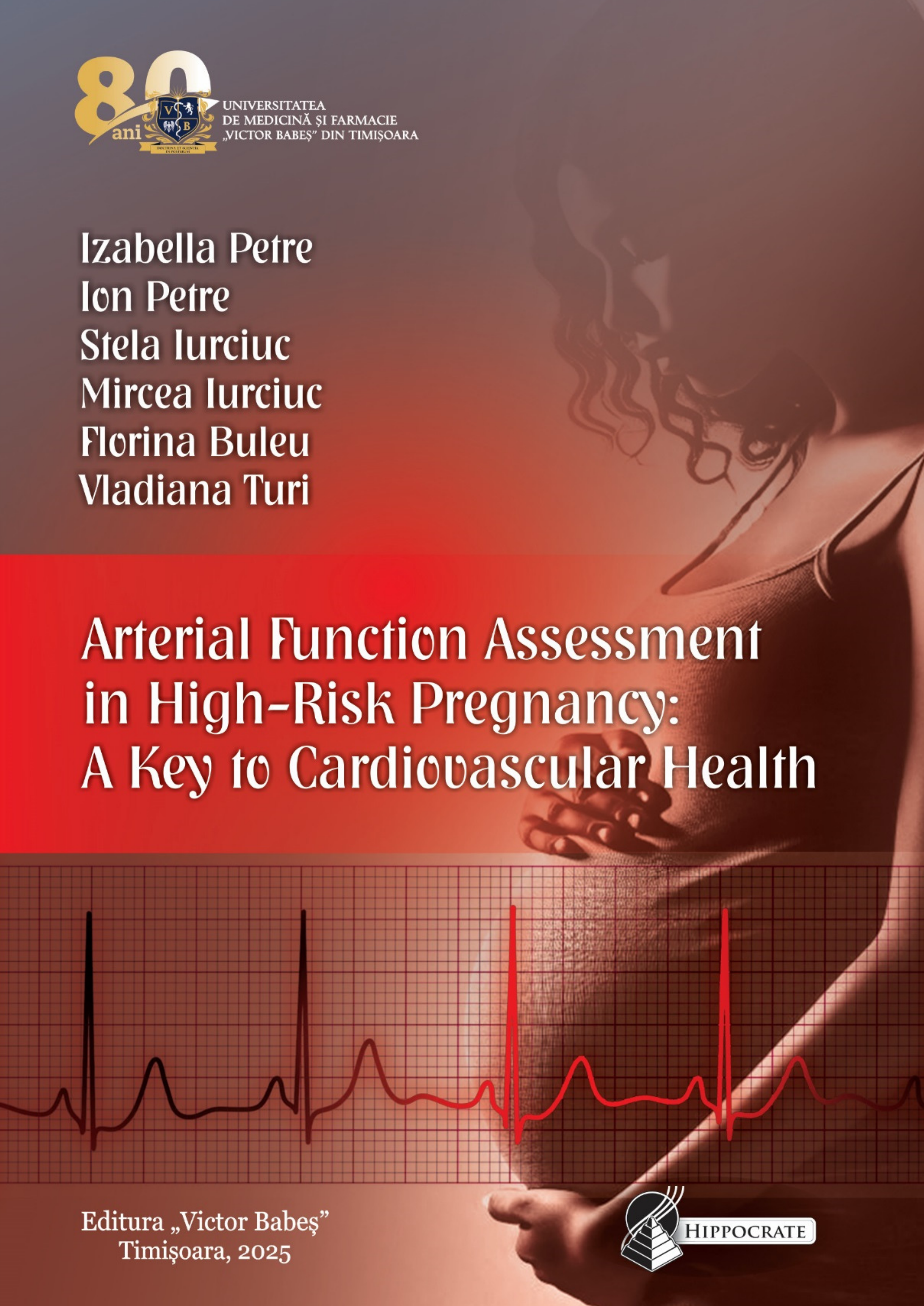

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CONTENT

INTRODUCTION

Hypertension related to pregnancy is a significant contributor to maternal and perinatal death and morbidity. The capacity to forecast these issues by straightforward assessments should enhance the management of these cases and improve outcomes in newborns of pregnant women with cardiovascular risk (pregnancy-induced hypertension/preeclampsia). (1-4)

Globally, numerous research indicate that hypertension problems complicate approximately 3-10% of pregnancies. (5-7)

Some writers attribute 10-15% of maternal fatalities globally to them. (8-10)

These illnesses significantly contribute to the rising incidence of maternal and fetal mortality and morbidity worldwide. Annually, around 30,000 maternal fatalities and 500,000 perinatal deaths globally are attributed to this issue. (10-12)

Pregnancy-induced hypertension is characterized by elevated blood pressure that occurs after 20 weeks of gestation. This criterion is somewhat arbitrary, as there are no distinct physiological changes at this gestational age that appear to initiate the onset of preeclampsia.

The expectation of these complications may lead to early interventions, including heightened vigilance, frequent check-ups, symptomatic treatment, transfer to a larger care facility, and preterm delivery when necessary, potentially reducing morbidity and mortality in hypertensive conditions related to pregnancy.

We aimed to conduct a systematic analysis of research that identified possible predictors of worse maternal outcomes in women with pregnancy-related hypertension disorders and to connect these hemodynamic parameters with indices of newborn health.

Future research should explore the integration of tests inside multivariate models, rather than focusing on singular predictors, to identify pregnant women at risk for hypertensive cardiovascular conditions.

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CHAPTER 1

PREGNANCIES AT RISK AND PROGRESSION OF HEMODYNAMIC PARAMETERS DURING GESTATIONS

Pregnancies at risk

Currently, 88% of pregnancies progress physiologically, however 12% are classified as high-risk, need further assistance and particular interventions. All pregnant women should be supervised, given their potential for a normal pregnancy, until definitive evidence suggests otherwise. (1)

Pregnancy is deemed high-risk when medical issues may jeopardize the health or life of the mother, fetus, or both. One significant risk factor for pregnancy is the woman's age; the rise in high-risk pregnancies over the past two decades can be attributed to the increasing average age of women who become pregnant. Furthermore, nutrition is crucial during gestation, and diabetes or autoimmune disorders frequently result in pregnancy complications. Risk factors for pregnancy include problems such as hypertension and infectious infections that may arise during its course. (1)

Numerous variables can render a pregnancy high risk, including pre-existing health disorders, maternal age, lifestyle choices, and health complications that arise before to or during gestation. (2)

Some risk factors include the mother's pre-existing conditions, such as:

Hypertension. Although hypertension poses risks to both the mother and fetus, the majority of women with mildly elevated blood pressure and no comorbidities experience successful pregnancies and births, as they manage their blood pressure effectively prior to conception. Uncontrolled hypertension can adversely affect the mother's kidneys and elevate the risk of low birth weight or preeclampsia. It is crucial for women to have their blood pressure monitored at each prenatal appointment to enable healthcare practitioners to identify any alterations and determine appropriate treatment options. (2)

Hypertensive disorders during pregnancy represent the most prevalent medical consequences, impacting 5-10% of pregnancies globally. They continue to be a significant contributor to maternal, fetal, and neonatal morbidity and mortality.

Maternal dangers including placental abruption, cerebrovascular accident, multiple organ failure, and disseminated intravascular coagulation. The fetus is at elevated risk for intrauterine growth restriction (25% of pre-eclampsia cases), prematurity (27% of pre-eclampsia cases), and intrauterine demise (4% of pre-eclampsia cases). (3)

Polycystic Ovary Syndrome (PCOS). Women with PCOS have elevated incidences of pregnancy loss prior to 20 weeks, gestational diabetes, preeclampsia, and cesarean delivery. (4)

Diabetes mellitus. Women with diabetes must regulate their blood sugar levels prior to conception and during pregnancy. In the initial weeks of gestation, frequently prior to a woman's awareness of her pregnancy, elevated blood glucose levels may lead to congenital anomalies. Women with well-managed diabetes may experience metabolic alterations during pregnancy that necessitate further attention or therapy to ensure a healthy delivery. (5) Infants born to moms with diabetes are typically of increased size and are predisposed to hypoglycemia shortly after delivery. This is an additional rationale for women with diabetes to maintain stringent management of their blood glucose levels.

Renal disease. Women with modest renal impairment frequently experience healthy pregnancies. Kidney disease can impede conception and maintenance of pregnancy, as well as lead to complications such as preterm delivery, low birth weight, and hypertension. Approximately 20% of women who experience early-onset preeclampsia are discovered to have undetected renal illness. (6) Pregnant women with renal disease necessitate supplementary therapies, dietary modifications, medication adjustments, and regular consultations with their healthcare professional. (7)

Autoimmune disorder. Conditions like lupus and multiple sclerosis might elevate a woman's risk for complications during pregnancy and childbirth. Women with lupus have an elevated risk of preterm birth and stillbirth. Some women may have symptom alleviation during pregnancy, while others may encounter exacerbations and additional difficulties. Some medications for autoimmune illnesses may pose risks to the fetus, necessitating that a woman with an autoimmune condition collaborates closely with a healthcare practitioner during pregnancy. (8)

Thyroid pathology. The thyroid is a little gland located in the neck that produces hormones regulating heart rate and blood pressure. Unmanaged thyroid disorders, including hyperthyroidism or hypothyroidism, can lead to complications for the fetus, including as cardiac failure, inadequate weight gain, and neurological development issues. Thyroid disorders are typically manageable with pharmacological intervention or surgical procedures. (9)

Obesity. Obesity prior to pregnancy is linked to several risks for adverse pregnancy outcomes. Obesity elevates a woman's risk of acquiring diabetes during pregnancy, potentially leading to complicated deliveries. (10)

HIV/AIDS. HIV can be transmitted to a fetus throughout gestation, labor, delivery, and lactation. Fortunately, effective therapies exist that can diminish and avert the transmission of HIV from mother to fetus or kid. Pharmacological interventions for both the mother and infant, along with surgical delivery prior to the rupture of membranes and the use of formula feeding in lieu of breastfeeding, can effectively prevent mother-to-child transmission, resulting in a significant reduction in transmission rates to below 1% in the United States and other developed nations. (11)

Zika virus infection. Despite scientists and healthcare providers being aware of Zika for decades, the association between Zika infection during pregnancy and associated risks and birth abnormalities has only recently been elucidated. Studies indicate that infants born to moms infected with Zika shortly before and during pregnancy face an elevated risk of various neurological and cerebral complications. Microcephaly is the most prominent disorder, characterized by an abnormally tiny head size. Zika infection during gestation can elevate the risk of pregnancy loss and stillbirth for the woman. Researchers are still elucidating the potential pathways of Zika's impact on pregnancy. (12)

Maternal age is another significant risk factor.

Youth. Adolescent pregnant individuals are at a heightened risk of developing pregnancy-induced hypertension and anemia, as well as experiencing preterm labor and delivery, compared to older women. Adolescents are also more prone to being unaware of their sexually transmitted infection (STI) status. Certain sexually transmitted infections can adversely affect pregnancy or the fetus. Adolescents may exhibit a reduced likelihood of obtaining prenatal treatment or adhering to prenatal visit schedules. Prenatal care is essential since it enables a healthcare professional to assess, recognize, and address risks, such as advising adolescents against the use of specific drugs during pregnancy, often prior to these risks escalating into issues. (13)

Primiparity subsequent to the age of 35. While the majority of older first-time mothers experience normal pregnancies, evidence indicates that older women face an elevated risk for specific complications compared to their younger counterparts, (14) including:

- Gestational hypertension and gestational diabetes. (15)
- Pregnancy loss. (16)
- Ectopic pregnancy, a situation wherein the embryo implants outside the uterus, poses a potential life-threatening risk.
- Caesarean delivery (surgical).
- Delivery problems, including excessive hemorrhage.
- Extended labor (exceeding 20 hours).
- Unproductive labor.
- Genetic abnormalities, including Down syndrome, in the infant.
- In affluent nations, the trend of delayed childbearing has been increasingly pronounced during the past thirty years. (17)

Advanced maternal age (AMA) is perceived by patients and healthcare professionals as being associated with adverse pregnancy outcomes. This is primarily due to the increased prevalence of chronic medical disorders among older women. Women of AMA are frequently regarded as requiring the same degree of care as those with high-risk pregnancies, and they receive disparate treatment despite the absence of scientific justification or observable medical issues. (18) Nonetheless, pre-existing and pregnancy-related illness, along with elevated mother aspirations, necessitates more intervention for these women during pregnancy and childbirth. (18) Advanced maternal age (AMA) is linked to numerous detrimental maternal, fetal, and neonatal outcomes, categorizing these pregnancies as "high risk." Studies demonstrate that the perception of pregnancy risk significantly influences health care utilization and decision-making among pregnant women. (19)

Women of AMA possess elevated educational attainment, are more inclined to engage in employment while pregnancy, and exhibit higher medical risk ratings compared to younger women. Women of advanced maternal age feel a greater pregnancy risk for themselves and their fetuses compared to younger women. They assess their risks of cesarean delivery, mortality during pregnancy, preterm birth, and having a newborn with congenital anomalies or requiring admission to a neonatal intensive care unit as greater than those of younger women. No substantial variations exist between the two age groups regarding pregnancy-related anxiety, risk knowledge, perceived control, and health status. (19)

The present study primarily concentrated on individuals with hypertension and pre-eclampsia.

Hypertension, commonly referred to as high blood pressure, is prevalent. In the United States, hypertension occurs in 1 out of every 12 to 17 pregnancies among women aged 20 to 44. 33

Complications arising from maternal hypertension for both the mother and newborn may encompass the following:

- **For the mother**: hypertension, eclampsia, stroke, the necessity for labor induction, and placental abruption.
- **For the infant**: preterm delivery (birth occurring prior to 37 weeks of gestation) and low birth weight (when an infant is born weighing less than 5 pounds, 8 ounces). The mother's hypertension complicates the delivery of adequate oxygen and nutrients to the fetus, necessitating a potential early delivery.

Bateman et al. determined that hypertension affects around 8% of women of reproductive age. Significant disparities exist in the frequency of hypertension among racial and ethnic groupings. Obesity is a significant risk factor in this demographic, impacting over 30% of young women in the U.S., correlating with a more than fourfold increase in hypertension risk, and is amenable to modification. (20)

Hypertension, which complicates approximately 5% of the estimated 4 million pregnancies annually in the United States, is a significant contributor to maternal and fetal morbidity. Between 10% and 25% of women with persistent hypertension will develop superimposed preeclampsia. (21) The incidence of placental abruption is significantly increased, nearing 2% in certain studies. (22,23) Women with chronic hypertension experience a considerably elevated risk of life-threatening maternal outcomes, including stroke, renal failure, pulmonary edema, and mortality. (24,25) Chronic hypertension in women is linked to negative fetal outcomes, including preterm birth, intrauterine growth restriction, and a perinatal mortality risk that is elevated by around 2 to 4 times in their kids. (21,22,25)

Comprehending the epidemiology of hypertension in young women may assist physicians in identifying critical modifiable risk factors and enable public health officials to focus treatments, perhaps enhancing pregnancy outcomes and preventing cardiovascular illnesses. There is a lack of recent global data regarding the epidemiology of hypertension in this significant population.

Women with chronic hypertension should undergo evaluation before to conception or during their initial prenatal appointment. Based on this assessment, they can be classified into "high risk" or "low risk" categories of chronic hypertension. Women at high risk should undergo intensive hypertension treatment and regular assessments of maternal and fetal health, while physicians should advocate for lifestyle modifications. Furthermore, these women have heightened risk for postpartum sequelae including pulmonary edema, renal failure, and hypertensive encephalopathy; thus, they require stringent blood pressure management and vigilant monitoring. In women with low-risk (essential uncomplicated) chronic hypertension, the advantages and disadvantages of antihypertensive medication remain ambiguous. Antihypertensive medicines are advised and commonly utilized in these women, despite a lack of data about their benefits or detriments. These recommendations are founded on dogma and consensus rather than empirical evidence. There is an immediate necessity to perform randomized studies in women experiencing mild chronic hypertension during pregnancy. (26)

Preeclampsia is a reasonably prevalent complication of pregnancy, occurring in 3% to 5% of cases. (27) It is the primary cause of illness and mortality among pregnant women in developed nations and imposes a substantial cost burden on healthcare systems. Despite extensive research over many decades, a comprehensive theory elucidating the etiology and mechanisms of preeclampsia in women without identifiable risk factors remains elusive. The placenta has been the primary, enduring focus of preeclampsia research, which is unsurprising given that placental abnormalities linked to preeclampsia were documented as early as 1940.

Sibai et al. conducted a comprehensive study involving several pregnant women, employing rigorous diagnostic criteria to delineate hypertension, proteinuria, and preeclampsia. The occurrence of preeclampsia in a prior pregnancy, sustained hypertension for a minimum of four years, and an early diastolic blood pressure of at least 100 mm Hg were substantially correlated with an increased incidence of preeclampsia. (22)

These findings aligned with two more studies indicating that the incidence of preeclampsia was elevated in women exhibiting a diastolic blood pressure of at least 100 mm Hg during early pregnancy. (21,28)

Furthermore, their findings corroborated the results of a longitudinal research indicating an elevated risk of superimposed preeclampsia in women with chronic hypertension and a prior history of preeclampsia. (28)

They observed that neither advanced maternal age (35 years or older) nor black race constituted a risk factor for superimposed preeclampsia, despite reports indicating a higher frequency of superimposed preeclampsia among black women with chronic hypertension. The incidence of superimposed preeclampsia remained unchanged with low-dose aspirin treatment, corroborating other research findings.

The existence of proteinuria prior to 20 weeks of gestation in hypertensive women indicates the likelihood of recognized or undiagnosed renal impairment. In numerous cases among these women, renal impairment may be negligible, and the existence of underlying renal conditions may remain unrecognized until proteinuria is identified during pregnancy.

Prolonged gestation, along with an aggravation of maternal hypertension or an elevation in urine protein excretion, may indicate the onset of preeclampsia or a worsening of the preexisting renal condition.

Sibai et al. employed stringent criteria to diagnose superimposed preeclampsia in women presenting with proteinuria and hypertension at baseline. Based on these criteria, they determined that early pregnancy proteinuria in these women did not constitute a risk factor for preeclampsia.

Chronic hypertension in pregnant women is posited as a risk factor for abruptio placentae, (26) and there is consensus that the incidence of abruptio placentae is elevated in women with hypertension and superimposed preeclampsia. (28) Moreover, certain studies indicated a higher incidence of abruptio placentae in women with significant hypertension during the first trimester.

The research by Sibai et al. indicated an incidence of abruptio placentae at 1.5%, which was notably elevated to 3% in women with superimposed preeclampsia. The incidence of abruptio placentae was unaffected by the duration of hypertension, the presence or absence of baseline proteinuria, early diastolic blood pressure, or the use of low-dose aspirin treatment. (26)

The incidence of unfavorable newborn outcomes was greater in mothers with preeclampsia compared to those without the condition. Furthermore, the occurrence of preeclampsia correlated with a heightened incidence of perinatal mortality. (26)

Women with early positive proteinuria experienced increased rates of preterm deliveries, a higher incidence of infants classified as small for gestational age, elevated admissions of infants to neonatal intensive care units, and poorer neonatal outcomes compared to women without early proteinuria. Adverse newborn outcomes transpired despite comparable rates of superimposed preeclampsia in both groups and the absence of abruptio placentae among women with baseline proteinuria.

Sibai et al. identified that a diastolic blood pressure of no less than 100 mm Hg, hypertension persisting for a minimum of four years, and a prior history of preeclampsia are risk factors for preeclampsia in women with chronic hypertension. The prevalence of proteinuria early in pregnancy and the onset of preeclampsia in these women correlate with negative neonatal outcomes. (26)

➢ Progression of hemodynamic parameters in pregnant women

Cardiovascular fatalities continue to be the predominant cause of pregnancy-associated mortality. Pregnancy entails distinct cardiovascular adaptations, as maternal physiology modifies throughout gestation to accommodate the needs of the developing fetus. In addition to the uterus, several organs, including the skin, kidneys, and breasts, exhibit heightened blood demands during pregnancy. Nevertheless, findings about the degree and timing of increases in cardiac output during normal pregnancy have been conflicting. (29)

An explicit comprehension of the alterations in cardiac output and other hemodynamic parameters during normal pregnancy may facilitate the prompt and precise detection of maladaptive cardiovascular physiology associated with certain pregnancy problems, potentially mitigating future repercussions. There is notable interest in the effects of hypertensive disorders of pregnancy on cardiac function, as they affect up to 20% of pregnancies and are linked to alterations in cardiac output, cardiac dysfunction, and heightened risks of cardiovascular diseases in later life for both mother and child. (29)

Pregnancy prompts alterations in the cardiovascular system to accommodate the heightened metabolic requirements of the mother and fetus. At 32 weeks of gestation, plasma volume and cardiac output (CO) attain a peak of 40-50% above baseline, with 75% of this augmentation occurring by the conclusion of the first trimester. The elevation in cardiac output is attained through an augmentation in stroke volume during the initial half of pregnancy, followed by a progressive rise in heart rate thereafter. Atrial and ventricular dimensions expand but ventricular function remains intact. In women with cardiac disease, the adaptation of the left ventricular (LV) and right ventricular (RV) to pregnancy may be inadequate. (30-33) Maternal cardiac dysfunction is associated with compromised uteroplacental circulation and inferior fetal outcomes. Systemic and pulmonary vascular resistances diminish during pregnancy. (34-36)

Pregnancy is a hypercoagulable condition linked to an elevated risk of thromboembolism. The heightened activity of liver enzyme systems, glomerular filtration rate, plasma volume alterations, modifications in protein binding, and reduced serum albumin levels influence the pharmacokinetics of numerous medications. (37)

Uterine contractions, positioning (left lateral versus supine), discomfort, anxiety, exercise, hemorrhage, and uterine involution induce substantial hemodynamic alterations during labor and postpartum. Anesthesia, hemorrhage, and infection may provoke supplementary cardiovascular stress. Blood pressure (BP) and cardiac output (CO) elevate during labor and the postpartum period. The physiological modifications during pregnancy affect the assessment and interpretation of heart function and clinical condition.

