Cardiac output increase from 5 to 6.5 L/min, as a result of increase both, stroke volume about 10% and pulse rate by about 15 beats/min (11).

1.3.5 Blood pressure

Mean arterial blood pressure falls by about 11% during the first trimester and continues until third trimester, then blood pressure rise again. Systolic blood pressure stays relatively constant during the pregnancy by about 108 mmHg otherwise diastolic blood pressure decrease during the first half to a value of 62mmHg at 20 gestations week then will increase significantly by week 38 at 72 mmHg (12).

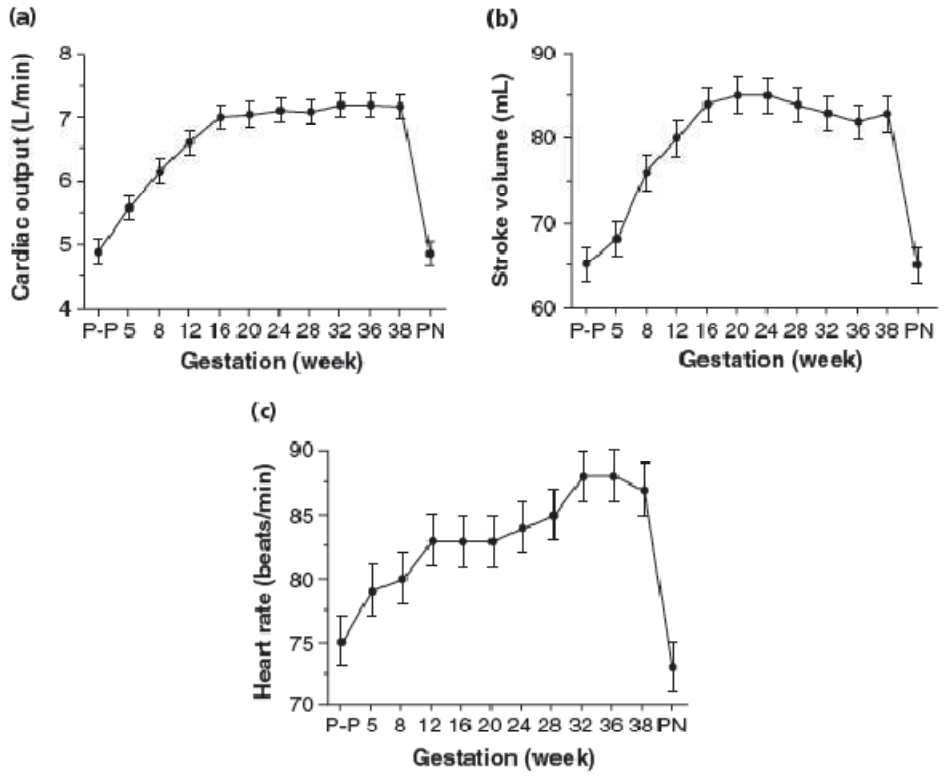


Figure 1.8 Changes in CO, HR and SV during normal pregnancy, obtained from Heart Disease in Pregnancy by C.K.Silverside,J.M. Colman (12).

Hormonal change produces decrease of systemic vascular resistance which causes blood pressure to fall during first and second trimester by about 10-20 mmHg.

The balance between vasodilatation and vasoconstrictor substance represents the basic mechanisms of blood pressure regulation during pregnancy and in case of any dysfunction occurs development hypertension disease in pregnancy (11, 13).

1.4 Hypertensive disorders during the pregnancy

Hypertensive diseases are the most common complication appears during the pregnancy, affecting 5-10% of all pregnancies and a common cause of maternal morbidity and mortality (15). Women over 35 years have an increase on morbidity and mortality, three to fourfold higher morbidity appears at black women (14). The disease spectrum ranges from mildly to severe hypertension and organ dysfunction. Incidence of hypertensive disorders

during pregnancy is determinated from different demographic parameters (maternal age, race, medical condition). (15).

Hypertension during pregnancy increases the incidence of placental abruption, eclampsia, preterm delivery, renal insufficiency, pulmonary edema and in the worst case death. In the last 10 years because the increase of obesity in the world is also the incidence of hypertension in general population by about 50% increased. The table below introduces the systemic classification of hypertension in pregnancy and their definition recommended from The American College of Obstetricians and Gynecologist (ACOG) (14, 13).

Table 1.1 Classification and definitions of hypertension during pregnancy (15).

Disorder	Definition
Gestational Hypertension	Hypertension after 20 pregnancy week or first 24 hours p.p without proteinuria/sings of pre-eclampsia.
Transient Hypertension	Hypertension by 12 week p. p
Chronic Hypertension	Hypertension occurs not by 12 week p.p
Pre-eclampsia or eclampsia	Hypertension occurring after 20 pregnancy week with proteinuria; eclampsia (seizure activity without other identifiable cause).
Chronic Hypertension	Prior hypertension by 20 weeks gestation or after 12 week p.p
Pre-eclampsia superimposed	By women with prior pre-eclampsia or chronic hypertension

1.5 Pre-eclampsia

Pre-eclampsia is a multisystem disorder during pregnancy, affecting 5%-10% of all pregnancies with maternal /fetal morbidity and mortality, also 25% responsible for premature deliveries (17).

Pre-eclampsia is combination disorder appearing in pregnancy, occurrence of hypertension (Blood pressure > 140/90 mmHg) with proteinuria (>300mg/24-h urine at >20 gestations week).Appearance of pre-eclampsia < 20 gestations week is unusual und may suggest as trophoblastic disease or molar pregnancy, 90% of pre-eclampsia cases occur in > 34 gestations week.(14,13)

1.5.1 Diagnosis of pre-eclampsia

There are two known subdivided form of pre-eclampsia, mild and severe pre-eclampsia, which diagnosis criteria are described in the Table 1.2 and Table 1.3 (15).

Table 1.2 Diagnosis criteria for mild Pre-eclampsia (15).

Diagnosis of mild Pre-eclampsia
Blood pressure>140/90, in 6 hours apart, after 20 gestations week.
Proteinuria (300 mg / 24 h) or > 1+ on two random samples urine dipsticks at least 6 hour apart.

Table 1.3 Diagnosis criteria for severe Pre-eclampsia (15).

Diagnosis of severe Pre-eclampsia
SBP >160 mmHg /DBP> 110mmHg, occurring at least 6 hours apart.
Proteinuria (5gr/24h) or 3+ or greater on two random urine samples collected at least 4 hour apart.
Oligouria <500 cc in 24 h
Thrombocytopenia < 100.000/mm^3
Epigastric pain
Pulmonary edema

Cerebral/ visual disturbance

SBP >160 mmHg and DBP > 110mmHg, at least by 6 hours apart.