The principal hemodynamic alterations associated with pregnancy encompass elevated cardiac output, augmented blood volume, and reduced systemic vascular resistance and blood pressure. These modifications facilitate optimal fetal growth and development while safeguarding the mother from delivery-related hazards, including hemorrhage. Understanding these cardiovascular adaptations is essential for accurately interpreting hemodynamic and cardiovascular assessments in pregnant women, predicting the impact of pregnancy on those with preexisting cardiac conditions, and comprehending the implications of maternal cardiac illnesses on the fetus. (38)

Meah et al. conducted a meta-analysis that thoroughly delineated the alterations in cardiac output throughout a healthy pregnancy. A series of meta-analyses of previously published cardiac output data during healthy singleton pregnancies was conducted. The PubMed and Scopus databases were examined for studies published from 1996 to 2014. Included studies documented absolute values at specified gestational ages (non-pregnant, late first trimester, early and late second trimester, early and late third trimester, early and late postpartum). Cardiac output was assessed via echocardiography, impedance cardiography, or inert gas rebreathing. Observational data were subjected to meta-analysis at each gestational age utilizing a random-effects model. If documented, associated hemodynamic parameters were assessed. A total of 39 studies were deemed appropriate for inclusion, with pooled sample sizes varying from 259 to 748. Cardiac output escalated during pregnancy, to its zenith in the early third trimester at 1.5 L/min, which is 31% higher than non-pregnant levels. The findings from this investigation demonstrated a non-linear increase to this juncture. In the early postpartum period, cardiac output reverted to non-pregnant levels. They determined that cardiac output reaches its zenith in the early third trimester, exhibiting a non-linear adaption pattern; nevertheless, this requires validation through longitudinal research. (39)

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CHAPTER 2

ARTERIAL STIFFNESS AND CARDIOVASCULAR DISEASES IN PREGNANCY

Arterial stiffness

Innovative biomarkers could enhance risk stratification. Nevertheless, when these prospective biomarkers are incorporated into risk prediction models, such as Framingham, they do not significantly enhance risk prediction beyond that already offered by recognized risk variables like blood pressure, blood glucose, and cholesterol. Attention has also been directed towards indicators of tissue or end-organ damage, such as carotid intima-media thickness, which has been incorporated into the guidelines of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC). (1) Nonetheless, despite the endorsement in established guidelines, carotid intima-media thickness is infrequently assessed in standard clinical practice, and its efficacy remains contentious. (2-4)

The elasticity of the aorta, a major conduit rich in elastin, is crucial for mitigating oscillatory fluctuations in blood pressure. Local modifications to vascular tone in the smooth muscle predominant in smaller arteries and arterioles also contribute to the regulation of arterial blood flow. Common indicators of large-artery elasticity and vascular tone modulation encompass arterial stiffness, arterial wave reflection, and endothelial function. (5)

Hypertension is recognized to diminish arterial flexibility and systemic compliance. Age and hypertension are significant contributors to big artery remodeling and rigidity, which are cardiovascular risk factors for heart and kidney damage. (6)

Aortic stiffness increases gradually and constantly with age for both men and women. Cross-sectional studies indicate that aortic and carotid stiffness, assessed using pulse wave velocity, escalates with age by roughly 10% to 15% over a decade. Women consistently exhibit 5% to 10% lower stiffness compared to men of equivalent age. (7)

Increased arterial stiffness alters pulsatile hemodynamics, which is linked to left ventricular hypertrophy (LVH), diminished coronary perfusion, and impairment of the blood-brain barrier (BBB), resulting in coronary and cerebral atherosclerosis. Endothelial dysfunction, oxidative stress, vascular remodeling, extracellular matrix (ECM) accumulation, and common risk factors such as aging, hypertension, diabetes, and dyslipidemia are factors that connect increased arterial stiffness with the development and progression of atherosclerosis. (8)

Cardiovascular diseases (CVD) are responsible for over one-third of global mortality each year. Systemic arterial hypertension (SAH) is associated with about fifty percent of cardiovascular disease (CVD) outcomes. Type 2 diabetes mellitus is an autonomous risk factor for subarachnoid hemorrhage due to its capacity to induce functional and structural impairment of the artery wall, resulting in increased stiffness. Numerous studies have linked oxidative stress, free radical production, and neuroendocrine and genetic alterations to the pathophysiology of vascular aging. Indirect methods for analyzing the aging process have been extensively researched, with pulse wave velocity (PWV) regarded as the gold standard for assessing arterial stiffness due to substantial epidemiological evidence supporting its predictive value for cardiovascular events, and its minimal technical requirements for execution. (9)

Pulse wave velocity (PWV), the predominant metric for assessing arterial stiffness, has proven to be an effective instrument for diagnosing and stratifying the risk of cardiovascular disease (CVD). The assessment of PWV is straightforward, non-invasive, and consistent. (8)

Over the past decade, substantial data has emerged indicating that arterial stiffness is a significant risk factor for cardiovascular disease. Aortic stiffness can be evaluated using several methods, although aPWV is considered the gold standard, supported by substantial evidence correlating it with cardiovascular risk. aPWV may be evaluated in a standard clinical environment utilizing various commercially accessible technologies, rendering it a potentially appealing cardiovascular biomarker. Assessment of arterial stiffness is incorporated in the ESH/ESC guidelines; (1) nevertheless, the American College of Cardiology Foundation and American Heart Association determined that there is inadequate evidence to advocate for arterial stiffness measurements in asymptomatic individuals.

A comprehension of fundamental hemodynamic principles is essential to fully recognize the benefits and constraints of the diverse approaches and indices employed to evaluate arterial stiffness, as well as their possible therapeutic applications.

Physicists such as Young (1808), Poiseuille (1840), Moens (1878), and Korteweg (1878) pioneered hydraulic and elastic theory. Physiologists and physicians, including Marey (1860), Mahomed (1872), and Mackenzie (1902), created diverse sphygmographs and significantly advanced the analysis of pressure waves. (10)

Subsequently, it became evident that the mechanical behavior of vast arteries was highly intricate, presenting significant challenges in both theoretical and technical domains. Arteries demonstrate significant anisotropy, display non-linear viscoelastic characteristics, and possess robust adaptation mechanisms. (11)

Furthermore, no individual artery segment possesses identical viscoelastic characteristics, making it unfeasible to generalize segmental arterial features to the entire vascular system.

A pulse wave is produced with each heart contraction and propagates through the artery network until encountering peripheral resistance or a bifurcation point, which results in the formation of a reflected wave. In youth, arteries exhibit more elasticity; hence, the reflected wave arrives later in the cardiac cycle, reaching the heart during diastole. In elderly individuals, the reflected wave occurs earlier, arriving at the heart during systole. PWV serves as a crucial indicator for vascular damage, significantly aiding in the assessment of a patient's overall cardiovascular risk. (9)

In the Windkessel model, the arterial system is analogous to a fire-hose system: the inverted air-filled dome, which mitigates flow pulsations produced by an intermittently functioning pump, represents the large arteries, the wide-bore hose serves as a conduit, and the fire-hose nozzle corresponds to the peripheral arterioles. (12)

The Windkessel model, meanwhile, possesses two significant weaknesses. The arterial tree does not possess distinct conduit and cushioning capabilities; these roles are characteristics of the aorta and its principal branches, which are elastic tubes. A gradual decline in cushioning function occurs from the ascending aorta, the most elastic artery, to the more muscular and less elastic peripheral arteries, resulting in a more pronounced conduit role of major arteries extending from the heart to the periphery. Secondly, the Windkessel model assumes that pulse-wave velocity (PWV) is unlimited. This cannot be the case due to the variability of pressure wave velocity across the arterial tree. The varying degrees of cushioning and conduit roles in neighboring artery segments dictate this variability. Peripheral arteries have more stiffness than central arteries in healthy individuals, resulting in an elevation of the pressure wave amplitude in the veins, from the heart to the periphery, referred to as pressure amplification. The stiffness of medium-sized peripheral arteries is influenced by vasomotor tone, which is contingent upon endothelial function, the sympathetic nervous system, or the renin-angiotensin system. (13,14)

Consequently, it is likely more advantageous to implement propagative models inside the circulatory system. These presume that the velocity of a pulse wave propagating through a certain artery have a finite value. In 1920, Frank, along with Bramwell and Hill in 1922, formulated the Moens-Korteweg equation, expressed as $c_o = \sqrt{(Eh/2R\rho)}$, where co denotes wave speed, E signifies the Young's modulus in the circumferential direction, h represents wall thickness, R indicates radius, and p stands for fluid density. This was derived as $c_o = \sqrt{(V \cdot dP/\rho \cdot dV)}$, where dV denotes the alteration in arterial volume (V) and dP signifies the variation in pressure that induces the change in volume. This equation is extensively utilized in clinical research and clearly demonstrates that the propagation of the pulse wave is inversely correlated with the distensibility of the arterial vessel, represented as dV/V.dP. Consequently, instead of the Windkessel model, a more accurate representation of the arterial tree would be a propagative model comprising a basic distensible tube that concludes at the peripheral resistance, yet possesses distributed elastic properties that facilitate the generation of a pressure wave traveling along the tube. (15)

The elastic characteristics of conduit arteries differ across the arterial tree, exhibiting greater elasticity in proximal arteries and increased stiffness in distal arteries. The heterogeneity arises from the molecular, cellular, and histological composition of the arterial wall, which varies throughout different regions of the arterial tree. (16-19)

Major arteries have a crucial role in mitigating cyclical fluctuations in blood pressure by diminishing peak pressure, sustaining diastolic pressure, and regulating blood flow. Increased arterial stiffness, which arises with aging, genetic predisposition (e.g., genes associated with the differentiation of vascular smooth muscle cells) (20), and pathological conditions such as atherosclerosis, leads to an overall elevation in pulse pressure, culminating in isolated systolic hypertension. The recurrent cyclical stress of elevated pulse pressure induces a cycle of increased arterial stiffness due to the fatigue fracture of the elastic components in the arterial wall. (5)

The variability in arterial stiffness has significant physiological and pathological implications. A pressure wave traveling through a viscoelastic tube without reflection points experiences gradual attenuation, exhibiting exponential decay along the length of the tube. Conversely, a pressure wave traveling through a viscoelastic tube with several branches is increasingly intensified from the central to the distal conduit arteries due to wave reflections. In peripheral arteries, wave reflections can enhance the pressure wave due to the proximity of reflection sites to peripheral locations compared to central arteries, coupled with a higher pulse wave velocity in stiffer peripheral arteries. The outcome is that the amplitude of the pressure wave is greater in peripheral arteries compared to central arteries, referred to as the "amplification phenomenon". (10)

Consequently, due to pulse pressure amplification between central and peripheral arteries, utilizing brachial pulse pressure as a substitute for aortic or carotid pulse pressure is imprecise, especially in younger individuals. Local stiffness, defined as the ratio of pulse pressure to the relative change in diameter, may be exaggerated by using brachial pulse pressure rather than central pulse pressure in the calculations. (10)

In humans, the pulse wave velocity (PWV) escalates from 4-5 m/s in the ascending aorta to 5-6 m/s in the abdominal aorta, and subsequently reaches 8-9 m/s in the iliac and femoral arteries. (18)

In middle-aged normotensive individuals, the cross-sectional distensibility, evaluated using echotracking devices, diminishes from 40 $kPa^{-1} \times 10^{-3}$ in the thoracic aorta to 10–20 $kPa^{-1} \times 10^{-3}$ in the carotid artery and 5 $kPa^{-1} \times 10^{-3}$ in the radial artery. (21)

The variability in arterial stiffness has significant physiological and pathological implications. A pressure wave traveling through a viscoelastic tube without reflection points experiences gradual attenuation, exhibiting exponential decay along the tube. Conversely, a pressure wave traveling through a viscoelastic tube with several branches is increasingly intensified from the central to the distal conduit arteries due to wave reflections. In peripheral arteries, wave reflections can intensify the pressure wave due to the proximity of reflection sites to peripheral locations compared to central arteries, and the pulse wave velocity (PWV) is elevated in a stiffer peripheral artery. The outcome is that the amplitude of the pressure wave is greater in peripheral arteries compared to central arteries, referred to as the "amplification phenomenon". (10)

Consequently, due to pulse pressure amplification between central and peripheral arteries, utilizing brachial pulse pressure as a proxy for aortic or carotid pulse pressure is imprecise, especially in younger individuals. Local stiffness, defined as the ratio of pulse pressure to the relative change in diameter, may be exaggerated by use brachial pulse pressure rather than central pulse pressure in the computations. (10)

Carotid-femoral pulse wave velocity (cfPWV), an indicator of the inherent rigidity of the aorta wall, is a strong predictor of cardiovascular events. (22)

An age-related escalation in arterial stiffness has been seen in both healthy and pathological groups. Research indicates that in vivo aortic stiffness significantly declines over the first decade of life, attaining a nadir at 10 years of age, and then escalates with advancing age in both sexes. (23) This age-related escalation in central arterial stiffness is not influenced by mean blood pressure or the existence of other risk factors. (24)

The predictive significance of cfPWV is ascribed to its role as a comprehensive indicator of the influence of cardiovascular risk factors on the arterial wall and the detrimental hemodynamic consequences of aortic stiffness. (25) The latter involves an elevation in systolic blood pressure and pulse pressure, accompanied by heightened systolic load and diminished myocardial perfusion pressure. (26) The correlation between cfPWV, age, and blood pressure is widely documented. Prior research has indicated correlations between cfPWV and blood pressure?independent risk factors, such as dyslipidaemia (27), smoking (28), obesity (29), sex (30), heart rate (31), and diabetes mellitus (32). Nevertheless, the results of risk factors aside from age and blood pressure have been inconsistent, and many research did not emphasize negative findings. (33)

Tanaka et al. demonstrated that cfPWV and baPWV are metrics of arterial stiffness that show comparable relationships with cardiovascular disease risk variables and clinical outcomes. (34)

Pulse wave velocity (PWV) indicates arterial rigidity. PWV is correlated with additional indicators that represent the degree of atherosclerosis, including ultrasound findings of the carotid artery. Moreover, numerous studies have shown that elevated PWV is an indicator of impending cardiovascular events in individuals with hypertension or diabetes mellitus. Consequently, PWV is considered a relevant metric associated with the severity of atherosclerosis and/or the prediction of future atherosclerotic cardiovascular events. Age and blood pressure are significant determinants of pulse wave velocity (PWV), and these characteristics must be considered when utilizing PWV as an indicator of cardiovascular risk. Conversely, whereas anti-hypertensive medications or statins enhance PWV, it remains inadequately assessed whether these enhancements correspond to an improved prognosis. Consequently, the importance of PWV as a surrogate metric for managing atherosclerotic cardiovascular risk remains inadequately determined. Carotid-femoral pulse wave velocity is employed as a standard technique. (35)

Ito et al. aimed to determine the clinical utility and constraints of brachial-ankle pulse wave velocity (PWV) for assessing hypertension problems, in contrast to carotid-femoral PWV. They noticed that carotid-femoral PWV ($p<0.0001$; $r=0.521$) and brachial-ankle PWV ($p<0.0001$; $r=0.478$) but not femoral-ankle PWV were significantly correlated with age. (36)

Carotid-femoral PWV was markedly elevated in patients with concurrent clinical problems compared to those with target organ damage ($p<0.05$) and those without complications ($p<0.0001$). Brachial-ankle PWV was markedly elevated in patients with concomitant clinical problems ($p<0.05$) and target organ damage ($p<0.05$) relative to those without complications; however, no significant difference in brachial-ankle PWV was seen between the two groups. Furthermore, femoral-ankle PWV was markedly reduced in patients with concurrent clinical problems compared to those with target organ injury ($p<0.05$). Their research indicated that brachial-ankle PWV may underestimate arterial stiffness in hypertensive patients with a history of cardiovascular events. (36)

Munakata et al. investigated whether brachial-ankle Pulse Wave Velocity serves as an independent risk factor for microalbuminuria in individuals with essential hypertension. A cohort of 718 untreated hypertension patients was included in a prospective trial. Among the 718 patients, 500 had normoalbuminuria (69.6%), 191 presented with microalbuminuria (26.6%), and 27 had macroalbuminuria (3.8%). (37)

The incidence of microalbuminuria escalated with a progressive rise in brachial-ankle pulse wave velocity (17.6%, 22.8%, 28.2%, and 39.6%, $p<0.0001$). The prevalence of macroalbuminuria remained stable until the third grade of brachial-ankle pulse wave velocity, but dramatically increased in the highest grade compared to the lower grade groups (2.3, 3.2, 2.3, 9.9%, $p<0.0001$). Age, systolic and diastolic blood pressure, pulse pressure, heart rate, and fasting glucose concentration were substantially elevated with an increase in brachial-ankle pulse wave velocity ($p<0.0001$ for all). Multiple logistic regression analysis indicates that systolic blood pressure, fasting blood glucose, and brachial-ankle pulse wave velocity are significant risk factors for microalbuminuria. Upon controlling for additional risk factors, the odds ratio for a 200 cm/s increase in brachial-ankle pulse wave velocity was 1.192 (95% confidence interval: 1.022?1.365; $p<0.05$). The data indicated that brachial-ankle pulse wave velocity is an independent risk factor for microalbuminuria and may serve as a diagnostic for early vascular injury in untreated hypertension patients. (37)

Their findings are crucial for the current investigation, as a non-invasive measure like PWV can identify future difficulties in pregnant women prior to the onset of microalbuminuria or proteinuria.

Najjar et al. demonstrated that BMI and MAP (mean arterial pressure) were independently correlated with elevated SBP; furthermore, PWV was also independently linked to increased SBP and accounted for 4% of its variance. They conducted repeated measurements of blood pressure at each follow-up visit to delineate the longitudinal variations in systolic blood pressure over time. They assessed the predictors of longitudinal changes in SBP utilizing linear mixed-effects regression models. The findings indicated that age, BMI, and MAP ($p = 0.09$, $p = 0.009$, $p < 0.0001$ correspondingly for the interaction terms with time) were predictors of the longitudinal variations in SBP. Furthermore, PWV served as an independent predictor of the longitudinal elevation in SBP ($p = 0.003$ for the interaction term with time). The impact of PWV on the mixed effects models was assessed by contrasting models with and without PWV: after controlling for other factors, PWV explained 16% of the variance in the longitudinal alterations in SBP. The primary effect of PWV was statistically significant ($p = 0.006$) when the model was executed without the interaction term between PWV and time. (26)

They assessed the factors influencing the longitudinal variations in PP using mixed-effects linear regression models. Within the entire cohort, age emerged as the sole independent predictor of the longitudinal increase in pulse pressure (PP) ($p < 0.0001$ for the interaction term with time), while pulse wave velocity (PWV) was merely a determinant of elevated PP ($p = 0.03$), without influencing longitudinal variations in PP. Upon reanalyzing the data by stratifying the cohort into age tertiles, PWV emerged as an independent predictor of the longitudinal rise in PP ($p = 0.04$ for the interaction term with time) in persons aged over 60 years (highest tertile). (26)

Given that PWV was an independent determinant of the longitudinal increase in SBP, the researchers further assessed whether PWV might forecast the future onset of HTN. During a median follow-up of 4.3 years (mean 4.7? 2.5 years, range 2 to 12 years), hypertension (HTN) was diagnosed in 105 individuals (34%). (26)

In the cohort with a follow-up duration exceeding the median, where all participants remained normotensive for the initial 4.3 years, age (hazard ratio [HR] 1.02 per 1 year, 95% confidence interval [CI] 0.99 to 1.04, $p = 0.2$) and systolic blood pressure (SBP) (HR 1.05 per 1 mm Hg, 95% CI 1.01 to 1.09, p = 0.006) were identified as significant factors. Additionally, high-density lipoprotein (HDL) (HR 0.96 per 1 mg/dl, 95% CI 0.93 to 0.99, p = 0.02) and pulse wave velocity (PWV) (HR 1.10 per 1 m/s, 95% CI 1.00 to 1.30, p = 0.03) emerged as independent predictors of incident hypertension (HTN). (26)

Liao et al. investigated the correlation between arterial elasticity and the onset of hypertension over a 6-year follow-up period in a population of 6,992 normotensive individuals aged 45 to 64 years at baseline. A one standard deviation reduction in arterial elasticity was linked to a 15% increased risk of hypertension, irrespective of known hypertension risk factors and baseline blood pressure levels. The findings indicate that diminished arterial flexibility correlates with the onset of hypertension. (38)

Dernellis et al. conducted a study to determine whether aortic stiffness could predict the progression to hypertension independent of traditional risk variables. The researchers evaluated the predictive significance of aortic stiffness regarding future hypertension in non-hypertensive individuals with blood pressure (BP) <140/90. The duration of follow-up was four years. In multivariate analysis, aortic strain, distensibility, and stiffness index (?) were strongly correlated with the advancement to future hypertension, even after adjusting for traditional risk variables in both genders and across various age groups. Aortic stiffness is an independent predictor of hypertension progression in nonhypertensive people. (39)

Satoh, Saijo, et al. demonstrated that in Japanese normotensive male individuals, BaPWV was a substantial and independent predictor of the onset of hypertension. Their findings indicate that BaPWV may serve as an effective screening tool to identify normotensive individuals who warrant interventions to prevent the onset of hypertension. (40)

The predictive significance of PWV for the incidence of CVD has been documented in both the general population and patients with diverse clinical conditions. A population study of 1,678 community participants, with a median follow-up of 9.4 years, demonstrated that aortic pulse wave velocity (PWV) predicted composite cardiovascular outcomes independent of established risk variables. (41) Pulse wave velocity (PWV) serves as an independent predictor of future cardiovascular disease (CVD) in hypertensive patients. (42,43)

Numerous meta-analyses demonstrate the predictive significance of PWV for impending cardiovascular events. A meta-analysis of ten studies indicated that elevated cfPWV is a strong predictor of future cardiovascular disease, regardless of Framingham risk factors. (44)

A recent meta-analysis of 19 studies indicated that a 1 m/s increase in cfPWV correlates with a 1.12-fold increase in future cardiovascular disease events. (45)

Results from an individual participant meta-analysis involving 17,636 patients across 16 trials indicated that a 1-SD change in loge cfPWV independently predicted future cardiovascular disease events with a 1.45-fold increase. (46)

A meta-analysis of 12 cohort studies revealed that a 1 m/s rise in baPWV correlates with a 12% elevation in the risk of cardiovascular disease (CVD) (41). A recent meta-analysis involving 14,673 Japanese adults devoid of pre-existing cardiovascular disease (CVD) indicated that each 1-standard deviation (SD) rise in baPWV correlated with a 1.19-fold elevation in CVD risk over a 6.4-year follow-up period. (47)

Yoab Ven-Schlomo et al. in their investigation corroborated the findings of a prior summary meta-analysis (48) indicating that aPWV is a predictor of future fatal and non-fatal cardiovascular events. They significantly enhanced this by including fresh data, enabling the analysis of critical sub-groups, and by explicitly assessing the prognostic significance of aPWV beyond existing risk factors. After complete adjustment, a 1 m/s rise in aPWV correlated with a 7% heightened risk of a cardiovascular event for a 60-year-old male (non-smoker, non-diabetic, not on any antihypertensive medication, with a systolic blood pressure of 120 mmHg, total cholesterol of 5.5 mmol/L, and HDL cholesterol of 1.3 mmol/L).

Yoab Ven-Schlomo et al. demonstrated that aPWV was a more significant risk factor in younger individuals, while it remained predictive in older individuals. This may be attributed to individuals with rigid aortae, who are predisposed to cardiovascular disease, experiencing reduced longevity (healthy survivor effect). Additionally, other risk factors may diminish the impact of aPWV in older populations, and/or systolic pressure may serve as a more accurate indicator of aortic stiffness in older individuals compared to younger ones; thus, incorporating aPWV into models that already include systolic pressure is likely to contribute minimal predictive value. The age-associated increase in systolic pressure and the emergence of isolated systolic hypertension closely correspond to the age-related elevation in aPWV. (49,50) In contrast, systolic hypertension in younger adults appears primarily influenced by increased cardiac output and stroke volume, rendering systolic or pulse pressure an inadequate indicator of arterial stiffness in this demographic. (50)

Yoab Ven-Schlomo et al. proved that the addition of aPWV to the adjusted cardiovascular prediction models only increased the C and D statistics to a modest degree, suggesting that aPWV may not add much to standard risk equations when all participants are analysed together. However, they are relatively insensitive methods for assessing the potential value of new biomarkers and do not specifically focus on people in whom better risk prediction is likely to make an important clinical difference i.e. those who are at moderate or intermediate risk. (51)

Indeed, many current guidelines advocate 10-year cardiovascular risk estimation and the targeting of therapy toward individuals whose estimated risk exceeds a particular threshold. However, refining estimation in those at high or low risk is unlikely to alter management or risk prevention in a substantial way. The performance of aPWV on the net reclassification improvement appeared more clinically informative in terms of risk stratification for those at intermediate cardiovascular risk and in younger subjects, though we have presented data on reclassifying subjects at both low (general population sample) and high (e.g. clinical sample) absolute risk for completeness. (46)

Yoab Ven-Schlomo et al. suggested that aPWV may be a suitable target for novel risk reduction strategies. (46) Although we did not investigate pathophysiological mechanisms underlying cardiovascular disease, previous studies suggest that aPWV attenuation is associated with improved survival. (52) The majority of existing drugs do not appear to lower aPWV in a blood pressure-independent manner, but long-term blockade of the renin-angiotensin system (53) and novel agents targeting elastic fibre cross-linking (54) or calcification may afford some benefit. However, these strategies remain to be tested directly and remain speculative. (55)

The study by Ven-Schlomo et al. (46) exhibited some shortcomings. The majority of studies involved Caucasian participants or those from the Far East, hence constraining the applicability of these findings to other ethnic groups. A range of methodologies and equipment were employed to evaluate aPWV, which are recognized to affect absolute values. They attempted to mitigate methodological influence by estimating study-specific effects, and their findings indicated no substantial heterogeneity among studies or devices. A sensitivity analysis investigating the methodology for calculating the distance of the carotid-femoral pathway found no evidence of heterogeneity. The results from short-term research were extrapolated to forecast a 10-year risk; hence, these findings should be approached with caution because to the scarcity of long-term data. Their CVD outcome measure primarily focused on myocardial infarction and stroke, hence the predictive efficacy of aPWV on heart failure has not been thoroughly investigated. (46)

The Rotterdam research has just published data on risk prediction (56), revealing a comparable 9% reclassification of individuals in the intermediate risk group. They (46) successfully incorporated data from multiple new research, including three unpublished studies, two of which have previously published data on their aPWV measurements. (57,58) All calculations obtained from observational studies and a prior meta-epidemiological analysis indicated that the effects of cardiovascular biomarkers were more pronounced in these investigations than in randomized controlled trials. (56)

The aorta is a significant conduit for assessing regional arterial stiffness for two primary reasons: the thoracic and abdominal aorta significantly contribute to arterial buffering, and aortic pulse wave velocity is an independent predictor of outcomes across many populations. Thirty-two to forty-two However, all arterial sites have potential interest. Indeed, the forearm circulation is where blood pressure is commonly measured, and the lower limb arteries are specifically altered by atherosclerosis. Measurement of local carotid stiffness may also provide important prognostic information, since the carotid artery is a frequent site of atheroma formation.