The pregnant women with mild pre-eclampsia or gestational hypertension may progress to fulminate disease, that's why they should be closed observated. The severe form of pre-eclampsia are HELP-Syndrome or eclampsia but the diagnosis are deceptive, 10 % of women who developed HELLP syndrome and 20% of women with eclampsia, hypertension and proteinuria may be absent.

1.5.2 Risk Factors for pre-eclampsia

There are several risk factors that are identified by women with pre-eclampsia, as null parity, chronic or vascular disease, fetal hydrops, molar pregnancy, multifetale gestation, obesity and insulin resistance, antiphospholipid antibody syndrome and thrombophilia, family history of pre-eclampsia or eclampsia, maternal infections, advance maternal age > 35 year, maternal susceptibility genes.(13-15)

1.5.3 Clinical features of pre-eclampsia

Pre-eclampsia is often asymptomatic, diagnosis based on raised blood pressure and proteinuria but there are also some characterized clinical features which can include nausea, general malaise, vomiting, frontal and occipital headaches, photophobia, flashing lights, epigastric pain, due to liver edema and pericapsular swelling (11).

1.5.4 Etiologic factors of pre-eclampsia

Etiologic factor responsible for pre-eclampsia are unknown but there are some theories believed as a mechanism how may come to development of pre-eclampsia as abnormal or increase immune response, genetic predisposition, abnormal coagulation or thrombophilias, abnormal angiogenesis, endothelial cell injury, abnormal cytotrophoblast invasion, abnormal calcium metabolism, increase oxygen free radicals, alternations in nitric oxide levels (15).

1.5.5 Pathophysiology of pre-eclampsia

The focus of pre-eclampsia research is based on two stage of pre-eclampsia. The first stage include abnormal placentation through trophoblast invasion, where the maternal spiral arteries undergoes to remodeling what in healthy pregnancy provide vasodilatation, in case of pre-eclampsia this remodeling could not be compiled, spiral arteries fail to dilate and leads to poor placental perfusion which is the root cause of pre-eclampsia and result with oligohydramnios, intrauterine growth restriction, placental abruption, fetal distress (18).

The second stage includes maternal systemic disorders. The hypertensive changes seem in pre-eclampsia involves misbalance between vasoconstrictive (thromboxan A,endothelin) and vasodilatation(prostacyclin, nitric oxide) substance, which provide higher blood pressure, reis on afterload. Another changes in cardiovascular system at the women with pre-eclampsia is lower intravascular volume through endothelial damage allows intravascular fluid and protein into interstitial space. Decrease of intravascular volume allows less tolerance for blood loss by delivery. There are also other abnormalities in maternal system as hematological, thrombocytopenia and activation of higher level of thromboxane A_2 , renal system is also involved, vasospasms lead to decrease of renal perfusion and decrease or glomerulo filtration rate, which in normal pregnancy increase above 50%,result with increase of serum creatin and oligouri and ate the end with renal failure. Hepatic damage in pre-eclampsia can be range from increase of liver enzyme levels to a sub capsular liver hematomas and hepatic rupture, which associate with HELP Syndrome (13, 15).

1.5.6 Management of mild pre-eclampsia

Mild pre-eclampsia refers to all women which do not have sings of severe disease, typically with blood pressure> 140/90 mmHg but not > 160/110mmHg and proteinuria >300mg/24 hour but not >5 gr/24 hour.

The main risks for the mother are: eclampsia, cerebral vascular damage, renal and liver failure, DIC and HELP –Syndrome. The main risks for the fetus are intrauterine growth restriction, intrauterine death and iatrogenic preterm delivery (11).

Patient with pre-eclampsia should be hospitalized for evaluation of maternal and fetal status, Table 1.4 range fetal and maternal evaluated parameter.

Delivery is the only treatment for pre-eclampsia und should be associated with balance between optimal perinatal outcomes of fetus and reduce of maternal risks.

In case of preterm pregnancy all benefits of management are for fetus and by term pregnancy the plan should be for delivery. In Figure 1.10 explains the algorithms of recommended management of mild pre-eclampsia (15).

Table 1.4 Maternal and fetal evaluation by mild pre-eclampsia (15)

Maternal Evaluation	Fetal Evaluation
Daily weight	Daily fetal movement
Urine dipstick daily,24-h protein once weekly	Nonstress test 2/week
Monitoring for severe pre-eclampsia symptoms	Ultrasound every 3-4 weeks.
Prenatal visits 2/week	
Lab test(Liver function test, hematocrit, platelet)	

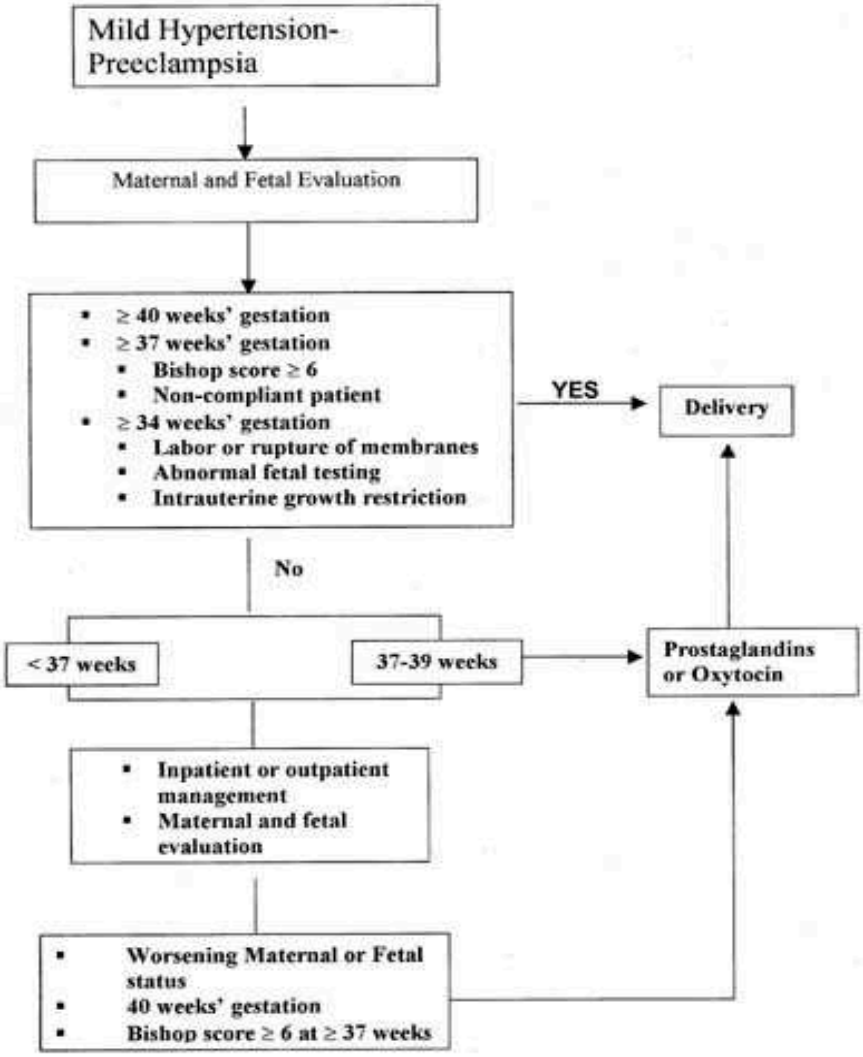


Figure 1.9 Recommended management of mild pre-eclampsia; obtain from Coppage, K, Sibai, B, Global library of women's medicine (20).

1.5.7 Management of severe pre-eclampsia

There are many women with severe pre-eclampsia which are asymptomatic but physical examination may reveal symptoms:

-central nervous system dysfunction,

-epigastria pain,

- pulmonary edema,

-blood pressure >160/110mmHg,

-eclampsia,

-fetal IUGR,

-proteinuria > 5g/24h,

- Renal failure,

-Oliguria,

-Thrombocytopenia,

-HELP syndrome

Any patient with severe pre-eclampsia should be observed in a labor and delivery unit, progression of disease clinical may be rapidly worst and complication are associated with increase of perinatal mortality and increase of maternal morbidity and mortality(11).

In delivery unit should be close maternal observance, blood pressure monitoring prevents from cerebrovascular stroke.

The antihypertensive allowed in hypertensive crisis are hydralazine 5mg in bolus every 10-15 min until blood pressure controlled is and max. 20 mg, labetolol 20-40 mg and nifedipine 10-20 mg per oral every 30 min, the management of severe pre-eclampsia should be continue as it is explained in the Figure 1.11 (15).

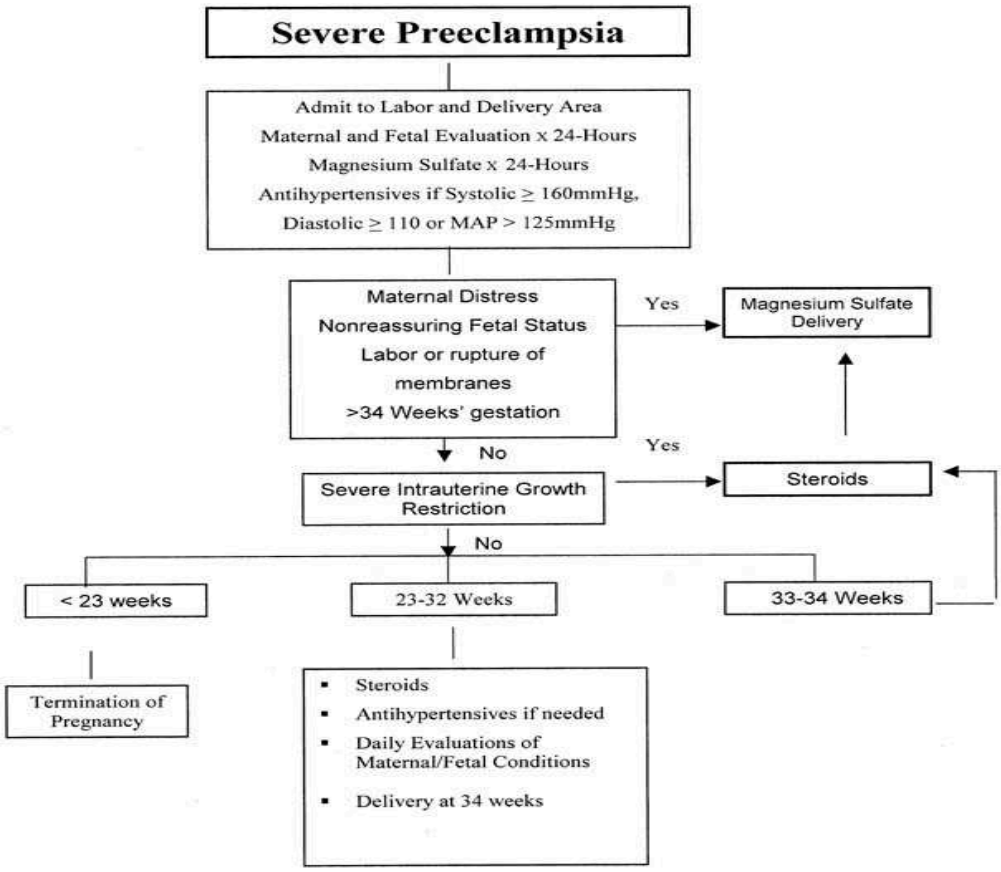


Figure 1.10 Recommended management of severe pre-eclampsia; obtain from Coppage, K, Sibai, B, Global library of women's medicine (20).

II Aims and objectives

This Diploma work explores cardiovascular regulation on physiological basis and then reviews relevant literature that shows how the cardiovascular system is affected by pre-eclampsia.

Based on existing literature I explain how the cardiovascular system is regulated in pregnancy, paying special attention to the role of the heart and blood vessels and then summarize what it known about pre-eclampsia.

The aim of the current Diploma work is to provide an update on existing literature related to cardiovascular regulation and how pre-eclampsia during pregnancy affects the cardiovascular regulation. Possible therapies that are used in the treatment of pre-eclmapsia are also discussed.

The question about how cardiovascular system is affected by pre-eclampsia is discussed through search for the past and current literature available on the web.

I would explain what happened to the cardiovascular system during the pregnancy including blood pressure regulation, fluid and volume regulation and how is associated with effects of pre-eclampsia. As pre-eclampsia can be life threatening disease, the pharmacological option which is presently available for pre-eclampsia was also outlined and discussed.

III Methodology

The subject of my search is „Cardiovascular regulation and vascular function in pregnancy and pre-eclampsia" .My special particular interest is directed in gynecology and obstetrics, while I searched about these topics I got curios to know cardiovascular adaption during pregnancy and pregnancy associated cardiovascular dysfunction. I also wanted to find out the cardiovascular changes associated by development of pre-eclampsia and that also led me to question how a normal pregnancy with physiological cardiovascular changes can develop to a pre-eclampsia and which are cardiovascular causes behind that, for this reason I decide to search the existing literature.

My construction strategy that helped me to collect systematically the relevant literature related to my research is based on some steps, which I will explain next.

To identify the required subject, I used the following keywords by using free text terms

-Cardiovascular system

-Regulation of blood pressure

-Maternal adaption in pregnancy

-Pre-eclampsia

Then I attempt searching the possible synonyms:

-''cardiovascular system'': cardiovascular anatomy, cardiovascular control, blood vessels function, and circulatory system

-''regulation of blood pressure'': long term and short term regulation

-''maternal adaption in pregnancy'': physiological change during pregnancy, cardiovascular system adaption in pregnancy

-''pre-eclampsia'': hypertension in pregnancy, gestation hypertension

At the end, through using the MESH database, to find out which terms mentioned above were represented in Pubmed, I could collect most of the topical papers. As I mark the terms, I start building my search.