Isnard et al. demonstrated a favorable correlation between elastic modulus and age ($r = 0.73$, $p < 0.01$) in hypertensive individuals, whereas no significant correlation was observed in normal patients ($r = 0.08$, NS). Their research was the inaugural demonstration, conducted noninvasively, that both the diameter of the aortic arch and the elastic modulus are elevated in individuals with persistent uncomplicated essential hypertension. The findings indicated that the elevation in elastic modulus may affect the progression of cardiac hypertrophy, whereas both age and blood pressure function independently as factors that modify the arterial wall in individuals with chronic essential hypertension. (59)

Arterial function is acknowledged as a significant 'risk marker' in the assessment of cardiovascular disease. Multiple measures are available to evaluate localized and global vascular function in both clinical and research contexts. (60)

A consensus paper from the European Network for Non-invasive Investigation of Large Arteries summarizes these findings; nevertheless, there is an absence of particular guidelines for their application in pregnant populations. This document delineates appropriate methodologies and instruments for evaluating vascular function during pregnancy and for analyzing the results. We provide a concise summary of significant studies on vascular function in both normal pregnancies and those with unfavorable outcomes.

➢ Arterial function in pregnancy

Foo, McEniery et al. investigated the impact of maternal vascular dysfunction on pregnancy-related conditions, including pre-eclampsia and intrauterine growth restriction. (59)

The 2018 European Society of Hypertension guidelines indicate that in cases of arterial hypertension, a carotid-femoral pulse wave velocity over 10 m/s is associated with subclinical organ damage and cardiovascular events. (61)

Arterial function is acknowledged as a significant 'risk marker' in the assessment of cardiovascular disease. Multiple measures are available to evaluate localized and global vascular function in both clinical and research contexts. These are encapsulated in a consensus report by the European Network for Non-invasive Investigation of Large Arteries. (10)

There is a deficiency of specific guidelines regarding their application in pregnant populations.

There are no established normal limits for PWV during pregnancy; nevertheless, a value below 10 m/s is considered within the range for healthy non-pregnant women. (61) PWV has been shown to rise considerably with maternal weight and age, but not with parity or smoking status. (20)

Large artery stiffness is the primary pathophysiological factor contributing to isolated systolic hypertension and the age-related elevation in pulse pressure. (20)

Carotid-femoral pulse wave velocity (PWV) is the definitive benchmark for assessing major artery stiffness. (20).

Reference values for PWV exist in both healthy populations and individuals at elevated cardiovascular risk. (62)

A PWV of 10 m/s is regarded as a cautious indicator of substantial changes in aortic function in middle-aged hypertensive individuals. (61)

Numerous research have indicated the additional significance of PWV beyond conventional risk variables, such as SCORE and the Framingham risk score. Nonetheless, the normal application of PWV measurement is impractical and not advised for standard practice.

➢ Arterial and Aortic Pulse Pressure

When the left ventricle expels blood into the aorta, the pressure within the aorta rises. The stroke volume is directly associated with the variation in aortic pressure during ejection. The maximum alteration in aorta pressure during systole (from the moment the aortic valve opens until peak aortic pressure is reached) constitutes the aortic pulse pressure, defined as the difference between systolic and diastolic pressure. (63)

Definition: Pulse Pressure = Systolic Pressure – Diastolic Pressure

➢ Pulse pressure

The systemic pulse pressure is roughly proportional to stroke volume, which is the volume of blood expelled from the left ventricle during systole, and inversely proportional to the compliance of the aorta. Pulse pressure is the differential between systolic and diastolic blood pressure. It is quantified in millimeters of mercury (mmHg). It signifies the force produced by the heart with each contraction. If the resting blood pressure is 130/80 mmHg, the pulse pressure is 50 mmHg. (64)

The typical resting pulse pressure in healthy persons in a seated position is approximately 30-40 mmHg. Pulse pressure elevates during exercise owing to an augmented stroke volume, with healthy values reaching approximately 100 mmHg, concurrently as total peripheral resistance diminishes. In healthy individuals, pulse pressure generally normalizes after around 11 minutes. (64)

Should the typical resting pulse pressure consistently exceed 100 mmHg, the most probable causes include arterial stiffness, aortic regurgitation, arteriovenous malformation, hyperthyroidism, or a combination thereof. A persistently elevated stroke volume is technically feasible, albeit exceedingly uncommon in practice. Certain antihypertensive medications may irreversibly elevate resting pulse pressure, whilst others, such ACE Inhibitors, have demonstrated the ability to reduce pulse pressure. An elevated resting pulse pressure is detrimental and accelerates the natural aging of bodily organs, especially the heart, brain, and kidneys. An elevated pulse pressure, accompanied by bradycardia and an erratic respiratory pattern, indicates increasing intracranial pressure and necessitates prompt notification to a physician. Cushing's triad is observed in patients with head trauma along with cerebral hemorrhage or edema. (64)

Causes of sustained increased pulse pressure include: anemia, pregnancy, atherosclerosis, aortic dissection, aortic regurgitation, fever, and distributive shock. (64)

Farida Munawar et al. determined in their study that pulse pressure serves as an effective predictor for cardiac output assessments. In females, cardiac output and pulse pressure exhibit a favorable reaction following exercise. (64)

The increase in aortic pressure from diastolic to systolic values is influenced by aortic compliance and ventricular stroke volume. The aorta exhibits the maximum compliance in the vascular system, attributable to a comparatively larger ratio of elastin fibers to smooth muscle and collagen. This performs the crucial role of attenuating the pulsatile output of the left ventricle, thus diminishing the pulse pressure (systolic minus diastolic arterial pressure). If the aorta were a rigid conduit, the pulse pressure would be exceedingly elevated. The aorta's compliance allows its walls to expand in response to the increased blood volume expelled into it. The pressure increase during aortic expansion is dictated by the aorta's compliance in the specific volume range. If the aorta exhibits greater compliance, the pressure fluctuations during ventricular ejection are diminished (i.e., reduced pulse pressure). Aortic compliance is a significant factor, alongside stroke volume, in determining pulse pressure. (63)

The primary mechanisms of arterial stiffness are as follows:

- A more compliant aorta (i.e., less rigid, normal aorta) exhibits a reduced pulse pressure for a specific stroke volume compared to a stiff, low-compliance aorta.
- A greater stroke volume results in an increased pulse pressure at any certain compliance.
- Aortic compliance diminishes with age due to structural alterations, resulting in age-related increases in pulse pressure.
- For a specific stroke volume, compliance influences pulse pressure rather than mean aortic pressure.
- Nonetheless, due to the dynamic compliance of vasculature, an elevation in the rate of ventricular ejection (as seen with heightened ventricular inotropy) will augment the pulse pressure relative to the same volume ejected at a reduced pace. (63)

The standardization of subject conditions and indices of regional stiffness encompasses: devices employing specific methodologies and designated measurement sites, including Complior (mechanostranducer for aortic PWV), Sphygmocor (tonometer for aortic PWV), WallTrack (echotracking for aortic PWV), Artlab (echotracking for aortic PWV), and ultrasound systems utilizing Doppler probes for aortic PWV. (65 - 69)

Various devices, methodologies, and measurement locations are utilized for local stiffness assessment: WallTraack employs echotracking on the common carotid artery (CCA), common femoral artery (CFA), and brachial artery (BA) (70); NIUS utilizes echotracking for the radial artery (71); Artlab implements echotracing on CCA, CFA, and BA (68); multiple systems apply ultrasound echotracking on CCA, CFA, and BA (68); and an MRI device employs cine-MRI for the aorta. (68)

For systemic stiffness (waveform shape analysis), the following methods, instruments, and measurement sites are utilized: area method -> diastolic decay (72); HDI PW CR-2000? -> modified Windkessel (73); stroke volume/pulse pressure (SV/PP) -> stroke volume and pulse pressure. (74)

Concerning wave reflections, there are two instruments: Sphygmocor, which measures Aix throughout all superficial arteries (75), and Pulse Trace, which employs finger photoplethysmography. (76)

Specific measurements are necessary (10) for accurate assessments, including the following:

- Room temperature

- Rest: a minimum of 10 minutes in a supine position. - Time of day: consistent timing for repeated measurements.

- Subjects must abstain from smoking and eating for a minimum of 3 hours prior to measurements, especially from consuming caffeinated beverages.

- Alcohol -> abstain from alcohol use for 10 hours prior to measurements

- Speaking and sleeping: Subjects are prohibited from speaking or sleeping during measurements.

- Position -> the supine position is preferred. Position (supine, sitting) must be specified - White coat phenomenon -> impact on blood pressure and pressurerigidity depends on

- Cardiac arrhythmia -> be mindful of potential disturbances

There are precise words and definitions (units) for these measures of the artery's elastic characteristics as a whole:

• Stroke change in diameter -> Change in diameter during systole = systolic diameter (Ds) – diastolic diameter (Dd) (mm)

• Alteration in lumen area during systole -> $\Delta A=\pi(Ds^2-Dd^2)/4$ (mm^2), where D represents the internal diameter.

• Wall cross-sectional area -> The surface area of a cross-section of the artery wall, calculated as $WCSA=\pi(De^2-Di^2)/4$ (mm^2), where De represents the external diameter and Di denotes the internal diameter, both measured during diastole.

There exist distinct names and definitions (units) for the elastic characteristics of artery wall material:

• Cross-sectional distensibility coefficient (DC) represents the relative alteration in lumen area during systole for a specified pressure change, defined as $DC=\Delta A/A \cdot \Delta P$ (kPa−1), where ΔP denotes local pulse pressure.

• Cross-sectional compliance coefficient (DC) -> The absolute alteration in lumen area during systole for a certain pressure variation, $CC=\Delta A/\Delta P$ (m^2kPa□^{1}), where ΔP represents local pulse pressure.

• Absolute change in lumen area during systole for a specific pressure variation is represented as $CC=\Delta A/\Delta P$ (m^2kPa□^{1}), where ΔP denotes local pulse pressure.

• Peterson elastic modulus -> The reciprocal of the distensibility coefficient: the alteration in pressure that induces a rise in relative lumen area. $Peterson=A \cdot \Delta P/\Delta A$ (kPa) Young's elastic modulus or incremental elastic modulus is defined as $Einc=[3(1+A/WCSA)]/DC$ (kPa), serving as the index of arterial stiffness applied to the geometrical measurements of major arteries using ultrasonography. (77)

➢ Cardiovascular diseases in pregnant women

Cardiovascular diseases (CVD) are projected to cause 17 million deaths annually, accounting for one third of all global fatalities. Among those cardiovascular diseases, 9.4 million are associated with arterial hypertension, a significant risk factor for stroke, coronary artery disease, heart failure, and occlusive peripheral arterial disease. (78)

The risk of cardiovascular disease during pregnancy has escalated in the western world due to the rising age of first-time mothers. World Atlas indicates that the ten countries with the highest mean age at first birth had an average age ranging from 28.8 to 31.2 years. (79)

The slight rise in maternal age does not warrant an escalation in cardiovascular disease during pregnancy attributable to maternal age. Pregnancies throughout the late reproductive years (ages 40–50) are increasingly linked to a higher prevalence of cardiovascular risk factors, particularly diabetes, hypertension, and obesity. In Western nations, maternal heart disease is the primary cause of maternal mortality during pregnancy. (80)

From 2003 to 2009, hemorrhage, hypertensive diseases, and sepsis accounted for over fifty percent of maternal fatalities globally. (81)

In 2010, over 287,000 maternal fatalities were recorded globally, predominantly in low-income and middle-income nations, and were largely preventable.

Women with a history of hypertensive disorders of pregnancy (HDP) are almost twice as likely to develop cardiovascular disease (CVD) compared to those who maintain normotension during pregnancy. (82)

Stuart et al. conducted a study with 58,671 parous participants who were free of cardiovascular disease and relevant risk factors at baseline. Women were monitored for self-reported physician diagnoses of chronic hypertension, hypercholesterolemia, and confirmed type 2 diabetes mellitus (T2DM) from their first childbirth until 2013; the mean follow-up duration varied from 25 to 32 years across these endpoints. In comparison to women who maintained normotension during pregnancy, those experiencing gestational hypertension (2.9%) or preeclampsia (6.3%) in their initial pregnancy exhibited elevated incidences of chronic hypertension, type 2 diabetes mellitus, and hypercholesterolemia. Despite these women exhibiting a higher propensity for developing cardiovascular disease risk factors during the follow-up period, the relative risk for chronic hypertension was most pronounced within five years following their initial childbirth. The researchers determined that women with hypertensive disorders of pregnancy (HDP) during their initial pregnancy exhibited elevated rates of chronic hypertension, type 2 diabetes mellitus (T2DM), and hypercholesterolemia, which persisted for several decades. They suggested that these women may benefit from lifestyle modifications and early screening to mitigate their lifelong risk of cardiovascular disease (CVD). (82)

This data should guide evidence-based reproductive health care policies and services at both regional and national levels. Enhancing capacity to increase the quality of burden-of-disease research will further substantiate future projections. (80)

This study concentrated on hypertension among all cardiovascular illnesses during pregnancy.

Significant advancements have been achieved in comprehending the epidemiology, pathophysiology, and risks linked to hypertension, with ample evidence indicating that reducing blood pressure (BP) can markedly decrease premature morbidity and mortality. (83)

Essential laboratory assessments advised for the surveillance of hypertensive patients during pregnancy encompass urinalysis, complete blood count, hematocrit, liver enzyme levels, serum creatinine, and serum uric acid (elevated in clinically apparent pre-eclampsia; hyperuricemia in hypertensive pregnancies indicates women at heightened risk for unfavorable maternal and fetal outcomes). (84)

All pregnant women must undergo evaluation for proteinuria throughout early gestation to identify pre-existing renal conditions and, in the latter half of pregnancy, to screen for pre-eclampsia. A dipstick test result of ≥1+ necessitates additional investigations, including an albumin:creatinine ratio (ACR), which can be promptly assessed with a single spot urine sample. A number below 30 mg/mmol can safely exclude proteinuria in pregnancy; (85) nonetheless, a positive result may warrant a further 24-hour urine collection.

In instances with proteinuria above 2 g/day, vigilant monitoring is essential. Nonetheless, the outcome of a 24-hour urine sample is frequently imprecise and postpones the identification of pre-eclampsia. Thus, an ACR threshold of 30 mg/mmol can be employed to detect substantial proteinuria.

Alongside fundamental laboratory assessments, the subsequent examinations may be contemplated:

- Ultrasound examination of the adrenal glands, along with plasma and urinary fractionated metanephrine assays, in hypertensive pregnant women exhibiting clinical signs indicative of pheochromocytoma.

- Doppler ultrasonography of uterine arteries, conducted after 20 weeks of gestation, is effective in identifying individuals at elevated risk for prenatal hypertension, pre-eclampsia, and intrauterine growth restriction. (86)

- A sFlt1 to placental growth factor (sFlt1: PIGF) ratio of ≤38 can effectively preclude the onset of pre-eclampsia during the subsequent week when clinically suspected. (87)

The definition of hypertension in pregnancy is based only on office (or in-hospital) BP values [systolic BP (SBP) ≥140 mmHg and/or DBP ≥90 mmHg] (88) and distinguishes mildly (140–159/90–109 mmHg) or severely (≥ 160/110 mmHg) elevated BP, in contrast to the grades used by the joint ESC/ESH Hypertension Guidelines. (89)

Hypertension during pregnancy is not a singular condition but encompasses: (88)

- **Pre-existing hypertension**: occurs before to pregnancy or manifests before 20 weeks of gestation. It typically endures for over 42 days postpartum and may be linked to proteinuria.

- **Gestational hypertension:** arises after 20 weeks of gestation and typically resolves within 42 days postpartum.

- **Pre-eclampsia**: gestational hypertension accompanied with substantial proteinuria (>0.3 g/24 h or ACR ≥30 mg/mmol). It is more prevalent during the initial pregnancy, in multiple gestations, in hydatidiform mole, in antiphospholipid syndrome, or in the presence of pre-existing hypertension, renal disease, or diabetes. It is frequently linked to fetal development restriction resulting from placental insufficiency and is a prevalent cause of preterm. The only cure is delivery. Proteinuria may indicate a late manifestation of pre-eclampsia and may be recognized when new-onset hypertension is accompanied by headache, visual abnormalities, stomach pain, or abnormal laboratory results, particularly low platelet counts and/or impaired liver function.

- **Pre-existing hypertension accompanied by superimposed gestational hypertension with proteinuria.**

- **Antenatal unclassifiable hypertension** refers to the diagnosis of hypertension when blood pressure is initially recorded after 20 weeks of gestation; re-evaluation is required 42 days postpartum.

Recent statistics reveal that hypertension remains inadequately managed in numerous communities globally. The determinants affecting individual responses to antihypertensive therapy require elucidation. Pulse wave velocity (PWV), an indicator of arterial stiffness, has been shown to have significant correlations with blood pressure (BP) progression; nevertheless, there is limited information regarding the role of PWV in BP regulation.

Recent statistics from multiple nations suggest that hypertension management is inadequate. (90) Although awareness and treatment of hypertension have increased among several populations, the effectiveness of antihypertensive treatment shows the need for continuing improvements.

Arterial hypertension frequently correlates with additional cardiovascular risk factors (CVRF), including smoking, obesity, elevated cholesterol levels, and type 2 diabetes mellitus (DM). This association, particularly with DM, markedly heightens the risk of micro- and macrovascular complications, as well as the prevalence of cardiovascular disease (CVD). (91)

Numerous studies indicate that diabetes mellitus is an independent and significant risk factor for both functional and structural damage to the arterial wall, leading to early arterial stiffness.The combination of those CVRF, mainly AH and DM, contributes to potentiate vascular damage and early arterial aging. (92)

Some theories explain the normal aging process, and, can be generally divided into evolution and physiological or structural theories. From the cardiovascular viewpoint, the major theories include oxidative stress, production of free radicals, neuroendocrine changes and genetic predisposition. The confluence of those factors, acting mainly on myocytes and arterial media-intima layer, increases ventricular and vascular stiffness, a phenomenon closely related to the cardiovascular aging process. (93)

The newest ESC Guideline for management of cardiovascular diseases during pregnancy issued in 2018 was mandatory because the previous was published in 2012 and new recommendations were necessary.

Oxidative stress is involved in the pathogenesis and maintenance of pregnancy-related disorders, such as intrauterine growth restriction (IUGR) and preeclampsia (PE). (94)

D. Surico et al. concluded in their study that in pathological pregnancies, body mass index, serum acid uric, pulsatility index in uterine and umbilical arteries and markers of oxidative stress were higher than those found in physiological ones. Moreover, in PE and IUGR, a relation was observed between laboratory and clinical findings and the increased levels of oxidative stress. (94)

Arterial stiffness is defined by a VPWV value greater or equal to 10.

Arterial stiffness is now included in the guidelines of the European Society of Hypertension. In this paper, we review the evidence for the predictive value of arterial stiffness. More than 11 longitudinal trials have proven the predictive value of aortic stiffness measured through carotid to femoral pulse wave velocity, beyond and above classical risk factors. Such evidence is scarcer for central pressure and local arterial stiffness. If we add this evidence to the easiness of performing such measure, carotid to femoral pulse wave velocity is the reference technique for assessing arterial stiffness. Its place in the investigation of patients remains to be established.

Arterial stiffness occurs as a consequence of biological aging and arteriosclerosis. Inflammation plays a major role in arteriosclerosis development, and consequently it is a major contributor in large arteries stiffening.

Arterial stiffness predicts a higher risk of cardiovascular events. Inflammation plays a major role in large arteries stiffening. Different studies showed significant correlations between the severity of arterial stiffness and inflammatory markers, such as white blood cell count, neutrophil/lymphocyte ratio, adhesion molecules, fibrinogen, C-reactive protein, cytokines, microRNAs, and cyclooxygenase-2, in patients with a broad variety of diseases, such as metabolic syndrome, diabetes, coronary heart disease, peripheral arterial disease, malignant and rheumatic disorders, polycystic kidney disease, renal transplant, familial Mediterranean fever, and oral infections, and in women with preeclampsia or after menopause. (95)

There is strong evidence that inflammation plays an important and, at least, partly reversible role in the development of arterial stiffness, and inflammatory markers may be useful additional tools in the assessment of the cardiovascular risk in clinical practice. Combined assessment of arterial stiffness and inflammatory markers may improve non-invasive assessment of cardiovascular risk, enabling selection of high-risk patients for prophylactic treatment or more regular medical examination. (95)

The elasticity and distensibility of arteries maintain a relatively constant blood pressure, despite the pulsating nature of the blood flow by every heartbeat. Arteries expand by receiving blood ejected from the heart during systole and expel it to the periphery during diastole to supply the peripheral circulation with a steady flow of blood during both cardiac cycles. (96) However, as a hallmark of normal aging and apart from that also in association with many diseases compliance and distensibility of arteries decrease and the term "arterial stiffness" is used to qualitatively indicate these decreased elastic vessel wall properties. (97) An increased arterial stiffness leads to a decreased buffer capacity of the arteries and an increase in pulse pressure (PP) and pulse wave velocity (PWV), causing an early return of the reflected waves and thereby an augmentation of late systolic pressure. (98) As a consequence, the left ventricle has to generate an extra workload to overcome the augmented pressure, which is associated with an increased demand of oxygen and in the long-term development of left ventricular hypertrophy and heart failure. (99) Insufficient arterial compliance furthermore transmits the increased pulsatile pressure deeper into the periphery and damages microvasculature of distal-end organ systems, especially in the kidney and the brain. (100)

Arterial stiffness is recognized increasingly as an important component in the determination of cardiovascular risk. (101)

Vascular stiffness increases left ventricular afterload and decreases coronary perfusion, leading to CVD. Increased vascular stiffness, as measured by pulse wave velocity (PWV), is associated with increased cardiovascular and all-cause mortality in patients with end-stage renal-failure. (102)

Deloach et al. studied the vascular dynamics, the determinants of PWV with accent to nephrology area. It was proven that dialysis patients who have a decrease in PWV in response to BP lowering have lower mortality rates compared with those who do not have a decrease in PWV. (102)

Early recognition and modification of vascular stiffness may enable us to reduce CVD events in this population.

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CHAPTER 3

PREDICTING HYPERTENSION AND PREECLAMPSIA IN PREGNANCY: THE ROLE OF BLOOD PRESSURE CONTROL AND PULSE WAVE VELOCITY

In our research, we sought to address several critical questions regarding the cardiovascular health of pregnant women, with a particular focus on arterial rigidity and its implications. First, we aimed to explore the progression of arterial rigidity in pregnant women, both with and without associated risk factors, to better understand the influence of pre-existing conditions and pregnancy-related changes on vascular health.

Second, we investigated how arterial stiffness parameters evolve with gestational age. By examining these changes across different trimesters, we sought to identify patterns and establish whether certain stages of pregnancy are associated with heightened cardiovascular strain.

Another key focus of our study was the impact of medical gymnastics and controlled physical exercises on arterial stiffness parameters. We aimed to evaluate whether structured, supervised exercise programs could mitigate vascular rigidity and promote better cardiovascular outcomes during pregnancy.

Finally, we examined the potential value of measuring hemodynamic parameters in pregnant women as a predictive tool for future complications. Our goal was to assess whether early identification of changes in hemodynamic function could serve as a reliable indicator for managing and preventing adverse maternal and fetal outcomes.

Through these inquiries, our research aimed to contribute valuable insights into the management and prevention of cardiovascular complications in pregnancy, ultimately improving outcomes for both mothers and their babies.

This study aimed to predict the likelihood of developing hypertension in pregnant women who were normotensive at baseline, evaluate the effectiveness of blood pressure management in those diagnosed with hypertension, and assess the risk of preeclampsia in pregnant women presenting with elevated pulse wave velocity (PWV) early in pregnancy.

Reducing maternal mortality remains a critical goal in global health and international development. Achieving meaningful progress in this area requires the foundation of reliable and accurate data to inform evidence-based health policies and programs. In this context, our study sought to address three key objectives: first, to predict the likelihood of developing hypertension in pregnant women who were normotensive at baseline; second, to evaluate the effectiveness of blood pressure management in women already diagnosed with hypertension during pregnancy; and third, to assess the risk of preeclampsia in pregnant women presenting with elevated pulse wave velocity (PWV) at the start of pregnancy. These investigations aim to contribute to the development of targeted interventions that improve maternal and fetal outcomes.

Between 2011 and 2018, statistical data on births revealed significant trends in natality and pregnancy outcomes. The total number of births reached its peak in 2017, following a steady increase from 2011, after which a decline was observed. Premature births, however, showed a consistent rise starting in 2014, culminating in a maximum in 2018. Interestingly, premature births attributed to hypertension and preeclampsia peaked in 2012 but have since steadily decreased. This reduction can be attributed to the implementation of regular prenatal check-ups and effective treatment protocols for women diagnosed with these conditions.

The motivation for this study lied in the need to better understand the complexity of managing pregnancies complicated by hypertension and preeclampsia. By exploring these trends and focusing on predictive tools, the study aims to identify and mitigate complications, such as morbidity and mortality, in both mothers and newborns, ultimately improving outcomes for this high-risk patient group.

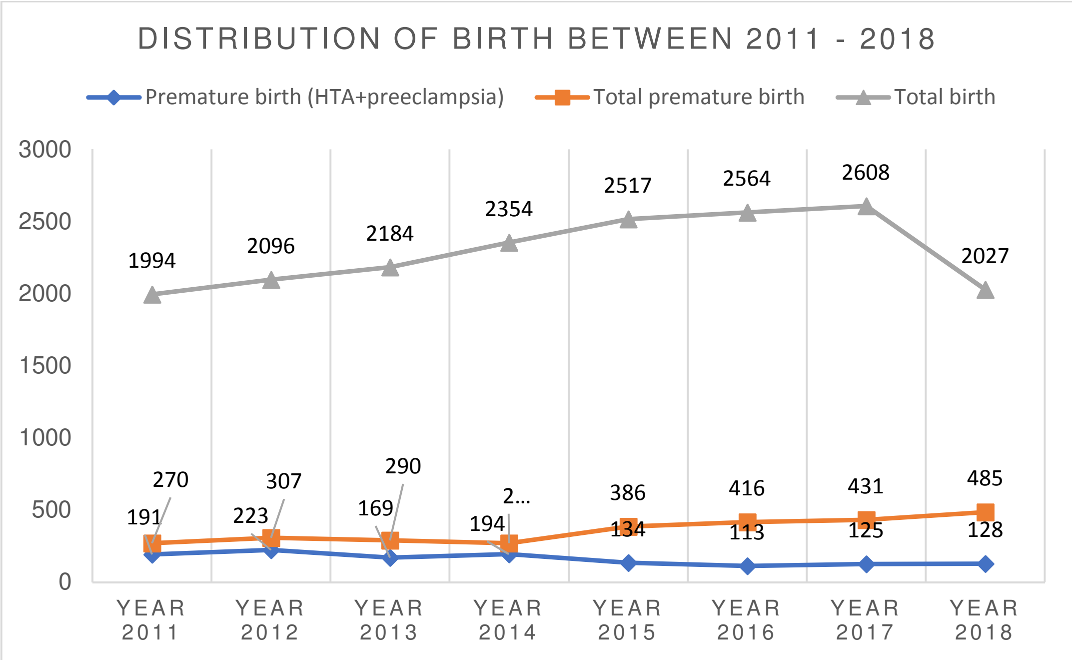


Figure 1: *The distribution of births in our clinic from 2011 to 2018*

This case-control follow-up study was conducted between 2017 and 2018 at the Bega Obstetrics and Gynaecology Departments of the Pius Brinzeu County Clinical Hospital in Timișoara. A total of 300 patients participated, all of whom provided informed consent in adherence to the ethical standards outlined in the Helsinki Declaration. The study received full approval from the Ethics Commission of the Victor Babes University of Medicine and Pharmacy in Timișoara, ensuring compliance with the highest ethical guidelines for medical research.

The statistical analysis for this study was conducted using three software tools: Microsoft Excel for database management, SPSS v17 for statistical testing, and EPI Info v7 for advanced analysis. These programs were licensed through the Victor Babes University of Medicine and Pharmacy, ensuring access to reliable and validated tools for data processing.

The dataset comprised 300 participants, categorized into three equal groups:

1. **Group 1:** 100 pregnant women who developed hypertension or preeclampsia during pregnancy.
2. **Group 2:** 100 healthy pregnant women.
3. **Group 3:** 100 healthy non-pregnant women (control group).

Specific statistical analyses were performed for each group to explore differences and trends, and when appropriate, the dataset was assessed as a whole to derive comprehensive insights. This structured approach allowed for an in-depth examination of the relationships between pregnancy, hypertension, and cardiovascular health.

Normality Testing: Methodology and Application

To assess data distribution, the SPSS v17 software was employed for normality testing. This process utilized two distinct tests, both of which were applied in this study:

1. **Kolmogorov-Smirnov Test:**
   This test was used for datasets with a sample size greater than 50.
2. **Shapiro-Wilk Test:**
   This test was applied to smaller sample sizes, specifically those with fewer than 50 subjects.

The normality tests provided p-values, displayed in the column labeled "Sign" within SPSS output tables. A p-value less than 0.05 indicated that the data were not normally distributed, necessitating the use of nonparametric tests. Conversely, if the p-value was greater than or equal to 0.05, the data were considered normally distributed, allowing for the application of parametric tests.

Parametric vs. Nonparametric Tests

- **Parametric Tests:** Used for data with a normal distribution, these tests assume specific statistical properties about the dataset.
- **Nonparametric Tests:** Applied to datasets that do not meet the assumptions of normality, these tests offer a generalized approach to data analysis without relying on specific distributional assumptions.

This dual approach ensured a robust statistical evaluation tailored to the nature of the data, enhancing the reliability and accuracy of the study's findings.

Statistical Tests Employed in the Study

The following statistical methods were utilized to analyze numerical variables, ensuring robust evaluation of the data depending on its distribution and study design:

1. **Comparing Two Independent Means:** When comparing the means of two independent samples at a single point in time, the choice of test depended on the distribution of the data:

- **Mann-Whitney Test:** Applied when the data did not follow a normal distribution (nonparametric test).
- **Unpaired T-Test:** Used when the data followed a normal distribution (parametric test).

2. **Comparing Two Time Points in the Same Sample:** To evaluate differences at two separate time points within the same sample, the following tests were used:
    - **Wilcoxon Signed Rank Test:** Utilized for non-normally distributed data (nonparametric test).
    - **Paired T-Test:** Applied when the data were normally distributed (parametric test).
3. **Quantifying Variance Across Multiple Samples:**
    - The **One-Way ANOVA** test was used to analyze the variance among three or more groups, providing a method to assess differences in mean values across multiple samples.

These statistical approaches were chosen based on the characteristics of the dataset and the research objectives, ensuring accurate and meaningful interpretation of the findings. Each method was carefully selected to match the distribution and type of data being analyzed, enhancing the reliability of the study's conclusions.

Statistical Methods for Variable Analysis

1. **Comparison of Proportions:**
For all types of variables, including numerical, ordinal, and qualitative, the **Chi-Square (χ^2) test** was employed to compare proportions. This test is widely used to evaluate associations between categorical variables and determine whether observed differences are statistically significant.
2. **Correlation and Regression Analysis:**
Correlation and regression analysis were used to assess the relationship between two independent numerical variables. These methods help quantify the strength and nature of associations:
    - **Pearson Correlation Coefficient (rr):**
    The Pearson coefficient measures the intensity and direction of the association between two variables and is expressed within a range of [−1,1][-1, 1]:
        - r>0r > 0: Indicates a positive, direct correlation (as one variable increases, so does the other).
        - r<0r < 0: Indicates a negative, inverse correlation (as one variable increases, the other decreases).

        - $r=1r = 1$: Perfect positive correlation.
        - $r=-1r = -1$: Perfect negative correlation.
        - $r=0r = 0$: No correlation; the variables are independent.

To interpret the strength of the correlation, Colton's empirical guidelines (1974) were applied:

        - $[-0.25,0.25][-0.25, 0.25]$: Weak or no correlation.
        - $[0.25,0.5][0.25, 0.5]$: Weak to moderate correlation.
        - $[0.5,0.75][0.5, 0.75]$: Moderate to strong correlation.
        - $|r|>0.75|r| > 0.75$: Strong correlation, with $r=\pm1$r = \pm 1 indicating a perfect correlation.
    - **Determination Coefficient ($R2R$^2):**
    - The $R2R$^2 value represents the proportion of variance in one variable that can be explained by the variance in the other variable. It is calculated as $R2=r2R$^2 = r^2 and ranges from 0 to 1, providing insight into the strength of the relationship but not its causation.

3. **Correlation vs. Regression Models:**
    - **Correlation Model:** Applied when both variables vary and can influence each other. It is used to measure the strength of the association without assuming causality.
    - **Regression Model:** Used when one variable (predictor) is fixed, and the other (response) varies. In this model, the predictor variable is presumed to influence the response variable.

By combining these statistical techniques, the analysis provided a robust framework for evaluating relationships between variables, supporting both exploratory and predictive objectives within the study.

- ***Risk analysis***
    - The Risk analysis was run with Epi Info v7 program.
    - The present research can be included in a follow up study. At baseline, all patients were considered healthy; patients came for regular pregnancy check-ups. One part of the entire group ($N1=100$ patients) presented pathological findings during pregnancy and were closely assessed for possible causes. Another 100 patients had a normal pregnancy. Information for these patients was gathered in the period 2016 – 2018.
    - The data presentation for the risk analysis – contingency tables

Table 1: *Contingency table*

	B+	**B-**	**Total**
E+	a	b	a+b
E-	c	d	c+d
Total	a+c	b+d	a+b+c+d

- In this type of study (follow up) e Risk Ratio (RR) parameter and the Odds Ratio (OR) parameter were calculated
- RR= the probability of occurrence of the disease in the exposed group divided to the probability of occurrence of disease in the unexposed group
- $RR = \frac{a(c+d)}{c(a+b)}$
- OR = measures the highest possible chance of illness in the exposed group compared to the unexposed group, relative to those who do not get ill
- $OR = \frac{a \cdot d}{b \cdot d}$
- For the statistical significance we will compute the 95% confidence interval for RR and OR and we will apply the χ^2 test.

- ***Statistical conclusion*** – used for the whole thesis. We considered $\alpha = 0.05$ as significance level
  - if $p \geq 0.05 \Rightarrow$ it implies that the differences / correlations / risk found **are not significant** for the whole population (95%)
  - if $p < 0.05 \Rightarrow$ it implies that the differences / correlations / risk found **are significant** for the whole population (95%)
  - if $p < 0.01 \Rightarrow$ it implies that the differences / correlations / risk found are **very significant** for the whole population (99%)
  - if $p < 0.001 \Rightarrow$ it implies that the differences / correlations / risk found are **extremely significant** for the whole population (99.9%)

Clinical and Diagnostic Changes During Pregnancy

Pregnancy induces a multitude of significant physiological changes in the maternal body, many of which manifest as clinically relevant general and localized signs. These changes serve as valuable diagnostic indicators when correlated with paraclinical investigations, enabling the accurate determination of pregnancy status, gestational age, and fetal viability.

In the **first trimester**, the confirmation of pregnancy primarily relies on thorough clinical examinations. The subtle yet critical changes observed in the maternal body during this early phase are key to establishing a positive diagnosis.

As pregnancy progresses into the **second and third trimesters**, the diagnostic focus shifts. While maternal body changes remain important, the presence and development of the fetus within the uterine cavity provide more definitive diagnostic elements. Advanced imaging and investigative techniques during these stages offer highly accurate insights into the health and viability of the fetus, ensuring precise monitoring and management of the pregnancy.

The Role of Ultrasound in Pregnancy Monitoring

Ultrasound plays a critical role in the systematic and repeated assessment of pregnancy, offering precise and reliable diagnostic information about the development of the pregnancy and the viability of the fetus. As a non-invasive, fast, and cost-effective medical investigation, ultrasound provides a wealth of information in a short time, making it an indispensable tool in prenatal care.

Doppler Ultrasound (11–14 Weeks)

In the early stages of pregnancy, Doppler ultrasound is used to determine gestational age with high accuracy. It enables comprehensive measurements of the fetus's major structures, including the brain, heart, spine, kidneys, and other internal organs, offering essential insights into early development.

Abdominal Ultrasound (17–18 Weeks)

During the mid-second trimester, abdominal ultrasound is recommended to further evaluate fetal growth and development. Key assessments during this period include:

- Determining gestational age based on fetal size and position.
- Evaluating the placenta, amniotic fluid levels, and umbilical cord characteristics.
- Detecting congenital malformations, such as neural tube defects (e.g., spina bifida) or heart anomalies.
- Identifying the baby's sex.

Foetal Morphology Ultrasound (22–24 Weeks)

Foetal morphology ultrasound, often regarded as the most comprehensive ultrasound during pregnancy, is performed during this period. At this stage, most fetal organs are fully formed, allowing for a detailed analysis of all anatomical structures. This exhaustive examination is crucial for identifying any abnormalities or developmental concerns. A follow-up ultrasound of this type may also be performed around 32 weeks to monitor ongoing fetal health and development.

Pre-Birth Abdominal Ultrasound (40 Weeks)

In the final weeks of pregnancy, an abdominal ultrasound is conducted to confirm and consolidate the findings from previous ultrasounds. This last pre-birth evaluation provides additional information critical for delivery planning, ensuring optimal outcomes for both mother and baby.

Ultrasound technology remains a cornerstone of prenatal care, enabling healthcare providers to monitor fetal development, detect potential issues early, and support informed decision-making throughout pregnancy.

➢ Prematurity – definition and classification

Weight at birth is part of the newborn birth assessment criteria, along with the Apgar score, maturity according to gestation time and other history and clinical elements that allow the child to be classified as a in high-risk newborn.

The premature has the weight according to gestational age.

***Table 2:** Premature degrees according to ICD – International Code of Disease*

Premature baby	Gestational age	Birth weight
Low birth weight (LBW)	GA<37weeks	BW = 2499g – 1500g
Very low birth weight (VLBW)	GA<32weeks	BW =1499g– 1000g
Eextremely low birth weight (ELBW)	GA<28weeks	BW = 999 - 700g
Incredible low birth weight (ILBW)	GA<24weeks	BW < 700g

➢ APGAR score

The Apgar score provides an accepted and convenient method for reporting the status of the new-born infant immediately after birth and the response to resuscitation if needed.

The Apgar score is determined by evaluating the new-born baby on five simple criteria on a scale from zero to two, then summing up the five values thus obtained.

The resulting Apgar score ranges from zero to 10. The five criteria are summarized using words chosen to form a backronym (**A**ppearance, **P**ulse, **G**rimace, **A**ctivity and **R**espiration).

The test is generally done at 1 and 5 minutes after birth and may be repeated later if the score is and remains low.

Scores:

- ≥7 = normal;
- 4 to 6, fairly low;
- ≤ 3 = critically low and cause for immediate resuscitative efforts.

A low score on the one-minute test may show that the neonate requires medical attention but does not necessarily indicate a long-term problem, particularly if the score improves at the five-minute test. (1,2)

An Apgar score that remains below 3 at later times, such as 10, 15, or 30 minutes, may indicate longer-term neurological damage, including a small but significant increase in the risk of cerebral palsy. However, the Apgar test's purpose is to determine quickly whether or not a new-born needs immediate medical care. It is *not* designed to predict long-term health issues. (3,4)

A score of 10 is uncommon, due to the prevalence of transient cyanosis, and does not substantially differ from a score of 9. Transient cyanosis is common, particularly in babies born at high altitude. (5,6)

➢ Blood pressure assessment and hypertension classification:

Repeated BP readings should be performed, preferably on two occasions (7) ≥15 min apart in severe hypertension (i.e. ≥160/110 mmHg in the obstetric literature). (8)

The definition of hypertension in pregnancy is based only on office (or in-hospital) BP values [systolic BP (SBP) ≥140 mmHg and/or DBP ≥90 mmHg] (9) and distinguishes *mildly* (140–159/90–109 mmHg) or *severely* (≥ 160/110 mmHg) elevated BP, in contrast to the grades used by the joint ESC/ESH Hypertension Guidelines.(10)

Hypertension in pregnancy is not a single entity but includes the following: (9)

- Pre-existing hypertension
- Gestational hypertension
- Pre-eclampsia
- Pre-existing hypertension plus superimposed gestational hypertension with proteinuria.
- Antenatal unclassifiable hypertension

Smoking/non-smoking status was established according to the positivity for smoking in the last six months prior to the study.

➢ Procedure for assessing arterial stiffness using the Medexpert Arteriograph:

- The patient who meets the criteria for inclusion in the study / research will be prepared 24 hours before the test. Description of the determination procedure (in the "patient info" document);

- The investigation for the determination of the PWV will be performed according to the protocol in the technical book of the device, observing the patient's agreement;

- Determination will be done in a specially arranged room: medical cabinet (internal medicine standard) provided according to the legislation in force, and which complies with the following conditions:

- no noises,

- temperature between 22-25 degrees Celsius,

- the bed used is to be fitted with a mattress with a horizontal surface and positioned so that both the right arm and the left arm are accessible.

- Before starting the determination, the patient must be lying down to rest for about 10 minutes;

- If the patient has performed a physical activity before the investigation, the rest period must be extended to 20 minutes before the investigation;

- It is forbidden: smoking, eating, energy consumption and coffee less than 3 hours before the investigation;

- The patient is not allowed to speak or sleep during the investigation;

- Investigation is done only in clinostats;

- If the investigation values are erroneous, repeat 4 times (1-2 minute intervals between measurements) on the same arm;

- If the patient is more emotional and / or with a tachycardia component, the measurements are repeated 4 times or additional time is allocated between the measurements;

- In case of cardiac arrhythmias, the investigation is delayed until the return to the sinus rhythm;

- Preferably, such determination is made at hemodynamic values controlled according to the ESC guidelines;

- Pathological values obtained will require additional specialist consultations;

- The result of the determination is brought to the attention of the patient along with the information in the “info patient”;

- The result of the determination is GDPR compliant.

➢ Determination times with the PWV determination Medexpert Arteriograph:

- Place the patient lying down;
- Free the forearm and right and left arm from tight clothing so that they are accessible for measurements;
- Wait for about 10 minutes before beginning the measurements. Measure the circumference of the left and right arm. Measure the distance between the pubic symphysis and the sternum fork;
- Fill in the personal information in the software as well as the additional data from the anamnesis;

- Perform the anthropometric measurements and introduce them in the software;
- Position the cuff recommended by the software in the middle of the arm (cuff 1, 2 or 3), usually recommended to be tight as in a simple AP determination;
- Check the connection between the computer and the arteriograph;
- Execute the measurements;
- Visualize the pulse waves displayed on the screen;
- Finalize the measurements;
- If the standard deviation does not correspond (it is highlighted in red), resume determination (4 times with a 1-2 minute break between determinations);
- If expected results are not obtained, the cuff is shifted to the contralateral arm (observing the size of the cuff according to the software recommendation);
- The scientific coordinator may recommend the examination order: the left arm first then in case of failure: right arm;
- In the event that no results are obtained on the contralateral arm as well, manual measurements will be performed, as allowed by the software;
- Determinations are saved in PDF format and then transferred to Xcel for statistical processing.

➢ Blood tests

Dyslipidaemia

● Hypercholesterolemia was defined according to The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (with TC>200 mg/dl). Target level recommended in primary prophylaxis is <190mg/dl. Being under treatment for dyslipidemia was also considered diagnosis criterion.

Hypertriglyceridemia was diagnosed according to ACC/AHA guidelines if the value of TG was >150mg/dl.

● HDL-cholesterol (HDL-c) was used to calculate LDL-cholesterol (LDL-c) using Friedewald formula:

LDL-c = TC - HDL-c - triglycerides/5

Inflammatory markers

Interleukin 6 (IL-6) was determined from frozen serum and through electrochemiluminescence method (CLIA). Normal values are < 3.8 pg/mL. Higher levels are associated with negative prognosis and complications.

Markers for assessing the pre-eclampsia risk

SFlt-1/PIGF can differentiate between a normal pregnancy or one with pre-eclampsia before the onset of clinical symptoms. They were determined from frozen serum and through electrochemiluminescence method (CLIA). Serum level of PlGF and sFlt-1 (soluble fms-like tyrosine kinase-1 or VEGF receptor-1) is altered in pre-eclampsia patients. In normal pregnancies, PIGF increases in the first 2 trimesters and decreases as thee pregnancy evolves, while sFlt-1 remains stable at the beginning and middle of the pregnancy and decreases constantly until the due date. In women who will develop preeclampsia, sFlt-1 is higher, and PIGF lower compared to normal pregnancies.

Detection limit: 10 pg/mL for sFlt-1 and 3 pg/mL for PIGF

Reference values for preeclampsia estimation (11)

Table 3: *Reference values for preeclampsia estimation*

Weeks of pregnancy	**sFlt-1**	**PlGF**
10-14	652 – 2500	30-122
15-19	708-2800	66-289
20-23	572-3000	120-605
24-28	618-3200	170-1120
29-33	773-5160	115-1300
34-36	992-7360	78-980
> 37	1530-9200	54-860

How to interpret the results and apply the findings in the clinical practice

PE with early onset (at gestational age of 20-33+6 weeks)

Table 4: sFlt-1/PlGF ratio and clinical significance

sFlt-1/PIGF ratio	Meaning
<38	Excludes PE in the following week with a negative predictive value (NPV) of ≈99% and in the next 4 weeks with a PNV of ≈95%
38-85	High risk of PE (Positive predictive value of ≈40%)
>85	High probability of PE (sensibility 88%, specificity 99.5%)
>655	Very high risk of complications on short term and necessity to induce labour

PE with late onset (GA>34 weeks)

Table 5: sFlt-1/PlGF ratio and clinical significance

sFlt-1/PIGF ratio	Meaning
<38	Excludes PE in the following week with a negative predictive value (NPV) of ≈99% and in the next 4 weeks with a PNV of ≈95%
38-110	High risk of PE (Positive predictive value of ≈40%)
>110	High probability of PE (sensibility 58,2%, specificity 99.5%)
>201	Very high risk of complications on short term and necessity to induce labor

➢ Results

Descriptive Statistical Analysis

For descriptive statistics, each group was analyzed individually to provide a comprehensive characterization. Key measures of central tendency (mean, median) and dispersion (standard deviation, range) were calculated for the numerical variables.

To represent the data visually, the following methods were employed:

- **Histograms** for numerical variables to illustrate their distribution.

- **Line plots** for ordinal variables to depict trends and changes.
- **Pie charts** for qualitative variables to display frequency distributions effectively.

These visualization techniques ensured clear and accessible presentation of the results, facilitating a deeper understanding of the data across different variable types.

Study Design and Data Collection

Our study included 300 participants, divided into three equal groups to facilitate comparative analysis:

1. **Group 1:** 100 pregnant women who developed hypertension during pregnancy.
2. **Group 2:** 100 healthy pregnant women.
3. **Group 3:** 100 non-pregnant women, serving as the control group.