The search criteria were limited by: use of „AND" or „Or" or „NOT" helps me to focus in my research and to find the adequate article on a field of my interest. Therefore, I used combination as cardiovascular system AND pregnancy, pregnancy AND pre-eclampsia.

In addition, I putt quote (‘’) on the keywords which helped me finding the specific articles related to these keyword through using combination as ‘’Pregnancy’’ AND ‘’Pre-eclampsia’’.

Refining my search criteria: to avoid unnecessary article which were not relevant to my field of interest I used the word NOT to refine my search criteria during my research, therefore I used: (pregnancy NOT pregnancy disease) AND pre-eclampsia.

Another parameter which I used as search criteria was the publications dates of articles which include articles with publication dates in the last 20 years.

My research scores/database:

Pubmed was the first database I used regularly to summarize my research, covers most of the publication related to my research area, offers simple use and keeps all the time update, but for the other parts of articles which were not to find on Pubmed, I used **Web of Science** database. This database offers pretty much information about authors, was very easy to use and was very useful offering list of references of the articles, what for me were sometime more helpful as the article itself. I also used **Google** as score to find picture related to my introduction part of my thesis.

The criteria for the literature choice were as followed:

1. How considerable was it to my research?
2. Included articles were written in the last 20 years.
3. As primary included literature were abstracts and full texts.
4. Physiology books and online Google books were used as second literature

5. Most of the articles written in English and also some books written in German were used
6. Article from all countries were included
7. Publications relevant to cardiovascular regulation in pregnancy and pre-eclampsia were included, not other pregnancy disease.

How I saved the references

I used Refworks to save my references through online importing from Pubmed and Web of Science to my Refworks account and I could also format them to Vancouver style.

IV. CURRENT UPDATE OF THE LITERATURE

In this part of my Diploma work I will represents updates divided in two categories:

A) Updates provided from studies about physiological adaption of cardiovascular system during pregnancy, different views of cardiovascular changes occurring in women's body during different gestations week, hypothesizing that hemodynamic changes begins in the early stage of fetal-placental unit and morphological changes later in second and third trimester.

B) Updates provided from studies about pregnancies, which developed in pre-eclampsia and then I summarized updates from studies dealing with pre-eclampsia risk factors, predicting early diagnosis and also studies focused on how maternal cardiovascular system in postpartum stage is affected by pre-eclampsia.

A) <u>Studies about physiological adaption of cardiovascular system during pregnancy</u>

Table 1.5. Studies dealing with cardiovascular changes during pregnancy

Authors	Subjects	Measurements done on gestations weeks (g.w.)	Results
Charpman et al	n=13 pregnant women	6,8,10,12,24,36 g.w.	By 6 g.w. MAP↓, SVR↓, CO↑ PV↑, GRF↑, Plasma Renin↑, Aldosterne↑, Norepinephrine↓
Savu et al	n=64 pregnant women	1.Trimester/12-14 2.Trimester/22-24 3.Trimester/ 32 3-6 month postpartum	At 2 Trimester SBP+DBP ↓, MAP↓, SVR↓, CO↑, LV remodeling
Cong et al	n=68 pregnant women	2DE and 3DSTE : at 1-2-3Trimeseter and 6-9postpartum	Cardiac index33%↑, Ecc.hypetrophy of LV

Morris et al	n=28 healthy women compared to 17 pregnant women	Pre pregnancy and 30 months post pregnancy	MAP and PWV decrease from pre to post pregnancy
Clapp and Capeless	n=30 healthy, physically active women (15 nulliparous and 15 parous)	-before pregnancy, every 8 week during pregnancy, -12,24, 52 post pregnancy	early CO↑ , 17%↑ SV, 26%↑HR, MAP↓ early peak by 16 g.w, LV- EDV and SV ↑ by 8-16 g.w

Now I will explain the studies represented in the Table 1.5

Charpman(20) and his colleagues explains connections between hormonal and hemodynamic adaption in pregnancy, these data were assemble from following thirteen pregnancy women at identical gestational week 6,8,10,12,36,participants were between age 21 and 40 years and did not have history of cardiac or renal disease, hypertensions or diabetes mellitus.

The authors hypothesize that these changes in pregnancy occurs in early stage of pregnancy, at existence of fetal-placental unit.

Outcomes from these studies result with decrease of mean arterial pressure by six gestations week associated with increase of plasma volume, increase of CO and decrease SVR, also by six gestations week will increase glomerular filtrations rate, plasma rennin und aldosterone concentrations ,whereas norepinephrine stays unchangeable during the pregnancy.

Savu (21) et al explains morphological and functional adaption of the heart through normal pregnancy while considering the same parameters at postpartum period; therefore they did a study with 64 pregnant women at age range from 19 to 37 years, without cardiovascular disorders or under medication with cardiovascular effects.

These healthy pregnant women had four normal physical and 2D echocardiograph examinations, one examination during each pregnancy trimester (1.trimester at 12-14 week, 2.trimester at 22-24 weeks and 3.trimester at 32 weeks) and also the last one at 3 to 6 months postpartum., 13 women were exclude from data analyses, 4 because of image with poor quality, 4 because of lacking at least two examination during pregnancy and 5 others were exclude because of pathology during pregnancy.

The result during pregnancy showed decrease of systolic, diastolic and mean arterial pressure at second trimester followed with slight increase at third trimester, we have also a decrease of total vascular resistance which stays unchangeable until third trimester and a

progressively cardiac output increase because of early increase of SV and late increase of HR, also left ventricle showed eccentric hypertrophy because of increased cardiac performance while increase of preload and decrease of after load .Left ventricular strain (longitudinal deformation) will start to decrease in the late period of pregnancy until return to baseline value at 6 month post partum.

There is another study **Cong** (22) which investigates LV structure and systolic function of the heart during pregnancy by examination of 68 healthy pregnant women, without any diseases or under medication, by using two dimensional echocardiography and three dimensional speckle tracking echocardiography and also blood pressure and weight were measured.

The examinations were performed at 1.trimeseter (12-14 g.w.), 2.trimester (24-26 g.w.), 3.trimester (36-38 g.w.) and 6-9 weeks post partum, their mean age was 29.6 years and as control served 30, age matched, non pregnant healthy women.

Hemodynamic characteristics results with reduce of mean arterial pressure during 2 trimester followed by mild rise at 3 trimester and cardiac index increase by 33% between 1-3 trimesters as result of increase of HR and SV.