The data were collected between 2017 and 2018 and systematically recorded in an Excel database. Descriptive statistical analysis was performed using Microsoft Excel and SPSS v17 to ensure accurate and thorough evaluation of the data.

Collected Data by Group

Group 1 (Pregnant Women with Hypertension):

Data collected included:

- **Maternal characteristics:** Age, height, weight, body mass index (BMI).
- **Vascular parameters:** Augmentation index of the brachial artery corrected to 75% (Aix brachial) and pulse wave velocity (PWVao), measured in the second and third trimesters.
- **Blood pressure and cardiac metrics:** Systolic blood pressure (Sys), diastolic blood pressure (Dia), pulse pressure (PP), central systolic blood pressure (SBPao), and heart rate (HR).
- **Lifestyle factors:** Smoking status (smoker/non-smoker).
- **Pregnancy outcomes:** Gestational period, fetal APGAR score, fetal gender, fetal weight, and mode of delivery (natural or C-section).

- **Biochemical markers:** Interleukin 6 (IL6), proteinuria, placental growth factor (PIGF), soluble fms-like tyrosine kinase-1 (sFlt-1), the sFlt-1/PIGF ratio, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides.

Group 2 (Healthy Pregnant Women):

Collected data included:

- **Maternal characteristics:** Age, height, weight, BMI.
- **Vascular parameters:** Aix brachial and PWVao, measured in the second and third trimesters.
- **Blood pressure and cardiac metrics:** Sys, Dia, PP, SBPao, and HR.
- **Lifestyle factors:** Smoking status.
- **Pregnancy outcomes:** Gestational period, fetal APGAR score, fetal gender, fetal weight, and mode of delivery (natural or C-section).

Group 3 (Non-Pregnant Control Group):

Data collected included:

- **Maternal characteristics:** Age, height, weight, BMI.
- **Vascular parameters:** Aix brachial and PWVao.
- **Blood pressure and cardiac metrics:** Sys, Dia, PP, SBPao, and HR.
- **Lifestyle factors:** Smoking status.

Statistical Analysis

Each group was analyzed separately to provide a detailed characterization. Descriptive statistics included:

- **Numerical Variables:** Measures of central tendency (mean, median) and dispersion (standard deviation, range).
- **Qualitative Variables:** Frequency tables to summarize categorical data.

For visual representation of the results, the following methods were employed:

- **Histograms:** To illustrate the distribution of numerical variables.

- **Line Plots:** To depict trends in ordinal variables.
- **Pie Charts:** To represent the proportions of qualitative variables.

This structured approach allowed for a comprehensive evaluation of each group and facilitated meaningful comparisons across the study population. By combining detailed data collection with robust statistical analysis, the study aimed to uncover valuable insights into maternal and fetal health in different pregnancy conditions. All the results are presented in tables 6 and 7 and figures 2 and 3.

Group 1

Table 6: *Central tendency and dispersion parameters for the age [years], height [cm], weight [kg] and body mass index [Kg/m^2] (BMI) variables*

Statistics	Age	Height [cm]	Weight [kg]	BMI [Kg/m^2]
Mean	37.56	166.70	84.19	30.33
Standard Error	0.26	0.79	0.85	0.27
Median	38.00	167.00	85.00	29.78
Mode	38.00	167.00	85.00	33.20
Standard Deviation	2.65	7.86	8.47	2.71
Sample Variance	7.02	61.85	71.79	7.36
Range	19.00	30.00	31.00	8.85
Minimum	23.00	153.00	69.00	26.26
Maximum	42.00	183.00	100.00	35.11
Count	100.00	100.00	100.00	100.00

In Group 1, comprising pregnant women who developed hypertension, the average age was 37.56 ± 2.65 years, ranging from a minimum of 23 years to a maximum of 42 years. The mean height was 166.70 ± 7.86 cm, while the mean weight was 84.19 ± 8.47 kg. The average body mass index (BMI) for this group was calculated at 30.33 ± 2.71 kg/m^2.

We calculated the measures of central tendency and dispersion for several key hemodynamic and vascular parameters. These included the augmentation index of the brachial artery corrected to 75% (Aix brachial), measured during the second trimester (Trim II) and third trimester (Trim III) of pregnancy, as well as pulse wave velocity (PWVao) recorded during the same periods. Additional parameters analyzed were systolic blood pressure (Sys), diastolic blood pressure (Dia), pulse pressure (PP), central systolic blood pressure (SBPao), and heart rate (HR). These calculations provided a detailed understanding of the distribution and variability of these physiological measures across the study population.

Table 7: *The augmentation index of the brachial artery (Aix brachial), measured during the second trimester (Trim II) and third trimester (Trim III)*

Statistics	Aix brachial: [%] Trim II	PWVao [m/s] Trim II	Aix brachial: [%] Trim III	PWVao [m/s] Trim III	Sys [mmHg]	Dia [mmHg]	PP [mmHg]	SBPao [mmHg]	HR [b/min]
Mean	1.25	10.92	3.68	12.37	196.67	121.30	58.12	128.55	89.66
Standard Error	0.09	0.14	0.14	0.17	2.08	1.22	0.70	2.41	0.96
Median	1.05	10.82	3.22	12.58	189.50	117.50	56.00	116.00	88.00
Mode	1.05	13.18	3.32	12.58	178.00	111.00	54.00	116.00	86.00
Standard Deviation	0.86	1.36	1.36	1.68	20.79	12.24	6.99	24.11	9.61
Sample Variance	0.73	1.86	1.84	2.82	432.28	149.85	48.79	581.42	92.33
Range	3.21	4.86	4.85	5.29	66.00	39.00	28.00	89.00	44.00
Minimum	0.05	9.00	2.57	9.78	173.00	102.00	50.00	102.00	76.00
Maximum	3.26	13.86	7.42	15.07	239.00	141.00	78.00	191.00	120.00
Count	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

In the second trimester, the mean augmentation index of the brachial artery (Aix brachial) was 1.25 ± 0.86%, increasing to 3.68 ± 1.36% in the third trimester. The mean pulse wave velocity (PWVao) was recorded at 10.92 ± 1.36 m/s during the initial measurement and increased to 12.37 ± 1.68 m/s in subsequent assessments.

The mean systolic blood pressure (SBP) was 196.67 ± 20.79 mmHg, while the mean diastolic blood pressure (DBP) was 121.30 ± 12.24 mmHg. Pulse pressure (PP) averaged 58.12 ± 6.99 mmHg. Central systolic blood pressure (SBPao) had a mean value of 128.55 ± 24.11 mmHg, and the mean heart rate (HR) was 89.66 ± 9.61 beats per minute (bpm).

These findings highlight the hemodynamic changes observed during pregnancy in this population.

Table 8: *Central tendency and dispersion parameters for the gestational period [weeks], APGAR score, foetus weight [grams] values*

Statistics	Gestational Period [weeks]	APGAR score [1 min]	Foetus Weight [Grams]
Mean	34.30	7.61	2573.90
Standard Error	0.33	0.21	78.56
Median	35.00	8.00	2770.00
Mode	35.00	9.00	2900.00
Standard Deviation	3.28	2.14	785.55
Sample Variance	10.78	4.56	617090.70
Range	9.00	10.00	2800.00
Minimum	27.00	0.00	750.00
Maximum	36.00	10.00	3550.00
Count	100.00	100.00	100.00

The mean gestational age was 34.30 ± 3.28 weeks. The APGAR score ranged from 0 to 10, with a mean of 7.61 ± 2.14.

Table 9: *We calculated the central tendency and dispersion parameters for the interleukin 6 [pg/mL4] (IL6), proteinuria [mg/24h], PIGF, sFlt-1 values and the report of this values*

Statistics	IL6 [pg/mL^4]	Proteinuria [g/24h]	PIGF [pg/ml]	sFlt-1[pg/ml]	Ratio
Mean	32.01	1.14	209.19	1488.71	9.79
Standard Error	3.66	0.08	13.43	52.50	0.69
Median	14.15	0.95	170.80	1583.00	7.33
Mode	1.99	0.80	262.00	1694.00	6.47
Standard Deviation	36.62	0.75	134.28	525.03	6.90
Skewness	1.20	0.93	1.59	0.21	1.38
Range	144.20	3.40	648.80	2411.10	30.62
Minimum	1.20	0.10	36.00	486.90	2.48
Maximum	145.40	3.50	684.80	2898.00	33.11
Count	100.00	100.00	100.00	100.00	100.00

For the assessment of preeclampsia risk, the mean interleukin-6 (IL6) level was 32.01 ± 36.62 pg/mL□. Proteinuria averaged 1.14 ± 0.75 g/24h. The mean placental growth factor (PIGF) level was 209.19 ± 134.28 pg/mL, while the mean soluble fms-like tyrosine kinase-1 (sFlt-1) level was 1488.71 ± 525.03 pg/mL. The mean sFlt-1/PIGF ratio, a key marker in preeclampsia evaluation, was 9.79 ± 6.90. These values provide critical insights into the biochemical markers associated with preeclampsia in the studied population.

Table 10: *The central tendency and dispersion parameters for the total cholesterol [mg/dl], the HDL cholesterol [mg/dl], the LDL cholesterol [mg/dl] and the triglyceride [mg/dl] values*

Statistics	Total cholesterol [mg/dl]	HDL cholesterol [mg/dl]	LDL cholesterol [mg/dl]	Triglyceride [mg/dl]
Mean	261.74	26.57	191.81	332.21
Standard Error	3.01	0.40	2.00	11.64
Median	262.50	26.00	196.50	352.50
Mode	254.00	24.00	207.00	352.50
Standard Deviation	30.07	3.99	19.99	116.38
Sample Variance	904.01	15.88	399.59	13543.34
Range	136.00	18.00	69.00	419.00
Minimum	188.00	22.00	151.00	151.00
Maximum	324.00	40.00	220.00	570.00
Count	100.00	100.00	100.00	100.00

For the lipid profile assessment, the mean total cholesterol level was 261.74 ± 30.07 mg/dL. The mean high-density lipoprotein cholesterol (HDL-c) was 26.57 ± 3.99 mg/dL, while the mean low-density lipoprotein cholesterol (LDL-c) was 191.81 ± 19.99 mg/dL. Triglyceride levels averaged 332.21 ± 116.38 mg/dL. These values reflect significant variations in lipid metabolism within the studied population.

Table 11: *The frequency table for the smoker – non-smoker variable*

Smoker	Absolute Frequency	Relative Frequency (%)	Cumulate frequency (%)
No	57	57.00%	57.00%
Yes	43	43.00%	100.00%
Total	100	100.00%	

Smoking is another significant cardiovascular risk factor. In Group 1, nearly half of the patients (43%) reported smoking during pregnancy, highlighting a critical area for intervention to reduce associated health risks for both mother and fetus.

Table 12: *The frequency table for the foetus gender*

Fetus gender	Absolute Frequency	Relative Frequency (%)	Cumulate frequency (%)
male	60	60.00%	60.00%
female	40	40.00%	100.00%
Total	100	100.00%	

The gender of the foetus in 60% of the pregnancies was male.

Table 13: *We present the frequency table for the type of birth*

Type of birth	Absolute Frequency	Relative Frequency (%)	Cumulate frequency (%)
natural	17	17.00%	17.00%
C - Section	83	83.00%	100.00%
Total	100	100.00%	

The majority of the patients had a C-section type of delivery (85%).

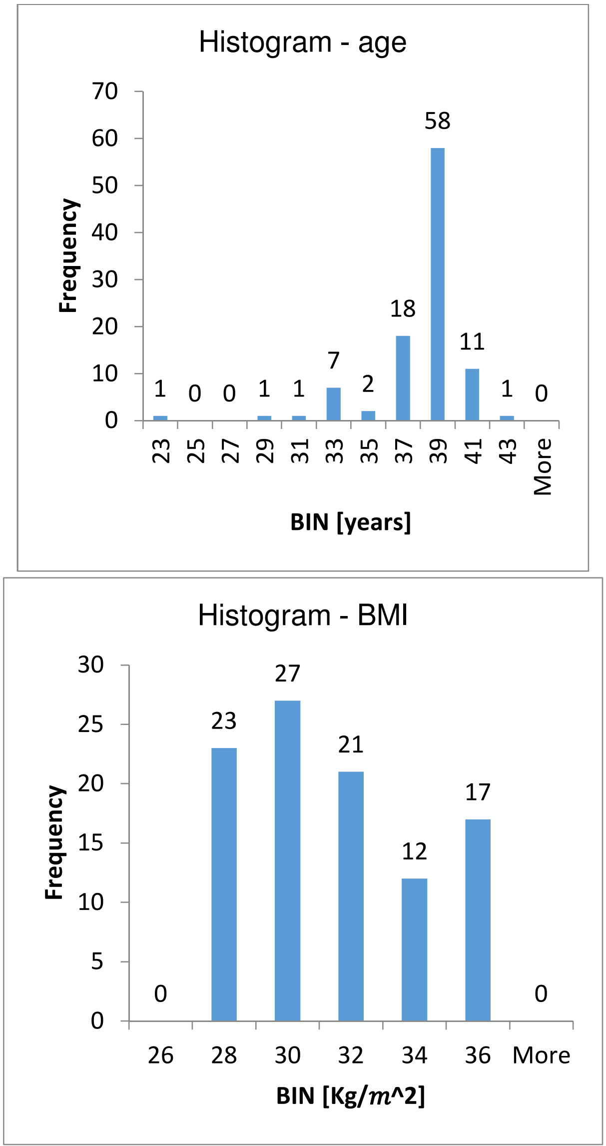


Figure 2: *The histograms for the age [years], and body mass index [Kg/m^2] (BMI) variables*

The histograms presented above illustrate a trend of advanced maternal age and elevated body mass index (BMI) among the study population. The majority of patients were 39 years old and categorized as having Stage I obesity, emphasizing the prevalence of these risk factors in the group.

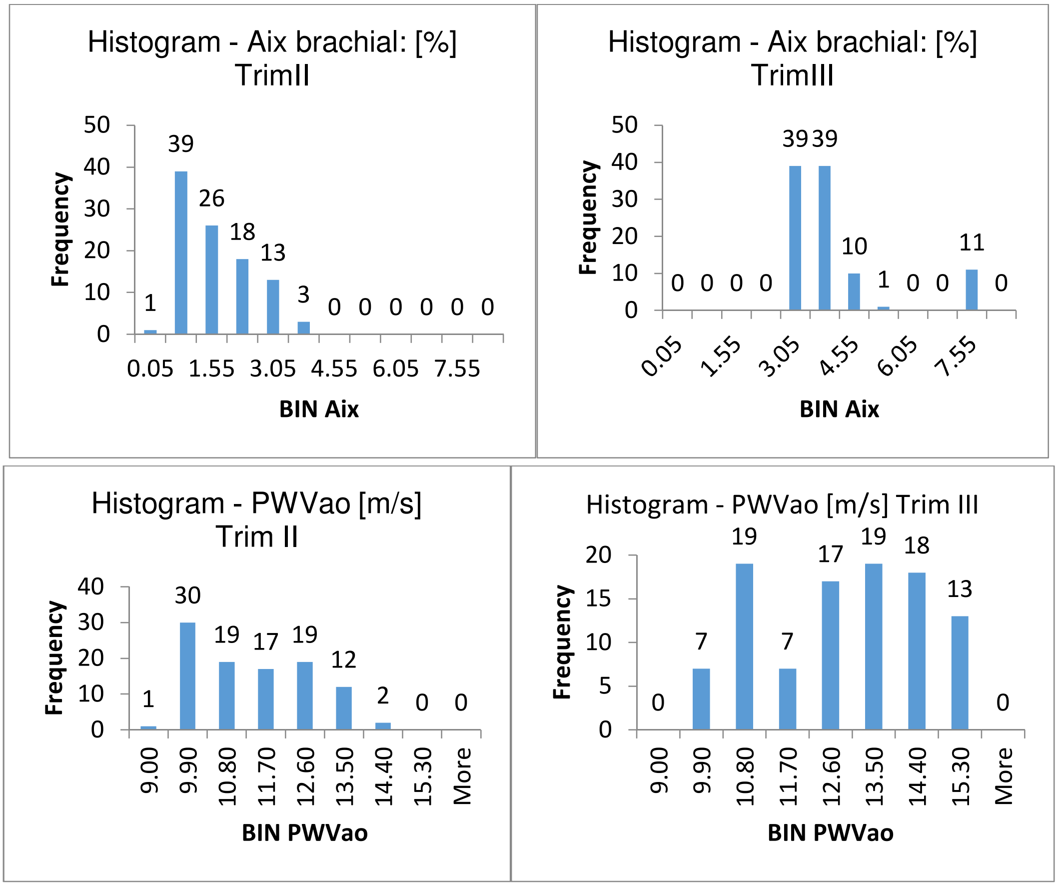


Figure 3: *The histograms for the augmentation index of branchial artery corrected to 75% [%] (Aix brachial) (in the second trimester (Trim II) and in the third trimester (Trim III) of pregnancy), pulse wave velocity [m/s] (PWVao) (in the second trimester (Trim II) and in the third trimester (Trim III) of pregnancy.*

The histograms show a tendency for Aix brachial in the second trimester for values around 0.80 and in the third trimester around 3.05% and for PWV from 9.90 m/sec (majority) in the 2nd trimester to 13.50 m/sec in the 3rd trimester

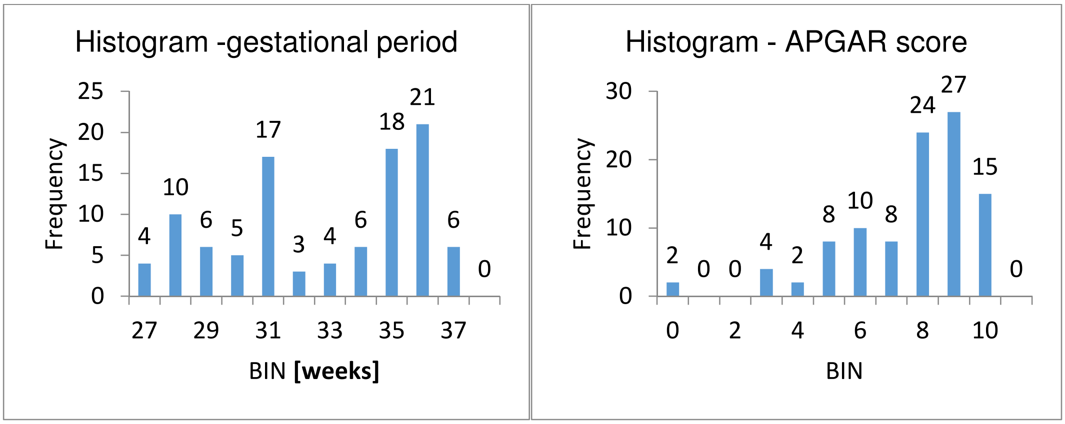
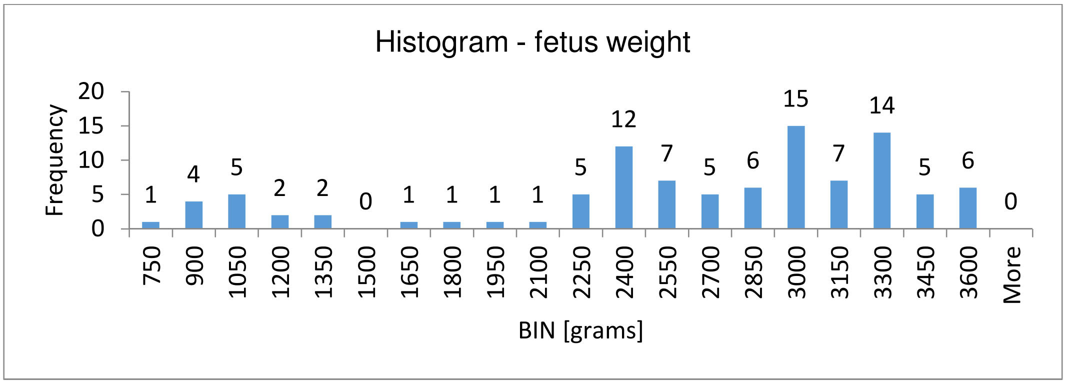
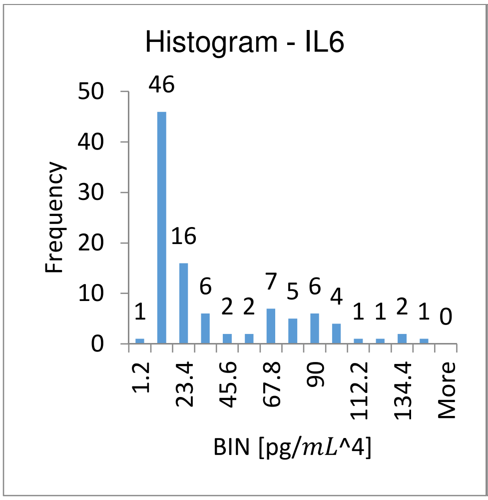


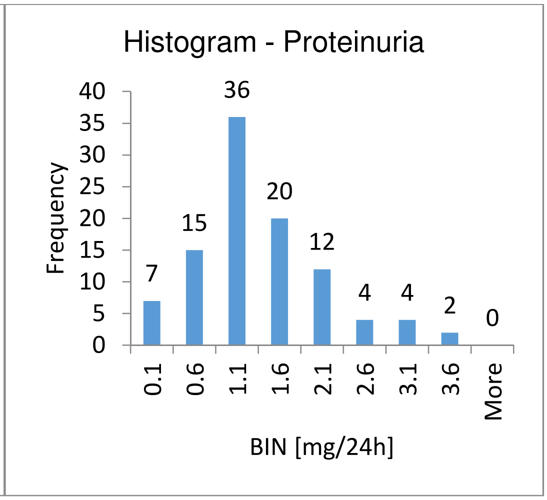
Figure 4: *The histograms for gestational period [weeks], APGAR score, fetus weight [grams], interleukin 6 [pg/mL^4] (IL6), proteinuria [mg/24h] and the report variables*

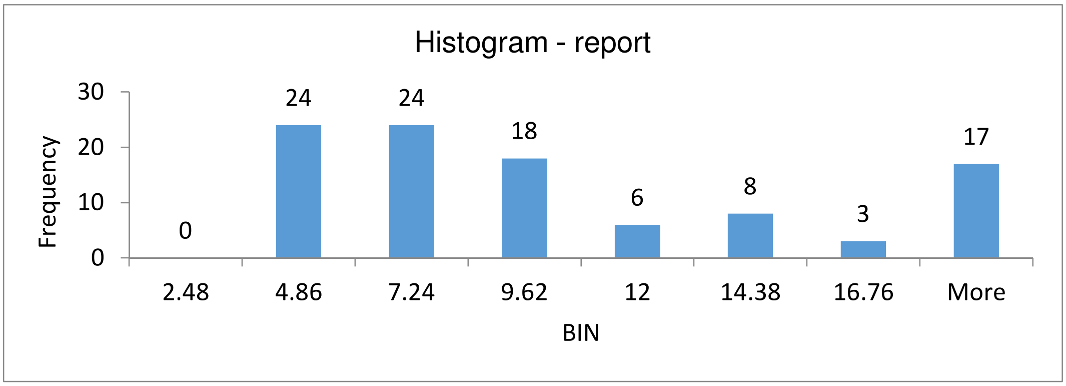
Histograms showed that most women reached 36-37 weeks of gestation. Most newborns had an APGAR score of 8 or 9, thus, good health.

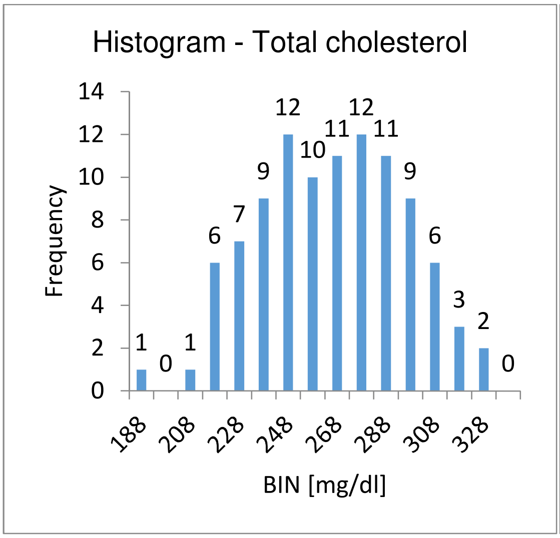


The weight of the babies ranged from 750g to 3600g, with the majority being around 3000g.









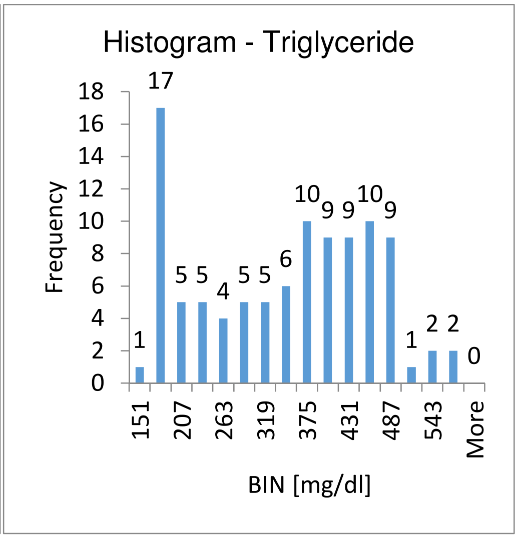


Figure 5: *The histograms for the total cholesterol [mg/dl] and the triglyceride [mg/dl] variables*

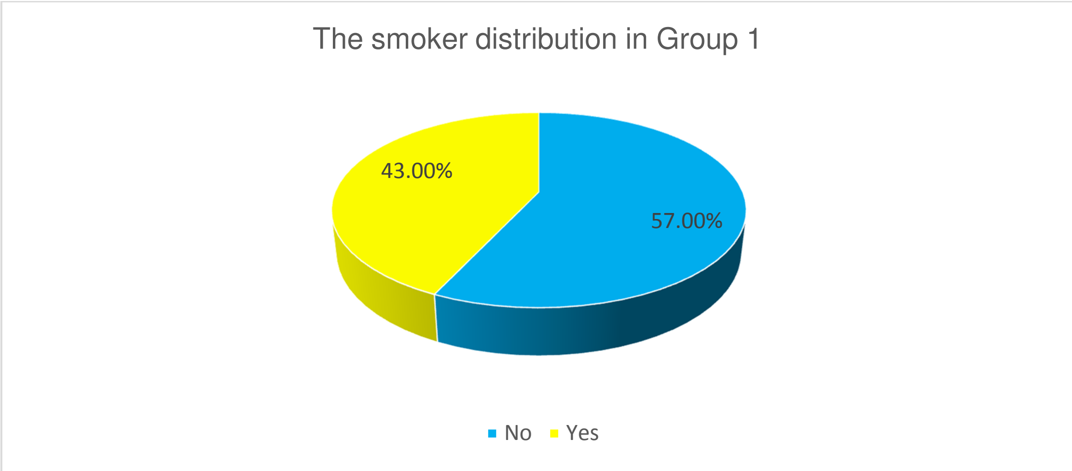


Figure 6: *The distribution of smokers in Group1*

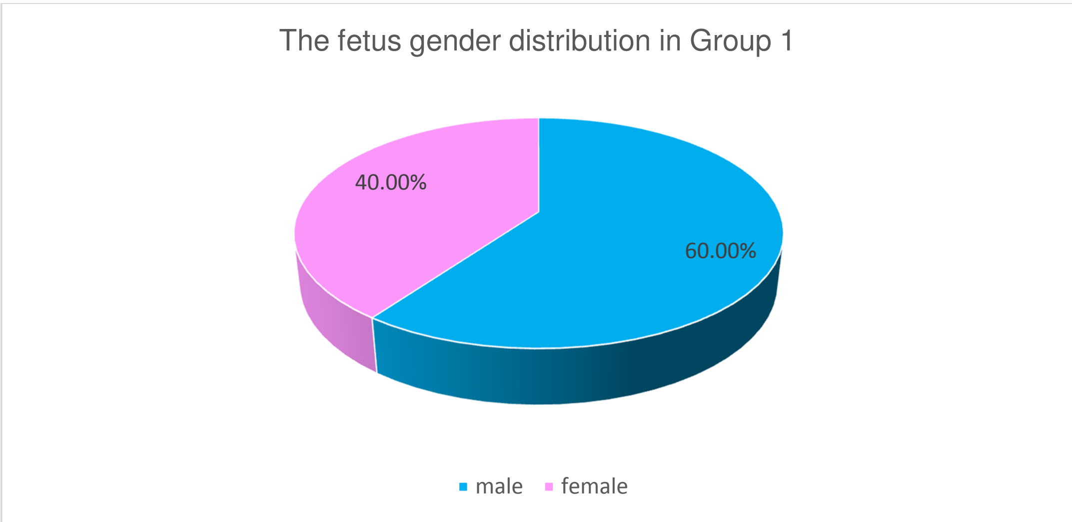


Figure 7: *The distribution of the foetus gender in Group1*

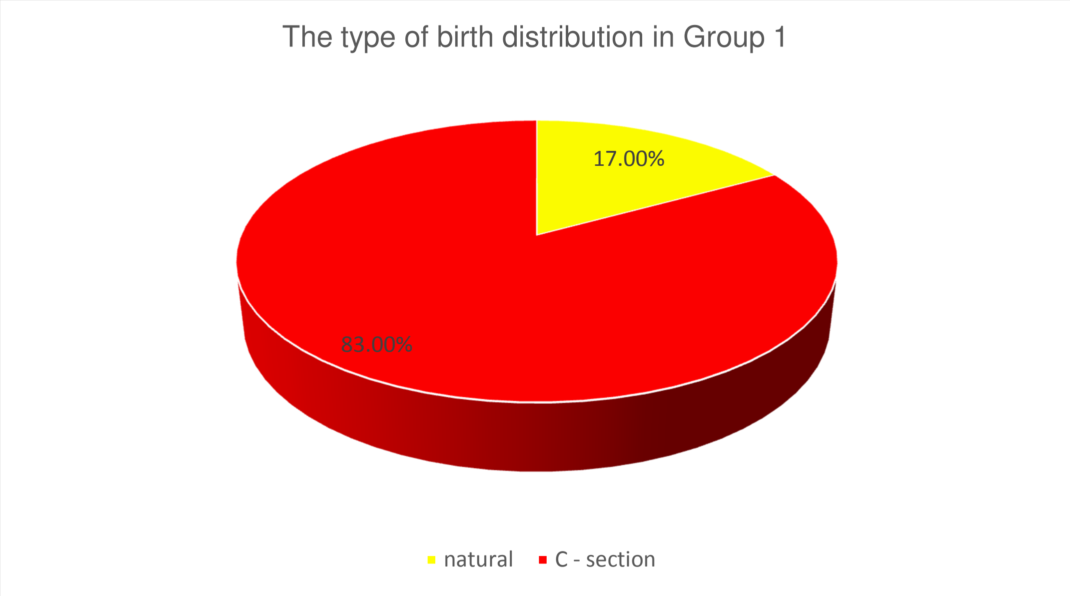


Figure 8: *The distribution of the birth type in Group1*

Group 2

Table 14: *The central tendency and dispersion parameters for the age [years], height [cm], weight [kg] and body mass index [Kg/m^2] (BMI) variables*

Statistics	Age	Height [cm]	Weight [kg]	BMI [Kg/m^2]
Mean	36.86	166.90	63.15	22.61
Standard Error	0.41	0.44	0.92	0.27
Median	38.00	168.00	67.00	24.45
Mode	38.00	169.00	69.00	24.45
Standard Deviation	4.10	4.40	9.21	2.75
Sample Variance	16.81	19.34	84.78	7.54
Range	25.00	23.00	31.00	7.75
Minimum	20.00	153.00	47.00	18.51
Maximum	45.00	176.00	78.00	26.26
Count	100.00	100.00	100.00	100.00

Table 15: *The central tendency and dispersion parameters for the augmentation index of branchial artery corrected to 75% [%] (Aix brachial) (in the second trimester (TrimII) and in the third trimester (Trim III) of pregnancy), pulse wave velocity [m/s] (PWVao) (in the second trimester (TrimII) and in the third trimester (Trim III) of pregnancy, systolic blood pressure [mmHg](Sys), diastolic blood pressure [mmHg](Dia), pulse pressure [mmHg] (PP), central systolic blood pressure [mmHg] (SBPao), heart rate [1\min] (HR) values*

Statistics	Aix brachial : [%] Trim II	PWVao [m/s] Trim II	Aix brachial : [%] Trim III	PWVao [m/s] Trim III	Sys [mmHg]	Dia [mmHg]	PP [mmHg]	SBPao [mmHg]	HR [1/min]
Mean	-18.99	8.21	-13.52	8.72	128.79	77.49	42.41	93.21	65.34
Standard Error	0.86	0.10	0.55	0.08	1.71	1.35	0.43	0.52	0.73
Median	-20.15	8.20	-15.52	8.73	135.00	75.00	43.00	96.00	66.00
Mode	-23.20	9.70	-14.91	9.80	145.00	100.00	43.00	96.00	73.00
Standard Deviation	8.63	0.99	5.49	0.75	17.05	13.54	4.27	5.24	7.30
Sample Variance	74.51	0.98	30.19	0.57	290.85	183.46	18.24	27.50	53.28
Range	33.60	3.70	21.60	3.61	54.00	50.00	16.00	19.00	29.00
Minimum	-36.40	6.20	-22.11	6.39	94.00	60.00	34.00	83.00	46.00
Maximum	-2.80	9.90	-0.51	10.00	148.00	110.00	50.00	102.00	75.00
Count	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

Table 16: *The central tendency and dispersion parameters for the gestational period [weeks], APGAR score, foetus weight [grams] values*

Statistics	Gestational Period [weeks]	APGAR score [1 min]	Foetus Weight [Grams]
Mean	38.91	9.14	3571.30
Standard Error	0.09	0.09	45.13
Median	39.00	9.00	3550.00
Mode	39.00	10.00	3550.00
Standard Deviation	0.90	0.85	451.35
Sample Variance	0.81	0.73	203712.43
Range	4.00	3.00	1030.00
Minimum	38.00	7.00	3200.00
Maximum	42.00	10.00	4230.00
Count	100.00	100.00	100.00

Table 17: *We present the frequency table for the smoker – non-smoker variable*

Smoker	Absolute Frequency	Relative Frequency (%)	Cumulate frequency (%)
No	60	60.00%	60.00%
Yes	40	40.00%	100.00%
Total	100	100.00%	

***Table 18**: We present the frequency table for the foetus gender*

Foetus gender	Absolute Frequency	Relative Frequency (%)	Cumulate frequency (%)
boy	55	55.00%	55.00%
girl	45	45.00%	100.00%
Total	100	100.00%	

***Table 19:** The frequency table for the type of birth*

Type of birth	Absolute Frequency	Relative Frequency (%)	Cumulate frequency (%)
natural	69	69.00%	69.00%
C - Section	31	31.00%	100.00%
Total	100	100.00%	

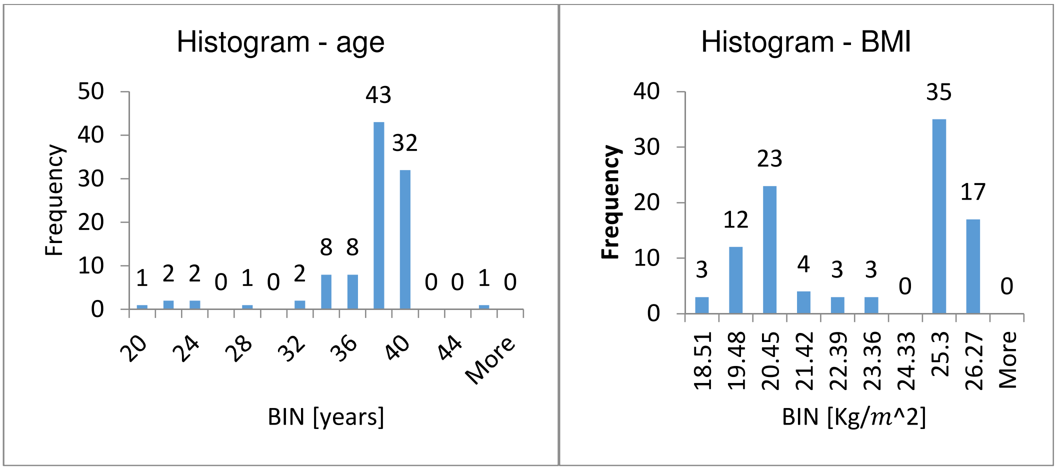


***Figure 9**: The histograms for the age [years], and body mass index [Kg/m^2] (BMI) variables*

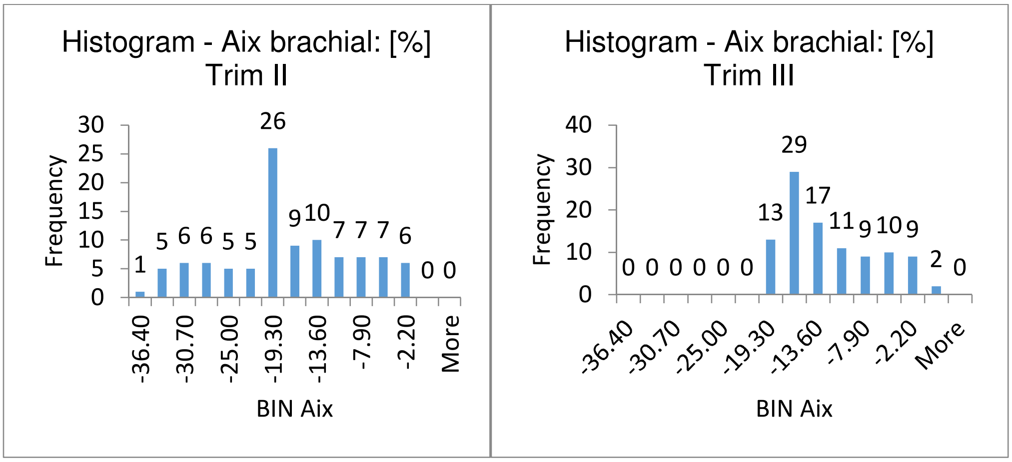


Figure 10: *The histograms for the augmentation index of branchial artery corrected to 75% [%] (Aix brachial) (in the second trimester (Trim II) and in the third trimester (Trim III) of pregnancy), pulse wave velocity [m/s] (PWVao) (in the second trimester (Trim II) and in the third trimester (Trim III) of pregnancy*

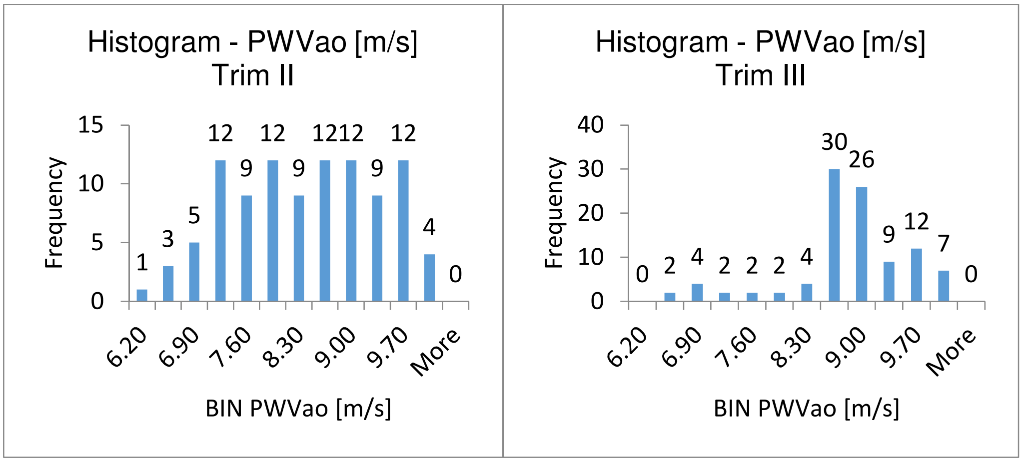
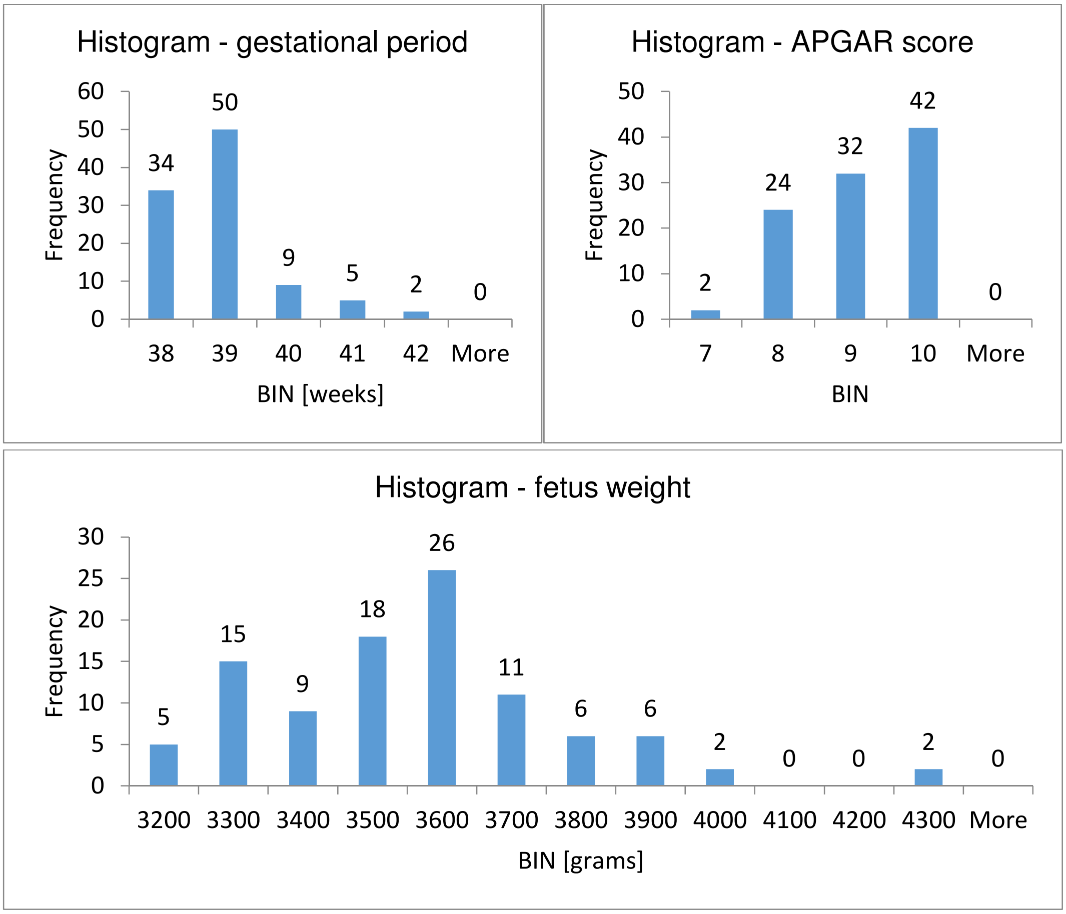


Figure 11: *The histograms for gestational period [weeks], APGAR score and foetus weight [grams] variables*



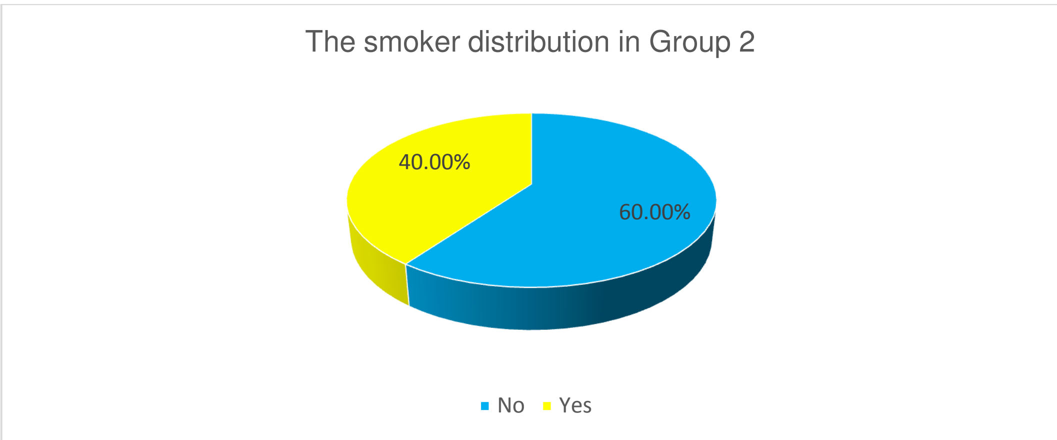


Figure 12: *The distribution of smokers in Group 2*

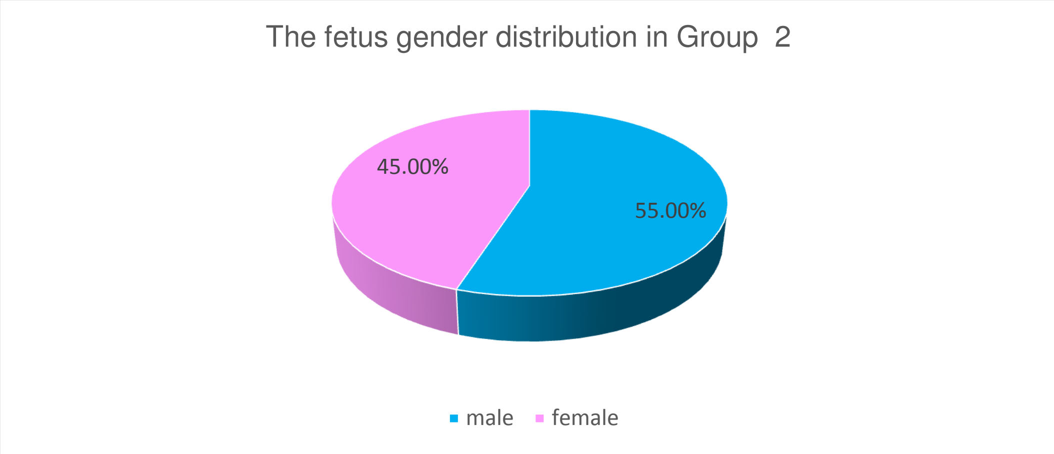


Figure 13: *The distribution of the foetus gender in Group 2*

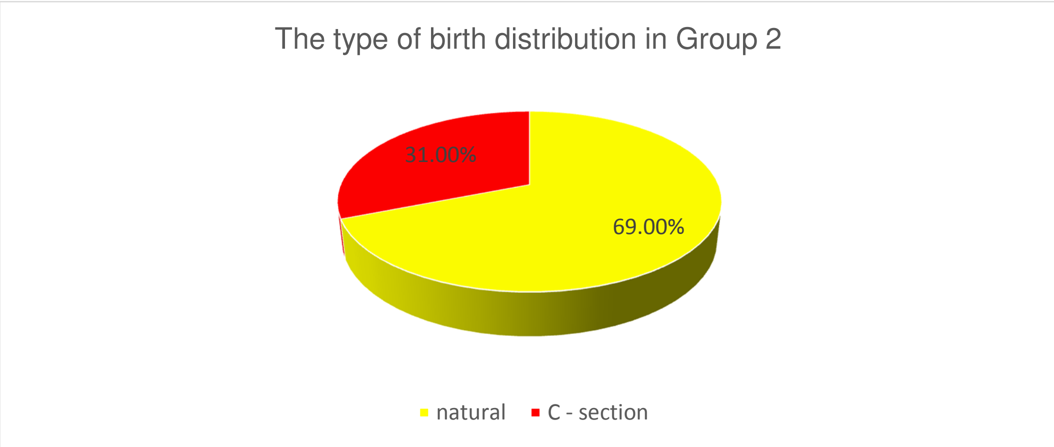


Figure 14: *The distribution of the birth type in Group 2*

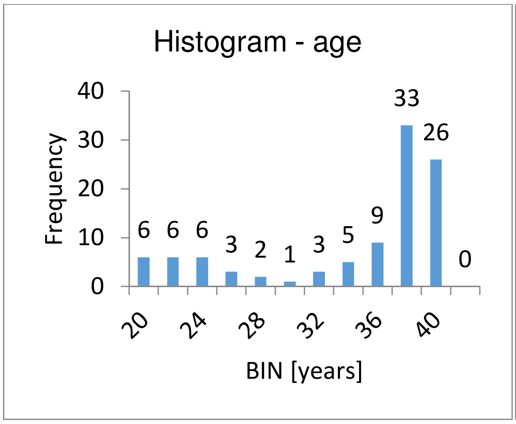
Group 3

Table 19: *The central tendency and dispersion parameters for the age [years], height [cm], weight [kg] and body mass index [Kg/m^2] (BMI) variables*