Data of 2DE shows an increase in LV diameter and wall thickness (cardiac hypertrophy), which will recover after the delivery, ejection fraction (EF) and peak myocardial velocity(s) will decrease between 2-3 trimester and get to normal after delivery.

Results from 3DE shows an increase on LV volume, LV mass index and CI during the pregnancy, which recovers postpartum. Also with 3DE were global directional strain (longitudinal, circumferential, radial) assessed, which shows a significantly decrease from 2-3 trimester and increase again postpartum.

Morris (23) and his colleagues invested a study who evaluates the continuous effect of pregnancy on maternal cardiovascular physiology compared with group of nonpregnant women. There were 54 nulliparous healthy women who went to cardiovascular evaluation before the conception and 30 months after delivery, 17 women conceived pregnancy, whereas remaining 28 women not interested in conception were recruited as control group.

All participants were young (between 18-40 years), healthy without history of disease known on affecting the blood pressure. There were measured MAP, CO, PV, pulse wave velocity (PWV) and uterine blood flow at each visit.

The outcome was a significant decrease in MAP from period before pregnancy to 30 months after delivery (pre-pregnancy 85.3 mmHg, post pregnancy 80.5mmHg) and no change at non pregnant control group. Pulse wave velocity shows decrease on pregnancy interval (pre-pregnancy 2.73 m/s, post pregnancy 2.49 m/s) without changes at control group.

Effect of other parameter as CO, PV, and uterine blood flow were not observed. These author hypotheses, that outcome with decreased MAP and PWV suggest a favorable effect of pregnancy on maternal cardiovascular remodeling and also may represent mechanism of reducing pre-eclampsia risk on future pregnancy.

Begin of vascular remodeling in early pregnancy stage and continues until 1 year p.p were hypothesis of **Clapp and Capless** (24).In this study participate 30 healthy, nonsmoking, physically active women, 15 were nulliparous and 15 parous women and they were 32 +-1 years. In this group of pregnant women were measurement HR, AP, LV volume, CO and SVR, in period pre-pregnancy, every 8 weeks during the pregnancy and 12,24, 52 weeks post partum.

Outcomes shows an increased heart rate in early pregnancy weeks, achieves the peak at term 15 beats/min and returned at baseline by 12 weeks after the delivery .Mean arterial pressure will decrease in the early pregnancy weeks, reaches its peak by 16 gestation week and return to baseline at the delivery term without any changes thereafter.

LV end diastolic volume and stroke volume increase by 8 and 16 week, then levels off without any significant changes after 24 gestations week, until the delivery term and throughout first post pregnancy year both parameter return to pre pregnancy level.

The outcomes represent also over 70% of the increase on CO and bigger than 85% decrease of systemic vascular resistance by 16 gestations week, without any significant changes after 24 weeks but there is 23% pregnancy associated increase on CO and 30% decrease on SVR still present at one year after the delivery.

During the pregnancy were calculated an increase on CO through 17% of increased SV and 26% increased HR. From these data is also known that ventricular volume, CO and SVR are greater during the following pregnancies as in the parous group.

B) Studies dealing with pre-eclampsia

1) Studies dealing with pre-eclampsia risk factors

Table 1.6 Studies dealing with pre-eclampsia risk factors.

Authors	Subjects	Measurements	Results	Pre-eclampsia Risk factor
Mohaghegh et al	n=41 preeclamptic pregnant women n=50 healthy pregnant women	-2ml venous mother blood -2ml from umbilical cord -Vitamin D serum level mother and neonates	-Vitamin D↓ in preeclamptic women vs.controll group (15.2±13.6 versus 23.3± 15.3 ng/ml) -Vitamin D↓ in their neonates (15.2±13.1 versus 21.6±12.6ng/ml)	Vitamin D serum level deficiency or insufficiency
Pare et al	n=2637 pregnant women	-mater. medical -mater. familiar -obstetric history - maternal height -(16-22 g.w,24-28 g.w and 34-38 g.w)BP urine samples, maternal weight and ultrasound results were	-237 (9%) from participants developed pre-eclampsia	Chronic hypertension Pregestational diabetes Multiple gestation African American race Prior pre-eclampsia -nulliparity Assisted reproductive techniques Being overweight(BMI greater

		recorded		than 25-30) or obesity (BMI over 35-40)
Connealy et al	n=606 pregnancies with prior pre-eclampsia	-frequency of preterm birth in women with prior pre-eclampsia -neonatal outcomes (spontaneous /medical indicated preterm birth)	-142 women delivered at <37 week:67 spontaneous preterm birth and 75 medical indicated preterm birth	Prior-pre-eclampsia
Laszlo et al	n=124553 -Cohort study Denmark (1978-2008) and Sweden (1973-2006)	Mothers who lost their closed relatives 6 months before or during pregnancy	-Risk increased for a women 6 months before pregnancy - during the first trimester	Psychosocial stress
North et al	n=3529 healthy nulliparous	-Pre-eclampsia -Preterm pre-eclampsia -14-16 gestations week	186 developed pre-eclampsia, including with 41 preterm pre-eclampsia	Age younger) Higher MAP, Obesity, Familiar pre-eclampsia history, Familiar history of coronary heart disease,

Now I will explain the studies represented in the Table 1.6

Mohaghegh (25) and his colleagues investigated a study about relationship between pre-eclampsia and vitamin D level deficiency or insufficiency, in the serum of the mothers and their neonates. In this case control study participate 41 preeclamptic women and 50 healthy women, 2 ml venous blood from mothers and 2 ml from umbilical cord were required to analysis level of vitamin D, under 20ng/ml were range

as deficit, between 21-29ng/ml were range as insufficiency and higher as 30ng/ml were considered as normal level.

The outcome shows a lower mean level of vitamin D in preeclamptic women (15.2 versus 23.3ng/ml) and their neonates (15.2versus 21.6 ng/ml) as in the control group. This existing deficiency level of vitamin D in preeclamptic mothers(by delivery) and their neonates represents a connections of serum level of vitamin D and pre-eclampsia, therefore a supplement with higher dose than 400IU with vitamin D were recommended in the early pregnancy weeks.

There was another prospective cohort study by **Pare** et al (26) which describes risk factors for pre-eclampsia in the twenty-one century. This study includes in analysis 2637 women from academic centers, two in Boston and another in Philadelphia from 2006 to 2008, where the demographic and clinical factor were taken from standardized chart review.

Maternal medical, familiar, obstetric history and maternal height were documented, whereas by each visit between 16-22 g.w,24-28 g.w and 34-38 g.w ,the blood pressure ,urine samples, maternal weight and ultrasound results were recorded,237 (9%) from participants developed pre-eclampsia.