Statistics	Age	Height [cm]	Weight [kg]	BMI [Kg/m^2]
Mean	34.03	163.88	57.04	21.24
Standard Error	0.67	0.58	1.15	0.42
Median	38.00	164.00	56.00	20.69
Mode	38.00	169.00	57.00	18.59
Standard Deviation	6.70	5.77	11.51	4.21
Sample Variance	44.94	33.30	132.42	17.71
Range	20.00	27.00	63.00	26.92
Minimum	20.00	151.00	38.00	13.54
Maximum	40.00	178.00	101.00	40.46
Count	100.00	100.00	100.00	100.00

Table 20: The central tendency and dispersion parameters for the augmentation index of branchial artery corrected to 75% [%] (Aix brachial), pulse wave velocity [m/s] (PWVao), systolic blood pressure [mmHg](Sys), diastolic blood pressure [mmHg](Dia), pulse pressure [mmHg] (PP), central systolic blood pressure [mmHg] (SBPao), heart rate [1\min] (HR) values

Statistics	Aix brachial: [%]	PWVao [m/s]	Sys [mmHg]	Dia [mmHg]	PP [mmHg]	SBPao [mmHg]	HR [1/min]
Mean	-48.24	6.55	114.02	68.06	45.96	103.50	69.59
Standard Error	1.39	0.09	1.07	0.82	0.59	1.05	1.03
Median	-50.75	6.50	113.50	68.00	45.00	103.00	70.00
Mode	-56.80	6.50	119.00	76.00	42.00	109.00	75.00
Standard Deviation	13.87	0.88	10.69	8.22	5.88	10.52	10.27
Sample Variance	192.37	0.77	114.22	67.61	34.58	110.76	105.56
Range	78.00	4.30	48.00	38.00	30.00	47.00	59.00
Minimum	-80.20	5.10	94.00	52.00	33.00	83.00	46.00
Maximum	-2.20	9.40	142.00	90.00	63.00	130.00	105.00
Count	100.00	100.00	100.00	100.00	100.00	100.00	100.00



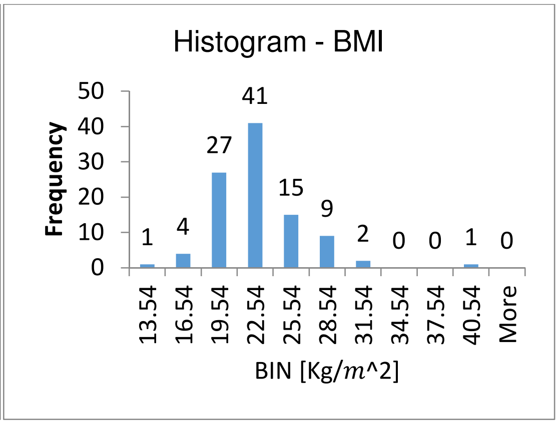
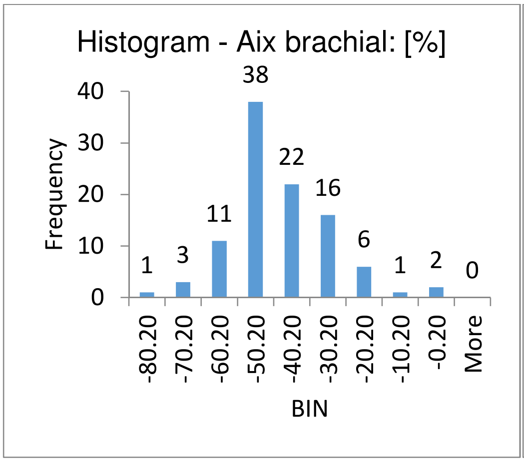


***Figure 15**: The histograms for the age [years], and body mass index [Kg/m^2] (BMI) variables*



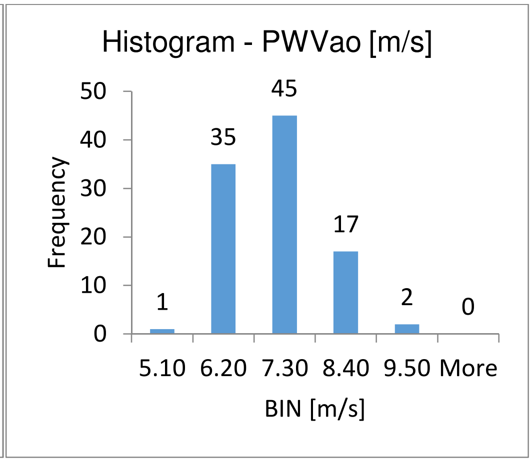


Figure 16: *The histograms for the augmentation index of branchial artery corrected to 75% [%] (Aix brachial), pulse wave velocity [m/s] (PWVao)*

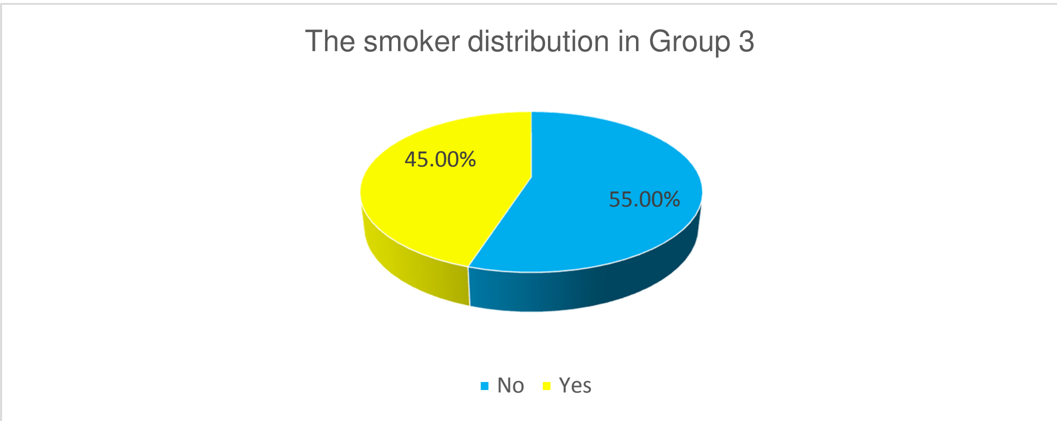


Figure 17*: The distribution of smokers in Group 3*

The data collected from the patients admitted to our clinic between the period of 2011 – 2018 (No=18344) revealed that premature babies born from mothers with hypertension or preeclampsia (No1=1247) are one of the most important aspects of this study.

Table 21: *Information regarding the year of admission in our clinic of the patients who give birth before the term (from mothers with hypertension or from preeclampsia pregnancies) compared to the total number of birth which took place in our clinic between 2011 and 2018*

Admission Year	Premature birth (HTA+ preeclampsia)	Total premature birth	Total birth	% premature birth (HTA + preeclampsia)	% premature birth (HTA + preeclampsia) from the total birth
Year 2011	191	270	1994	70.74%	9.58%
Year 2012	223	307	2096	72.64%	10.64%
Year 2013	169	290	2184	58.28%	7.74%
Year 2014	194	269	2354	72.12%	8.24%
Year 2015	134	386	2517	34.72%	5.32%
Year 2016	113	416	2564	27.16%	4.41%
Year 2017	125	431	2608	29.00%	4.79%
Year 2018	128	485	2027	20.21%	4.83%
Total	1247	2854	18344	43.69%	6.80%

Our research analysis was structured into four major steps to ensure a systematic and robust evaluation of the data.

1. **Testing Data Normality:**

The first step involved assessing the normality of the dataset. This analysis was crucial in determining whether to use parametric or non-parametric tests in subsequent analyses. By applying the appropriate normality tests, we identified the most suitable statistical methods for characterizing our database.

2. **Statistical Testing:**

Based on the results of the normality tests, we applied statistical methods to evaluate whether the differences observed in the descriptive analysis were significant for the entire population or specific to the sample studied. The confidence level for the entire analysis was set at $\alpha = 0.05$, ensuring rigorous interpretation of the findings.

3. **Correlation and Regression Analysis:**

To explore relationships between variables, we conducted correlation and regression analyses. These methods allowed us to identify and quantify significant associations among the studied variables, offering insights into potential interdependencies.

4. **Risk Analysis:**

In the final phase, we performed a risk analysis to evaluate whether certain habits or medical test results could be considered risk factors for premature birth. This step provided critical information on modifiable and non-modifiable factors that could influence pregnancy outcomes.

Through this structured approach, we aimed to derive meaningful conclusions and identify actionable insights to address key health challenges in pregnancy.

Normality Tests

To evaluate the distribution of data, we applied the Kolmogorov-Smirnov test to all three sample groups, as each group included more than 50 subjects. This test was used to determine whether the data followed a normal distribution. In the majority of cases, the p-values obtained were less than 0.05, indicating that the data did not exhibit a normal distribution. As a result, non-parametric tests were selected for subsequent analyses.

The detailed results of the normality tests are presented in Tables 22, 23, and 24.

This approach ensured the appropriate selection of statistical methods, enhancing the accuracy and reliability of the study's findings.

Table 22: *Kolmogorov-Smirnov test results for Sample 1 (100 pregnant patients who developed hypertension or preeclampsia during pregnancy). Significant results are highlighted in blue. Given that $p < 0.05$ in most cases, we concluded that the data for this group were not normally distributed.*

Statistical test →	**Kolmogorov-Smirnov**			**Shapiro-Wilk**		
Variables ↓	Statistic	df	Sig.	Statistic	df	Sig.
Age	.266	100	.000	.746	100	.000
Height [cm]	.107	100	.006	.960	100	.004
Weight [kg]	.099	100	.017	.963	100	.007
BMI (Kg/m^2)	.178	100	.000	.900	100	.000
Aix brachial: [%] TrimII	.118	100	.002	.933	100	.000
PWVao [m/s] Trim II	.097	100	.021	.938	100	.000
Aix brachial: [%] Trim III	.246	100	.000	.660	100	.000
PWVao [m/s] Trim III	.142	100	.000	.923	100	.000
Sys [mmHg]	.229	100	.000	.862	100	.000
Dia [mmHg]	.175	100	.000	.901	100	.000
PP [mmHg]	.140	100	.000	.902	100	.000
SBPao [mmHg]	.209	100	.000	.854	100	.000
HR [1/min]	.138	100	.000	.926	100	.000
Gestational Period [weeks]	.244	100	.000	.826	100	.000
APGAR score [1 min]	.232	100	.000	.862	100	.000
Fetus Weight [Grams]	.127	100	.000	.908	100	.000
IL6 [pg/mL^4]	.228	100	.000	.801	100	.000
Proteinuria [mg/24h]	.143	100	.000	.929	100	.000
PIGF	.154	100	.000	.852	100	.000
sFlt-1	.103	100	.011	.968	100	.016
Report	.233	100	.000	.833	100	.000
Total cholesterol [mg/dl]	.050	100	.200	.989	100	.613
HDL cholesterol [mg/dl]	.167	100	.000	.876	100	.000
LDL cholesterol [mg/dl]	.104	100	.010	.927	100	.000
Triglyceride [mg/dl]	.096	100	.024	.939	100	.000

Table 23: *Results of the Kolmogorov-Smirnov normality test for Group 2, comprising 100 healthy pregnant patients. Significant results are highlighted in blue. As the majority of p-values are less than 0.05, it is assumed that the data for this group do not follow a normal distribution, necessitating the use of non-parametric tests for further analysis.*

Statistical test →	Kolmogorov-Smirnov			Shapiro-Wilk		
Variables ↓	Statistic	Df	Sig.	Statistic	df	Sig.
Age	.300	100	.000	.673	100	.000
Height [cm]	.155	100	.000	.905	100	.000
Weight [kg]	.182	100	.000	.917	100	.000
BMI (Kg/m2)	.269	100	.000	.843	100	.000
Aix brachial: [%] TrimII	.085	100	.072	.973	100	.038
PWVao [m/s] Trim II	.069	100	.200*	.966	100	.012
Aix brachial: [%] Trim III	.161	100	.000	.926	100	.000
PWVao [m/s] Trim III	.152	100	.000	.942	100	.000
Sys [mmHg]	.228	100	.000	.868	100	.000
Dia [mmHg]	.138	100	.000	.909	100	.000
PP [mmHg]	.104	100	.010	.967	100	.013
SBPao [mmHg]	.213	100	.000	.929	100	.000
HR [1/min]	.141	100	.000	.935	100	.000
Gestational Period [weeks]	.300	100	.000	.784	100	.000
APGAR score [1 min]	.263	100	.000	.811	100	.000
Fetus Weight [Grams]	.179	100	.000	.949	100	.001

Table 24: *Results of the Kolmogorov-Smirnov normality test for Group 3, consisting of 100 healthy non-pregnant patients. Significant results are highlighted in blue. As the majority of p-values are greater than 0.05, we assume that the data for this group follow a normal distribution, allowing for the use of parametric tests in subsequent analyses.*

Statistical test →	Kolmogorov-Smirnov			Shapiro-Wilk		
Variables ↓	Statistic	df	Sig.	Statistic	df	Sig.
Age	.286	100	.000	.751	100	.000
Height [cm]	.058	100	.200	.992	100	.846
Weight [kg]	.121	100	.001	.893	100	.000
BMI (Kg/m2)	.139	100	.000	.845	100	.000
Aix brachial: [%] Trim II	.093	100	.031	.979	100	.114
PWVao [m/s] Trim II	.076	100	.168	.967	100	.013
Sys [mmHg]	.051	100	.200	.983	100	.234
Dia [mmHg]	.065	100	.200	.986	100	.360
PP [mmHg]	.085	100	.073	.974	100	.046
SBPao [mmHg]	.041	100	.200	.985	100	.293
HR [1/min]	.088	100	.052	.976	100	.065

In the subsequent part of the study, the most appropriate statistical tests were applied to derive the necessary conclusions. These analyses provided the statistical evidence required to support and articulate accurate and reliable medical insights.

To evaluate whether the differences observed in the augmentation index of the brachial artery (Aix brachial) between the second trimester (Trim II) and the third trimester (Trim III) of pregnancy were statistically significant, the Wilcoxon Signed Ranks test was applied. The analysis yielded a p-value of <0.001, indicating extremely significant differences between the two trimesters.

Using the same hypothesis, the Wilcoxon Signed Ranks test was also applied to assess the differences in pulse wave velocity (PWVao) values between Trim II and Trim III. This test similarly revealed extremely significant differences, with a p-value of <0.001. Additionally, it was noted that PWVao values were substantially higher in the third trimester compared to the second trimester.

All results from these analyses are summarized in Table 25, further highlighting the significant changes in vascular parameters across trimesters in this group.

Table 25*: Results of the Wilcoxon Signed Ranks test. The analysis revealed extremely significant differences (p<0.001p < 0.001) between the two time points, confirming substantial changes over the observed period.*

Statistics	Aix brachial: [%] Trim II	Aix brachial: [%] Trim III	PWVao [m/s] Trim II	PWVao [m/s] Trim III
Mean	1.25	3.68	10.9161	12.3659
Variance	0.73	1.84	1.858769485	2.819517
Observations	100	100	100	100
p – value	$p < 0.001$		$p < 0.001$	

A significant proportion of patients in this sample (76%) developed preeclampsia during pregnancy. Building on this observation, we sought to determine whether differences existed across various parameters, including age, height, weight, body mass index (BMI), and vascular metrics such as the augmentation index of the brachial artery corrected to 75% (Aix brachial) and pulse wave velocity (PWVao), both measured in the second (Trim II) and third trimesters (Trim III). Additional parameters analyzed included systolic blood pressure (Sys), diastolic blood pressure (Dia), pulse pressure (PP), central systolic blood pressure (SBPao), and heart rate (HR).

We also considered lifestyle factors such as smoking status, as well as pregnancy and neonatal outcomes, including gestational period, APGAR score, fetal gender, fetal weight, and mode of delivery (natural or C-section). Biochemical markers, such as interleukin 6 (IL6), proteinuria, placental growth factor (PIGF), soluble fms-like tyrosine kinase-1 (sFlt-1), the sFlt-1/PIGF ratio, total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride levels, were also evaluated.

To analyze these differences, we applied the Mann-Whitney test with a confidence level of $\alpha = 0.05$. The results of this analysis are presented in Table 26.

The analysis revealed the following key findings:

- **Significant differences ($p<0.05p < 0.05$)** were observed in the Aix brachial values during Trim III, gestational period, and PIGF levels between patients with and without preeclampsia.
- **Very significant differences ($p<0.01p < 0.01$)** were noted in height and diastolic blood pressure.
- **Extremely significant differences ($p<0.001p < 0.001$)** were identified for BMI, Aix brachial values in Trim II, PWVao values in Trim II and Trim III, systolic blood pressure, pulse pressure (PP), central systolic blood pressure (SBPao), heart rate (HR), total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride levels between the two groups.

These results underscore substantial physiological and biochemical variations within the group, highlighting critical factors associated with preeclampsia.

Table 26: *Results of the Mann-Whitney test applied to Group 1, comprising 100 pregnant patients who developed hypertension or preeclampsia during pregnancy. Significant results are highlighted in blue.*

Statistics → Variables↓	**Preeclampsia**	**Volume**	**Mean Rank**	**Sum of Ranks**	**p - value**
Age	absent present Total	24 76 100	52.25 49.95	1254.00 3796.00	$p = 0.73$
Height [cm]	absent present Total	24 76 100	67.52 45.13	1620.50 3429.50	$p = 0.001$
Weight [kg]	absent present Total	24 76 100	54.85 49.13	1316.50 3733.50	$p = 0.39$
BMI (Kg/m^2)	absent present Total	24 76 100	30.79 56.72	739.00 4311.00	$p < 0.001$
Aix brachial: [%] Trim II	absent present Total	24 76 100	30.17 56.92	724.00 4326.00	$p < 0.001$
PWVao [m/s] Trim II	absent present Total	24 76 100	30.19 56.91	724.50 4325.50	$p < 0.001$
Aix brachial: [%] Trim III	absent present Total	24 76 100	55.67 48.87	1336.00 3714.00	$p = 0.04$
PWVao [m/s] Trim III	absent present Total	24 76 100	30.17 56.92	724.00 4326.00	$p < 0.001$
Sys [mmHg]	absent present Total	24 76 100	32.50 56.18	780.00 4270.00	$p < 0.001$
Dia [mmHg]	absent present Total	24 76 100	34.73 55.48	833.50 4216.50	$p = 0.002$
PP [mmHg]	absent present Total	24 76 100	30.79 56.72	739.00 4311.00	$p < 0.001$
SBPao [mmHg]	absent present Total	24 76 100	31.04 56.64	745.00 4305.00	$p < 0.001$
HR [1/min]	absent present Total	24 76 100	30.96 56.67	743.00 4307.00	$p < 0.001$
Gestational Period [weeks]	absent present Total	24 76 100	56.90 48.48	1365.50 3684.50	$p = 0.04$
APGAR score [1 min]	absent present Total	24 76 100	48.50 51.13	1164.00 3886.00	$p = 0.69$
Fetus Weight [Grams]	absent	24	53.40	1281.50	

	present	76	49.59	3768.50	$p = 0.58$
	Total	100			
	absent	24	43.83	1052.00	
IL6 [pg/mL4]	present	76	52.61	3998.00	$p = 0.19$
	Total	100			
	absent	24	49.69	1192.50	
Proteinuria [mg/24h]	present	76	50.76	3857.50	$p = 0.87$
	Total	100			
	absent	24	60.13	1443.00	
PIGF	present	76	47.46	3607.00	$p = 0.04$
	Total	100			
	absent	24	55.48	1331.50	
sFlt-1	present	76	48.93	3718.50	$p = 0.34$
	Total	100			
	absent	24	45.60	1094.50	
Report	present	76	52.05	3955.50	$p = 0.34$
	Total	100			
	absent	24	30.21	725.00	
Total cholesterol [mg/dl]	present	76	56.91	4325.00	$p < 0.001$
	Total	100			
	absent	24	71.38	1713.00	
HDL cholesterol [mg/dl]	present	76	43.91	3337.00	$p < 0.001$
	Total	100			
	absent	24	30.15	723.50	
LDL cholesterol [mg/dl]	present	76	56.93	4326.50	$p < 0.001$
	Total	100			
	absent	24	30.17	724.00	
Triglyceride [mg/dl]	present	76	56.92	4326.00	$p < 0.001$
	Total	100			

- **Analysis of Smoking Influence**

To determine whether smoking habits affected the variables tested in this study, we applied the Mann-Whitney test. The analysis revealed no significant differences, as all p-values were greater than 0.05. Based on these results, we can conclude that smoking did not influence the medical parameters analyzed in this study.

Group 2 Analysis

To evaluate whether the conclusions from Group 1 applied to healthy pregnant women in Group 2, the Wilcoxon Signed Ranks test was employed. The analysis showed that, while the differences were less pronounced compared to Group 1, they remained extremely significant, with p<0.001p < 0.001 in both cases.

Specifically, both the augmentation index of the brachial artery (Aix brachial) and pulse wave velocity (PWVao) values increased significantly from Trim II to Trim III.

The detailed results of this analysis are presented in Table 27, confirming significant changes in vascular parameters even among healthy pregnant subjects.

Table 27*: Results of the Wilcoxon Signed Ranks test applied to the Aix brachial and PWVao values in Group 2. The analysis revealed extremely significant differences (p<0.001p < 0.001) between the two time points, highlighting substantial changes in these parameters from Trim II to Trim III.*

Statistics	Aix brachial: [%] Trim II	Aix brachial: [%] Trim III	PWVao [m/s] Trim II	PWVao [m/s] Trim III
Mean	-18.99	-13.52	8.2	8.72
Variance	74.51	30.19	0.98	0.56
Observations	100	100	100	100
p – value	$p < 0.001$		$p < 0.001$	

Analysis of Smoking Influence in Group 2

To evaluate whether smoking habits affected the variables in Group 2, we applied the Mann-Whitney test. The results indicated no significant differences, as all p-values were greater than 0.05. This finding confirms that the conclusions drawn from Group 1 also apply to Group 2, with smoking showing no measurable influence on the tested variables.

Comparison between Group 1 and Group 2

In this phase of the study, we examined differences between the variables in Group 1 (pregnant patients with pathology) and Group 2 (healthy pregnant patients). The analysis compared the mean values of all studied variables between the two groups. Using the Mann-Whitney test, we found extremely significant differences (p<0.001p < 0.001) for nearly all variables, with the exceptions of age and height, which showed no significant differences.

The detailed results of this comparative analysis are presented in Table 6.7, highlighting the substantial physiological and clinical differences between these two groups of pregnant patients.