The outcomes confirmed that chronic hypertension, pregestational diabetes, multiple gestation, African American race, prior pre-eclampsia, nulliparity, assisted reproductive techniques, being overweight(BMI greater than 25-30) or obesity (BMI over 35-40) were associated with pre-eclampsia. The most considerable risk factor were being overweight or obesity.

Connealy et al (27) investigated the commonness and type of preterm birth in the prior pre-eclamptic women and then compeared neonatal outcomes among spontaneous and medical indicated preterm birth.
This study analysis data from 606 pregnancies with prior pre-eclampsia, from them 142 women delivered at <37 week: 67 pregnancies delivered by spontaneous and 75 by medical indicated preterm birth.

The primary outcomes represents the rates of spontaneous and medical indicated preterm birth by gestations age, the overall rate of neonatal morbidity was 23% and rate of small gestations age of infants was increased in indicated as in spontaneous preterm birth.
This study shows that women with prior pre-eclampsia are at higher risk for preterm birth (indicated and spontaneous) as well increased risk for small gestation age.

Laszlo (28) and his colleagues investigated, if the role of stress before/during the pregnancy have a relationship with pre-eclampsia, in a cohort study of singleton birth

in Denmark (1978-2008) and Sweden (1973-2006) were considered mothers who lost their parents, sibling, partners or child 6 month before/during the pregnancy (n=124553).

The risk of developing the early pre-eclampsia were slightly increase for the women who lost their close relatives 6 month before conception or during the first trimester, therefore the results suggest that several stress may influence the placentation and in this way also as a risk factor for developing a pre-eclampsia.

North (29) and his colleges investigate a international multicenter cohort study, where participated 3529 healthy nulliparous women, with singleton pregnancy.

As main result measurement was pre-eclampsia (systolic BP >140mmHG, diastolic BP>90mmHg at least two occasions four hour apart after 20 g.w. with either proteinuria or any multisystem complication), preterm pre-eclampsia (women with pre-eclampsia with delivery before 37+0 g.w.) and as comparison group were women without pre-eclampsia.

The result shows that from participated group in 186 developed pre-eclampsia, including with 41 preterm pre-eclampsia. Risk factor at 14-16 g.w. were age (younger), higher mean arterial blood pressure, obesity, familiar pre-eclampsia history, familiar history of CHD, maternal low birth weight.

2) Studies dealing with prediction and diagnosis of pre-eclampsia

Table 1.7 Studies dealing with prediction and diagnosis of pre-eclampsia.

Authors	Subjects and study model	Measurements	Results
Rani Singhal et al	Prospective study n=125 pregnant women with pre-eclampsia after 20 gestations week	Total urine protein of 2-4-8-12 hour urine collection compeered to 24 hour urine collection	2-Hour urine proteins→proteinuria in pre-eclampsia instead gold standard 24 hour urine
Kashanian et al	Prospective cohort study n=394 pregnant women	Serum high – sensitivity C-reactive protein(hr-CRP) between 8-13 gestations week	-42 cases developed pre-eclampsia >7mg/L : 61.9% pre-eclampsia cases and 6.25% normotensive pregnancies - hs-CRP predicting pre-eclampsia
Herraiz et al	Case control study n=171(with fetal growth restriction (n=27),with and without pre-eclampsia or HELP syndrome (n=105) and pre-eclampsia or HELP Syndrome and fetal growth restriction (n=39)) -n=171control group	Median values of sFlt-1/ PIGF ratio 34 gestations week	Higher median values of sFlt-1/ PIGF ratio
	Prospective clinical study	Free plasma PGF and free sVEGF 1- were	n=409 uncomplicated pregnancies n=48 pre-eclampsia (median level of

Sunderji et al	n=457	measurement between 20-36 gestations week	sVEGF 1↑, PGF↓) Ratio of sVEGF 1/ PGF provided better test in diagnosis of pre-eclampsia
De Vivo et al	Prospective study n=52 preeclamptic n=52 pregnant healthy women	Endoglin , sFlt-1 and sFlt-1/PIGF 24-28 gestational weeks	Endoglin,PGF,sFLT-1are increased in pre-eclamtic group
Poon et al	Prospective screening study for early/late pre-eclampsia n=8061 subjects	Combination of maternal factors, uterine artery with lowest pulsatility index (L-PI), mean arterial pressure (MAP) and serum PAPP-A 11(+0)-13(+6) gestations week	37 early pre-eclampsia, 128 late pre-eclampsia 140 with gestational hypertension -In PE- MAP and uterine artery with lowest pulsatility index increase, PAPP-A decrees -GH- PAPP-A – unchangeable PAPP-A better screening performance for PE

Rani Singhal(34) and his colleagues observed a study to find out about the shortest time of urine collection for detection of proteinuria in pre-eclampsia.

In this prospective study participate 125 pregnant women with pre-eclampsia after 20 g.w. and total protein of urine collected in 2,4,8,12 hour urine were compeered to 24 hour urine collection.

The result showed that 2-hour urine proteins can be used for determination of proteinuria in pre-eclampsia instead of gold standard 24 hour urine collection for early diagnosis of pre-eclampsia and better patient compliance.

The study done from **Kashanian** et al (35) represents diagnostic value of maternal serum high –sensitivity C-reactive protein (hr-CRP) during first Trimester in predicting pre-eclampsia. In this prospective cohort study preformed 394 pregnant women at 8-13 g.w, out of them 42 cases were complicated by pre-eclampsia, of whom 23 had severe pre-eclampsia and hs- CRP was measured in tow groups with and without pre-eclampsia.

The results showed significant difference of serum hs-CRP level, more than 7mg/L was found in 61.9% cease of pre-eclampsia and 6.25% normotensive pregnancies, that's why hs-CRP level during first trimester can be used as predicting parameter for pre-eclampsia.

Another factor that may be important on early predicting and diagnosis of pre-eclampsia were observed in a case control study in two centers, Berlin and Madrid done from **Herraiz** et al (36). The aim of this study were to define the values of soluble fms-like tyrosine kinase-1(sFlt-1) to a PGF ratio in pregnancies (n=171) with fetal growth restriction (n=27), with/without pre-eclampsia or HELP syndrome (n=105) and pre-eclampsia or HELP Syndrome and fetal growth restriction (n=39), compeered by 171 control healthy pregnancies. Measurements of sFlt-1 and PGF of maternal serum were preformed after diagnosis, before at or after 34 gestation week.

The results represents an increase of median values of sFlt-1/ PGF ratio in the pregnancies with fetal growth restriction , pre-eclampsia or HELP syndrome and pre-eclampsia or HELP Syndrome with fetal growth restriction than control group, sFlt-1/ PGF may be used as predicting factor for preecmaplsia.

Sunderji et al (37) observed a prospective clinical study to assess PGF (proangiogenic protein) and soluble vascular endothelial growth factor 1 (sVEGF 1-antiangiogenic protein) in diagnosis of preterm pre-eclampsia.

During this study were evaluated 457 subjects, whom free plasma PGF and free sVEGF 1- were measurement between 20-36 gestations week, from these group 409 completed pregnancies without pre-eclampsia or any complication and by 48 subjects developed pre-eclampsia.

Outcomes represents that free PGF and sVEGF 1 were useful in predicting pre-eclampsia against normotensive women, median level of sVEGF 1 dramatically elevated and median level PGF decreased in 48 in a women diagnosed with pre-eclampsia against normotensive women but the ratio of sVEGF 1/ PGF provided better test in diagnosis of pre-eclampsia than either analyte alone.

De vivo et al (38) observed a prospective study to evaluate ability of endoglin, PGF and soluble form of vascular endothelial growth factor receptor (sFlt-1) on propose of predicting pre-eclampsia. In this study participate 52 preeclamptic and 52 pregnant healthy women, measurements were made between 24-28 gestational weeks.

Results showed increased level of endoglin , sFlt-1 and sFlt-1/PIGF ratio in a preeclamptic group and the authors concluded that endoglin,PIGF,sFLT-1 might be used as markers for predicting pre-eclampsia but sFlt-1/PIGF ratio need to be more exact.

Poon et al (39) researched prospective screening study for early/late pre-eclampsia and gestational hypertension, in propose to explain if addition of pregnancy-associated plasma protein A (PAPP-A) to maternal factor and biophysical markers may be used in determination of hypertensive disorders before clinical manifestation.

In this study participated 8061 subjects, 37 of whom developed early pre-eclampsia, 128 late pre-eclampsia and 140 with gestational hypertension. The screening performance were made at 11(+0)-13(+6) g.w. determinate by combination of maternal factors, uterine artery with lowest pulsatility index (L-PI), MAP and serum PAPP-A.

Results represent an increase of MAP and uterine artery with lowest pulsatility index and decrease of PAPP-A in early and late pre-eclampsia group compared to control group. In gestation hypertension PAPP-A was not different from control groups.

At the end authors concluded that measurement of PAPP-A improves the screenings performance for early and late pre-eclampsia implied by combination of maternal factor and biophysical test at 11-13 gestation weeks.

3) Studies dealing with postpartum cardiovascular system in women with pre-eclampsia history.

Table 1.8 Studies dealing with postpartum cardiovascular system in women with pre-eclampsia history.

Authors	Subjects	Measurements	Results
Evans et al	n=18 prior preeclamptic n=50 uncomplicated pregnant women	16 months postpartum Systemic hemodynamic and mechanics Endothelial function Left ventricle properties Blood biochemical analysis	Prior preeclamptic: ↑ (MAP,DP,VR, higher glucose level), No difference(SP, arterial compliance , LV properties, endothelial activation, dyslipidemia or oxidative stress) Cardiovascular disease risk later in life
Agatisa et al	n=16 with prior pre-eclampsia n=14 normotensive pregnancies n=20 never being pregnant as control group	6-12 month postpartum Forearm blood flow (FBF) HR BP	In prior preeclamptic women: -No difference FBF, HR, systolic and diastolic BP MAP ↑ Hypertension and heart disease risk later in life↑
Lwaleed et al	n=26 participant with prior pre-eclampsia n=26 age-matched without past history of pre-eclampsia	Tissue factor (TF) TF pathway inhibitor(TFPI) Up to 3 years post partum	Prior preeclamptic womenTF↑-TFPI↓ Maternal hyper coagulation state postpartum; Cardiovascular risk later in life
		6-12 months postpartum	In fromer pre-eclampsia group: Systolic and

Ghi T et al	n=16 were with prior severe pre-eclampsia n= 18 as control group	Systolic and diastolic BP Systolic/diastolic left ventricle parameter	diastolic BP ↑, Cardiac output, LV mass indexes to BSA and longitudinal contraction impaired, Significant injury of LV contractility and diastolic function

Evans (30) and his colleagues investigated a study about cardiovascular or blood biochemical parameter difference between women with and without prior pre-eclampsia, they exanimate 18 prior pre-eclamptic and 50 uncomplicated pregnant women at 16 months postpartum through measuring systemic hemodynamic and mechanics(Doppler echocardiography ,tonometry, oscillometric sphygmomanometry), endothelial function (plethysmography), left ventricle properties and blood biochemical analysis.

The prior pre-eclamptic women compared to the uncomplicated pregnancies shows higher mean and diastolic arterial pressure, higher vascular resistance but no difference on systolic blood pressure, arterial compliance and left ventricular properties. There were also no significant differences observed on endothelial activation, dyslipidemia or oxidative stress but prior preeclamptic women tended to have higher glucose level. The outcomes showed that differences in the prior preeclamptic women are associated with cardiovascular disease risk later in life.

Agatisa et al (31) investigated a study to determine if endothelial function is impaired 6-12 month postpartum in prior preeclamptic women compare to women with normal pregnancies. In this study took part 50 healthy women: 16 with prior pre-eclampsia, 14 normotensive pregnancies and 20 never being pregnant as control group.

They measurement forearm blood flow (FBF), HR, BP and hemodynamic variables were evaluated during mental stress test to release endothelium depend vasodilatation. The result showed that baseline for FBF, HR, systolic and diastolic BP did not differ between the groups, whereas MAP was greater in prior preeclamptic group.

These data demonstrate that prior preeclamptic women demonstrate weak endothelial function up to one year postpartum and this study may explain that women with prior pre-eclampsia are at increased risk for hypertension and heart disease later in life.

Lwaleed(32) and his colleagues examined connection among tissue factor (TF) and TF pathway inhibitor(TFPI) in the women with prior pre-eclampsia up to 3 years post partum as implication for the postpartum hyper coagulation state. Plasma TF and TFPI were measured in 26 participants with prior history of pre-eclampsia and 26 age-matched without past history of pre-eclampsia.

The results suggest an increase level of TF and reduced level of TFPI in the group with prior pre-eclampsia compared to the normal one. This imbalance between TF and TFPI may contribute on developing hyper coagulation state of the mother postpartum and predispose women for the cardiovascular risk later in life.

Ghi T. et al (33) examined postpartum maternal cardiac function in patient with severe pre-eclampsia through trans-thoracic echocardiography up to 6-12 months postpartum, from 34 participants, 16 were with prior severe pre-eclampsia and 18 as control group.

The result showed an increased level of systolic and diastolic BP in prior pre-eclampsia group. Significant difference were observed by systolic left ventricle parameter as cardiac output, LV mass indexes to BSA and longitudinal contraction, which result as impaired in former pre-eclampsia group. This results with significant injury of LV contractility and diastolic function among women with former severe pre-eclampsia.

V.SUMMARY AND FUTURE DIRECTIONS

During the pregnancy, the women's body undergoes in many hormonal changes which among other organs affects also morphological and functional adaption of maternal cardiovascular system. Based on studies that were explored in this Diploma work, maternal cardiovascular remodeling occurs in the early gestations weeks, at the present of fetal-placental unit.

At the 6 gestation week occurs a decrease on systemic vascular resistance (20) which stays unchangeable until third trimester(21),this provide also a decrease of the mean arterial pressure by 6 gestations week(20), who reaches its peak by 16 gestations week and return to baseline at the delivery term without any changes thereafter (24).

Cardiac output rise progressively because of early increase on stroke volume (17%) and late increase of heart rate (26%) also left ventricle shows eccentric hypertrophy because of increased cardiac performance while increase of preload and decrease of after load occurs (21).

Based on 2 dimensional echocardiography data studies, cardiac index increase by 33% between 1-3 trimester as result of increase of HR and SV and also this data showed a progressive rise in LV diameters and wall thickness (cardiac hypertrophy), which will recover after the delivery, ejection fraction (EF) and peak myocardial velocity(s) will decrease between 2-3 trimester and get to normal after delivery.

In the period of pregnancy may also come to complication that would causes maternal morbidity and mortality. Pre-eclampsia is strongly associated with hypertensive disorders who are liable for more than a half of maternal deaths worldwide (40).

Pre-eclampsia is a multisystem disorder defined by new onset hypertension (SBP $\geq$ 140mmHG and DBP $\geq$ 90mmHg, after 20 gestations week in the women previously without pre-eclampsia) and proteinunrie ($\geq$ 300mg/24h) but recently based on American College of Obstetricians and Gynecologist proteinunira is no longer required, instead of that, diagnosis is associated with thrombocytopenia less than 100.000/micro liter, elevated blood concentration of liver transaminases to twice as normal, serum creatinin greater than 1.1mg/dL, pulmonary edema , new onset cerebral or visual disturbance(41,49).Mild pre-eclampsia is now called pre-eclampsia without severe features (45).

Some studies in this Diploma work explored prediction of pre-eclampsia at the early pregnancy weeks through biochemical and biophysical maternal serum findings such as elevated serum levels of hs-CRP, endoglin, PIGF, sFLT-1, ratio of sVEGF 1/ PGF, sFlt-1/ PIGF ratio, decrease of PAPP-A(34-39).

In future direction these markers will play a major role on early prediction of pre-eclampsia in pregnancy.

Also based on explored studies there are some risk factor associated with pre-eclampsia such as Vitamin D maternal serum level deficiency or insufficiency, chronic hypertension, pregestational diabetes, multiple gestation, prior pre-eclampsia ,null parity assisted reproductive techniques ,being overweight(BMI greater than 25-30) or obesity (BMI over 35-40),familiar pre-eclampsia history, psychosocial stress and higher mean arterial blood pressure(25-29).

Pre-eclampsia is also noted as risk factor for developing the cardiovascular diseases later in life in women who experienced once a pregnancy with pre-eclampsia (57). Outcomes from studies refers significant changes on cardiovascular system in prior pre-eclampsia women such as increased MAP, SVR and diastolic blood pressure, higher glucose levels which shows an increased risk for developing hypertension later in life(30,31).

Increase level of TF and reduced level of TFPI in the group with prior pre-eclampsia may contribute on developing hyper coagulation state of the mother postpartum and predispose women for the cardiovascular risk later in life (32). Postpartum maternal cardiac function with significant injury of LV contractility and diastolic function because of increased level of systolic and diastolic BP in prior pregnancies with pre-eclampsia results with cardiovascular risk later in life too (33).

It has been proposed that pathophysiology of pre-eclampsia is characterized with abnormal placental development by failing the cytotrophoblast invasion on remodeling of spiral arteries that results with ischemia of placenta (42). In normal pregnancy PIGF and VEGF are proangiogenic substance that increase vasodilatatory abilities of prostaglandins and nitrous oxide and provide endothelial health(44), in pre-eclampsia ischemic placenta release anti angiogenic factor such as sFlt-1 (antagonizes PIGF and VEGF) and soluble endoglin (antagonize TGF-b and blocks nitrous oxide) as a result of this imbalance occurs maternal endothelial dysfunction and vasospasm (42,43).
Hypertension in pre-eclampsia occurs as a result of increased CO, increase inotropy (contractility) and reduced diastolic function (46).

The only treatment of pre-eclampsia remains still delivery of fetus and placenta (47) .Delivery decision is based on severity features of pre-eclampsia (SBP ≥ 160mmHg and DBP≥ 110 mmHg, thrombocytopenia ,visual and neurological symptoms, HELP syndrome, elevated blood concentration of liver transaminases, epigastric pain and pulmonary edema) , maternal and fetal condition and gestational age.

By pre-eclampsia without severe features delivery suggestion is after 37 gestations week, antihypertensive treatment is controversial, in favor of fetal maturation steroids should be given before 34 gestation week and close observance of maternal and fetal condition should be administrated.

In case of severe pre-eclampsia delivery may be considered after 34 gestations, this type of pre-eclampsia is associated with maternal and fetal complication such as HELLP syndrome, severe hypertension, eclampsia, pulmonary edema, fetal growth restriction, prenatal death and placental abruption. Management can be considered between 24-34 g.w. with antihypertensive therapy and MgSO4 preventation but by clinical severe features delivery should be proceed as soon mother achieves her stable condition. Based on guidelines from national institute for health and clinical excellence hypertension should be treated when SBP≥ 160mmHG and DBP≥ 110 mmHg.

Antihypertensive agents who can be used are Labetolol (200-1200 mg/d), Nifedipine (20-120 mg/d), Clonidine (225-450 ug/d) and Methyldopa (0,5-3g/d) otherwise ACE-Inhibitors and Angiotensin receptor blocker are contraindicated(50-56).

Recommendation from SOGC clinical practice guideline for preventing pre-eclampsia and its complication in women at low risk should be administrated before 16 gestations week with Calcium supplementation 1g/d, Foliate containing multivitamin, abstention from alcohol and exercise, on other side supplementation with low dose acetylsalicylic acid ,vitamin C and E, Magnesium or Zinc are not recommended.
Recommendation for preventing pre-eclampsia in women with increased risk are low dose acetylsalicylic acid (75-162mg/d) and calcium 1g/d, prophylactic dose of low molecular weight heparin , magnesium and prostaglandin precursor to prevent thrombo-embolic disease. Not recommended are vitamin C and E, antihypertensive therapy, calorie restriction in overweight women (48).

In summary this work researches the physiological basis of cardiovascular regulation, discusses relevant literature that shows how the cardiovascular system is affected in pre-eclmapsia, and summarize what is known about pre-eclampsia, including possible therapies and the management of pre-eclampsia.

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