Table 28: *Results of the Mann-Whitney test comparing Group 1 (pregnant patients with pathology) and Group 2 (healthy pregnant patients). Significant results are highlighted in blue. The analysis revealed extremely significant differences (p<0.001p < 0.001) across all tested variables, except for age and height, where the p-values exceeded 0.05, indicating no significant differences.*

Statistics → Variables↓	Sample	Volume	Mean Rank	Sum of Ranks	p - value
Age	1 2 Total	100 100 200	103.96 97.04	10396.00 9704.00	$p = 0.39$
Height [cm]	1 2 Total	100 100 200	98.86 102.14	9886.00 10214.00	$p = 0.69$
Weight [kg]	1 2 Total	100 100 200	146.58 54.43	14657.50 5442.50	$p < 0.001$
BMI (Kg/m^2)	1 2 Total	100 100 200	150.49 50.51	15049.00 5051.00	$p < 0.001$
Aix brachial: [%] TrimII	1 2 Total	100 100 200	150.50 50.50	15050.00 5050.00	$p < 0.001$
PWVao [m/s] Trim II	1 2 Total	100 100 200	145.39 55.62	14538.50 5561.50	$p < 0.001$
Aix brachial: [%] Trim III	1 2 Total	100 100 200	150.50 50.50	15050.00 5050.00	$p < 0.001$
PWVao [m/s] Trim III	1 2 Total	100 100 200	150.10 50.91	15009.50 5090.50	$p < 0.001$
Sys [mmHg]	1 2 Total	100 100 200	150.50 50.50	15050.00 5050.00	$p < 0.001$
Dia [mmHg]	1 2 Total	100 100 200	150.35 50.65	15035.00 5065.00	$p < 0.001$
PP [mmHg]	1 2 Total	100 100 200	150.25 50.75	15025.00 5075.00	$p < 0.001$
SBPao [mmHg]	1 2 Total	100 100 200	150.44 50.56	15044.00 5056.00	$p < 0.001$
HR [1/min]	1 2 Total	100 100 200	150.50 50.50	15050.00 5050.00	$p < 0.001$
Gestational Period [weeks]	1 2 Total	100 100 200	50.50 150.50	5050.00 15050.00	$p < 0.001$
APGAR score [1 min]	1 2 Total	100 100 200	77.13 123.87	7713.00 12387.00	$p < 0.001$
Fetus Weight [Grams]	1 2 Total	100 100 200	58.73 142.28	5872.50 14227.50	$p < 0.001$

- **Impact of Hypertension and Preeclampsia During Pregnancy**

The presence of hypertension or preeclampsia during pregnancy induces significant changes in various medical parameters. Among the most critical consequences is the increased risk of premature birth, which can lead to numerous complications for both the mother and, more significantly, the fetus.

Comparison between Group 1 and Group 3

In this part of the study, we examined differences between Group 1 (pregnant patients with hypertension or preeclampsia) and Group 3 (non-pregnant healthy women, serving as the control group). The analysis focused on common numerical variables shared between the two groups.

Using the Mann-Whitney test, we identified extremely significant differences ($p<0.001p < 0.001$) across nearly all tested variables. The only exception was the age variable, where no significant differences were observed.

The detailed results of this comparison are presented in Table 6.8, highlighting the substantial physiological distinctions between pregnant patients with pathology and healthy non-pregnant controls.

- **Extremely significant differences ($p<0.001p < 0.001$)** in all tested variables except height and age.
- **Very significant differences ($p<0.01p < 0.01$)** were observed for height.
- **No significant differences** ($p>0.05p > 0.05$) were found for the age variable.

These findings underscore the marked physiological differences between the two groups, with the exception of age, where no variation was detected.

Table 29: *Results of the Mann-Whitney test comparing Group 1 (pregnant patients with hypertension or preeclampsia) and Group 3 (healthy non-pregnant controls). Significant results are highlighted in blue. The analysis revealed the following:*

Statistics → Variables↓	**Sample**	**Volume**	**Mean Rank**	**Sum of Ranks**	**p - value**
Age	1 3 Total	100 100 200	114.08 86.93	11407.50 8692.50	$p = 0.07$
Height [cm]	1 3 Total	100 100 200	111.24 89.76	11124.00 8976.00	$p = 0.009$
Weight [kg]	1 3 Total	100 100 200	147.69 53.31	14769.00 5331.00	$p < 0.001$
BMI (Kg/m^2)	1 3 Total	100 100 200	147.78 53.22	14778.00 5322.00	$p < 0.001$
Aix brachial: [%] TrimII	1 3 Total	100 100 200	150.50 50.50	15050.00 5050.00	$p < 0.001$
PWVao [m/s] Trim II	1 3 Total	100 100 200	150.29 50.71	15029.00 5071.00	$p < 0.001$
Sys [mmHg]	1 3 Total	100 100 200	150.50 50.50	15050.00 5050.00	$p < 0.001$
Dia [mmHg]	1 3 Total	100 100 200	150.50 50.50	15050.00 5050.00	$p < 0.001$
PP [mmHg]	1 3 Total	100 100 200	143.06 57.95	14305.50 5794.50	$p < 0.001$
SBPao [mmHg]	1 3 Total	100 100 200	135.81 65.19	13581.00 6519.00	$p < 0.001$
HR [1/min]	1 3 Total	100 100 200	144.47 56.53	14447.00 5653.00	$p < 0.001$

Comparison between Group 1, Group 2, and Group 3

To compare the common numerical variables across Group 1 (pregnant patients with hypertension or preeclampsia), Group 2 (healthy pregnant patients), and Group 3 (healthy non-pregnant controls), an ANOVA One-Way test was applied with a confidence level of α=0.05\alpha = 0.05.

The analysis revealed significant differences in all tested variables across the three groups, indicating notable variance in the measured parameters. The detailed results of this comparison are presented in Table 30.

Table 30: *Results of the ANOVA One-Way test applied to Group 1 (pregnant patients with hypertension or preeclampsia), Group 2 (healthy pregnant patients), and Group 3 (healthy non-pregnant controls). Significant results are highlighted in blue.*

Variables ↓	Statistics ↓→	Sum of Squares	df	Mean Square	F	p - value
Age	Between Groups	698.66	2	349.33	15.24	$p < 0.001$
	Within Groups	6807.59	297	22.92		
	Total	7506.25	299			
Height [cm]	Between Groups	570.42	2	285.21	7.47	$p < 0.001$
	Within Groups	11334.56	297	38.16		
	Total	11904.98	299			
Weight [kg]	Between Groups	40568.98	2	20284.49	210.57	$p < 0.001$
	Within Groups	28609.78	297	96.32		
	Total	69178.77	299			
BMI (Kg/m2)	Between Groups	4799.83	2	2399.91	220.80	$p < 0.001$
	Within Groups	3228.08	297	10.86		
	Total	8027.91	299			
Aix brachial: [%] TrimII	Between Groups	123794.87	2	61897.43	693.86	$p < 0.001$
	Within Groups	26494.37	297	89.20		
	Total	150289.24	299			
PWVao [m/s] Trim II	Between Groups	972.86	2	486.43	404.49	$p < 0.001$
	Within Groups	357.16	297	1.20		
	Total	1330.02	299			
Sys [mmHg]	Between Groups	388562.32	2	194281.16	696.04	$p < 0.001$
	Within Groups	82898.66	297	279.12		
	Total	471460.98	299			
Dia [mmHg]	Between Groups	161424.62	2	80712.31	603.94	$p < 0.001$
	Within Groups	39691.63	297	133.64		
	Total	201116.25	299			
PP [mmHg]	Between Groups	13575.74	2	6787.87	200.38	$p < 0.001$
	Within Groups	10060.59	297	33.87		
	Total	23636.33	299			
SBPao [mmHg]	Between Groups	66076.74	2	33038.37	137.72	$p < 0.001$
	Within Groups	71248.34	297	239.89		
	Total	137325.08	299			
HR [1/min]	Between Groups	33744.32	2	16872.16	201.52	$p < 0.001$
	Within Groups	24865.07	297	83.72		
	Total	58609.39	299			

The analysis revealed **extremely significant differences (p<0.001p < 0.001)** across all tested variables, except for the height variable, where **very significant differences (p<0.01p < 0.01)** were observed. These findings emphasize substantial variations among the groups, reflecting key physiological differences.

Table 31: *Correlation Model for the Tested Variables*

Variables↓	**Statistics↓**	**Sys [mmHg]**	**Dia [mmHg]**	**PP [mmHg]**	**SBPao [mmHg]**	**HR [1/min]**
Aix brachial: [%] TrimII	Pearson Correlation	.989**	.932**	.981**	.973**	.969**
	Sig. (2-tailed)	.000	.000	.000	.000	.000
	N	100	100	100	100	100
****. Correlation is significant at the 0.05 level (2-tailed).**						

Correlation and Regression Analysis

In this phase of the analysis, we explored potential connections between the variables in each sample. Specifically, we examined correlations and interdependencies, focusing on the relationship between the augmentation index of the brachial artery (Aix brachial) and pulse wave velocity (PWVao) values across different groups (Sample 1, Sample 2, and Sample 3).

The strength of these associations was assessed using the Pearson correlation coefficient (rr), with the determination coefficient (R2R^2) calculated for the sample and population. Correlation and regression models were applied with a confidence level of α=0.05\alpha = 0.05.

Group 1 Analysis

Group 1 consisted of 100 pregnant patients who developed hypertension or preeclampsia during pregnancy. In the previous chapter, we identified significant differences between several variables in this group. This section aims to determine whether these variables are interdependent and if meaningful associations exist.

In the first part of the analysis, we tested the relationship between Aix brachial values and several cardiovascular parameters, including blood pressure (systolic and diastolic), pulse pressure (PP), central systolic blood pressure (SBPao), and heart rate (HR). The results indicated a strong, significant positive correlation between Aix brachial and all the tested variables, with r>0.75r > 0.75 and p<0.001p

< 0.001. These findings suggest a robust association, reflecting interdependent changes in vascular and hemodynamic parameters.

The table summarizes the results of the correlation model, highlighting significant positive correlations ($r>0.75r > 0.75$, $p<0.001p < 0.001$) in blue. These results provide clear evidence of the strong interdependence among the analyzed variables, reinforcing the critical role of these parameters in understanding hypertension and preeclampsia during pregnancy.

Extended Correlation Analysis

We further investigated potential associations between Aix brachial values and several key variables, including the gestational period, APGAR score, and fetal weight. Additionally, we examined correlations between Aix brachial values and biochemical markers such as proteinuria, PIGF, sFlt-1, their ratio, and lipid profile parameters (cholesterol and triglycerides). For each hypothesis, the Pearson correlation coefficient (rr) was calculated, and a correlation model was applied. The detailed results are presented in Tables 32, 33, and 34.

This section highlights the nuanced relationships (or lack thereof) between Aix brachial values and other critical clinical and biochemical parameters, underscoring the complexity of interpreting vascular changes during pregnancy.

Table 32*: Correlation Model for Gestational Period, APGAR Score, and Fetal Weight*

Variables↓	Statistics↓	Gestational Period [weeks]	APGAR score [1 min]	Fetus Weight [Grams]
Aix brachial: [%] TrimII	Pearson Correlation	-.114	-.079	-.025
	Sig. (2-tailed)	.258	.433	.807
	N	100	100	100
*. Correlation is significant at the 0.05 level (2-tailed).				

The analysis revealed a negative, weak, and statistically insignificant association ($r\in[-0.3;0.3]r$ \in [-0.3; 0.3], $p>0.05p > 0.05$) between Aix brachial values and the gestational period, APGAR score, and fetal weight. These findings suggest no meaningful correlation between these variables and Aix brachial values in this sample. Significant results, if any, are highlighted in blue.

The analysis revealed a negative, weak, and statistically insignificant association (r∈[−0.3;0.3]r \in [-0.3; 0.3], p>0.05p > 0.05) between Aix brachial values and proteinuria as well as PIGF levels. Conversely, a positive, weak correlation (r∈[−0.3;0.3]r \in [-0.3; 0.3], p>0.05p > 0.05) was observed between Aix brachial values and both sFlt-1 levels and their ratio. These results suggest that while some patterns exist, no significant associations were identified between Aix brachial values and the tested biochemical markers in this analysis. Significant findings, if any, are highlighted in blue.

***Table 33**: Correlation Model for Biochemical Markers*

Variables↓	Statistics↓	IL6 [pg/mL^4]	Proteinuria [mg/24h]	PIGF	sFlt-1	Report
Aix brachial: [%] TrimII	Pearson Correlation	-.122	-.143	-.071	.016	.016
	Sig. (2-tailed)	.227	.157	.482	.877	.877
	N	100	100	100	100	100
*. Correlation is significant at the 0.05 level (2-tailed).						

The analysis demonstrated a significant strong positive correlation (r>0.75r > 0.75, p<0.001p < 0.001) between Aix brachial values and total cholesterol, LDL cholesterol, and triglyceride levels. Conversely, a strong significant negative correlation (r<−0.75r < -0.75, p<0.001p < 0.001) was observed between Aix brachial values and HDL cholesterol levels. These findings indicate a robust association between vascular stiffness (Aix brachial) and lipid profile parameters. Significant results are highlighted in blue.

***Table 34**: Correlation Model for Lipid Profile Parameters*

Variables↓	Statistics↓	Total cholesterol [mg/dl]	HDL cholesterol [mg/dl]	LDL cholesterol [mg/dl]	Triglyceride [mg/dl]
Aix brachial: [%] TrimII	Pearson Correlation	.972**	-.844**	.925**	.960**
	Sig. (2-tailed)	.000	.000	.000	.000
	N	100	100	100	100
**. Correlation is significant at the 0.05 level (2-tailed).					

Correlation Analysis of Aix Brachial and PWVao Values

The analysis revealed that Aix brachial values in Trim II were extremely significantly correlated with blood pressure (systolic and diastolic), pulse pressure (PP), central systolic blood pressure (SBPao), heart rate (HR), and lipid profile parameters, including cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. Most correlations were positive, indicating that as one variable increased, the other also increased. However, for HDL cholesterol, a negative correlation was observed, suggesting an inverse relationship. The same conclusions were found for Aix brachial values in Trim III.

We also evaluated the association between PWVao values and cardiovascular parameters, including blood pressure, PP, SBPao, and HR. The results demonstrated a strong, significant positive correlation (r>0.75r > 0.75, p<0.001p < 0.001) across all tested variables.

The table summarizes the results, showing a significant strong positive correlation (r>0.75r > 0.75, p<0.001p < 0.001) for all tested variables. Significant results are highlighted in blue. These findings underscore the critical relationships between vascular stiffness (Aix brachial and PWVao) and cardiovascular and lipid parameters, highlighting their interconnected roles in pregnancy-associated hypertension and preeclampsia.

***Table 35**: Correlation Model for Tested Variables*

Variables↓	**Statistics↓**	**Sys [mmHg]**	**Dia [mmHg]**	**PP [mmHg]**	**SBPao [mmHg]**	**HR [1/min]**
PWVao [m/s] Trim II	Pearson Correlation	.973**	.949**	.960**	.944**	.952**
	Sig. (2-tailed)	.000	.000	.000	.000	.000
	N	100	100	100	100	100
****. Correlation is significant at the 0.05 level (2-tailed).**						

Extended Correlation Analysis of PWVao Values

We further investigated potential associations involving PWVao values and several key parameters. These included the gestational period, APGAR score, and fetal weight, as well as biochemical markers such as proteinuria, PIGF, sFlt-1, their ratio, and lipid profile parameters (cholesterol and triglycerides).

For these hypotheses, the Pearson correlation coefficient (rr) was calculated, and a correlation model was applied to evaluate the strength and direction of the associations. The detailed results of this analysis are presented in Tables 36, 37, and 38.

The analysis revealed a negative, weak, and statistically insignificant association (r∈[−0.3;0.3]r \in [-0.3; 0.3], p>0.05p > 0.05) between PWVao values and the gestational period, APGAR score, and fetal weight. These findings suggest no meaningful correlation between these variables and PWVao values in this study.

Table 36*: Correlation Model for Tested Variables*

Variables↓	Statistics↓	Gestational Period [weeks]	APGAR score [1 min]	Foetus Weight [Grams]
PWVao [m/s] Trim II	Pearson Correlation	-.125	-.079	-.023
	Sig. (2-tailed)	.214	.436	.820
	N	100	100	100
*. Correlation is significant at the 0.05 level (2-tailed).				

The analysis showed a negative, weak, and statistically insignificant association (r∈[−0.3;0.3]r \in [-0.3; 0.3], p>0.05p > 0.05) between PWVao values and proteinuria, PIGF, and sFlt-1 levels. Additionally, a weak positive correlation (r∈[−0.3;0.3]r \in [-0.3; 0.3], p>0.05p > 0.05) was observed between PWVao values and the sFlt-1/PIGF ratio. These results indicate no significant relationships between these variables and PWVao values in this study.

Table 37*: Correlation Model for Tested Variables*

Variables↓	Statistics↓	IL6 [pg/mL^4]	Proteinuria [mg/24h]	PIGF	sFlt-1	Report
PWVao [m/s] Trim II	Pearson Correlation	-.103	-.153	-.086	-.010	.011
	Sig. (2-tailed)	.306	.127	.393	.923	.913
	N	100	100	100	100	100
*. Correlation is significant at the 0.05 level (2-tailed).						

The analysis revealed a significant strong positive correlation (r>0.75r > 0.75, p<0.001p < 0.001) between PWVao values and total cholesterol, LDL cholesterol, and triglyceride levels. Conversely, a significant strong negative correlation (r<−0.75r < -0.75, p<0.001p < 0.001) was observed between PWVao values and HDL cholesterol levels. These results highlight robust associations between PWVao values and lipid profile parameters. Significant findings are highlighted in blue.

Table 38: Correlation Model for Tested Variables

Variables↓	Statistics↓	Total cholesterol [mg/dl]	HDL cholesterol [mg/dl]	LDL cholesterol [mg/dl]	Triglyceride [mg/dl]
PWVao [m/s] Trim II	Pearson Correlation	.983**	-.871**	.962**	.988**
	Sig. (2-tailed)	.000	.000	.000	.000
	N	100	100	100	100
**. Correlation is significant at the 0.05 level (2-tailed).					

Correlation Analysis of PWVao and Blood Pressure Parameters

The analysis revealed that PWVao values in Trim II were extremely significantly correlated with blood pressure parameters (systolic and diastolic), pulse pressure (PP), central systolic blood pressure (SBPao), heart rate (HR), and lipid profile markers, including cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. The correlations were positive, except for HDL cholesterol, where a negative correlation was observed. A positive correlation indicates that as one variable increases, the other also increases, whereas a negative correlation suggests an inverse relationship between the variables. Similar results were obtained for PWVao values in Trim III.

Correlation between Blood Pressure and Biochemical Markers in Group 1

For Group 1, we further explored potential associations between blood pressure parameters and biochemical markers such as proteinuria, PIGF, sFlt-1, and the sFlt-1/PIGF ratio. The Pearson correlation coefficient (rr) was calculated, and a correlation model was applied to evaluate these relationships. The detailed results are presented in Table 39.

The analysis revealed a strong, positive, and extremely significant association (r>0.75r > 0.75, p<0.001p < 0.001) between systolic and diastolic blood pressure values. A weak, negative, but statistically significant correlation (r∈[−0.3;0.3]r \in [-0.3; 0.3], p<0.05p < 0.05) was observed between blood pressure values and proteinuria levels. For all other variables, the correlations were weak and statistically insignificant (r∈[−0.3;0.3]r \in [-0.3; 0.3], p>0.05p > 0.05), indicating that these relationships cannot be generalized to the entire population. Statistically significant results are highlighted in blue.

***Table 39**: Correlation between Blood Pressure and Biochemical Markers*

Variables↓	Statistics↓	Sys [mmHg]	Dia [mmHg]	Proteinury [mg/24h]	PIGF	sFlt-1	Report
Sys [mmHg]	Pearson Correlation	1	.933**	-.179	-.049	.045	.019
	Sig. (2-tailed)		.000	.045**	.630	.660	.848
	N	100	100	100	100	100	100
Dia [mmHg]	Pearson Correlation	.933**	1	-.172	-.056	.017	.028
	Sig. (2-tailed)	.000		.047**	.581	.867	.782
	N	100	100	100	100	100	100
**. Correlation is significant at the 0.05 level (2-tailed).							

Analysis of Association between Aix Brachial and PWVao Values in Sample 1

At the conclusion of the study, we tested whether there was a significant association between Aix brachial values and PWVao values in Trim II and Trim III for Sample 1. To evaluate this, the Pearson correlation coefficient (rr) was calculated, and a regression model was applied. Trim II values were used as predictors, while Trim III values were considered responses.

- **Aix Brachial Values:**
  A positive, weak correlation was observed between the Trim II and Trim III Aix brachial values (r=0.18r = 0.18, R2=0.03R^2 = 0.03, p=0.048<0.05p = 0.048 < 0.05).
- **PWVao Values:**
  A positive, strong, and extremely significant correlation was found between the Trim II and Trim III PWVao values (r=0.98r = 0.98, R2=0.97R^2 = 0.97, p<0.001p < 0.001).

Conclusion

From a statistical perspective, these findings have a clear medical explanation: the Aix brachial index demonstrates greater sensitivity compared to PWVao. This distinction highlights the nuanced behavior of these vascular markers in response to physiological changes during pregnancy.

The results of these analyses are illustrated in Figures 18 and 19, which visually depict the relationships between Trim II and Trim III values for both Aix brachial and PWVao.

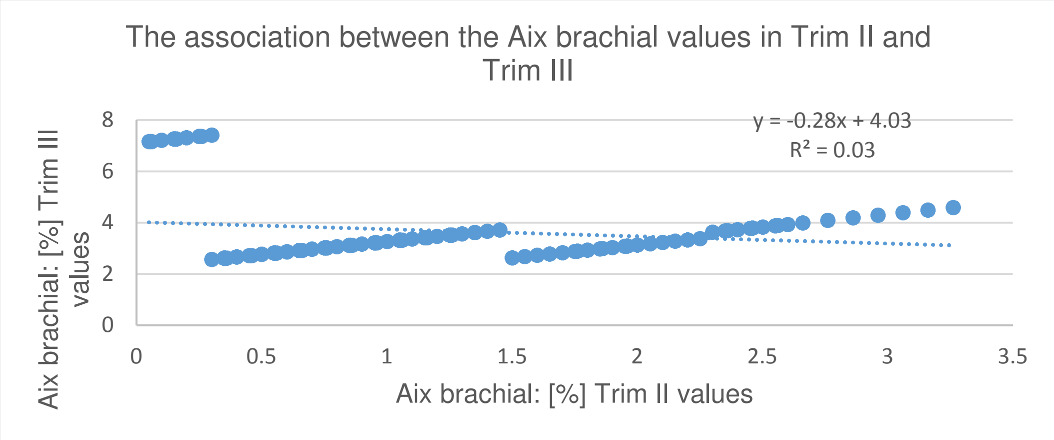


***Figure 18**: The association of Aix brachial values in Trim II and Trim III*

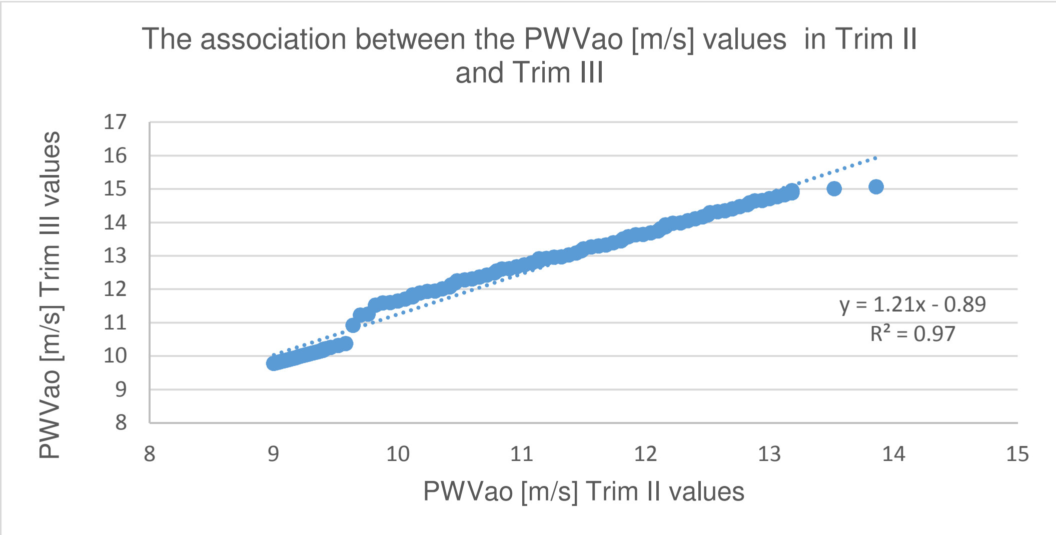


***Figure 19**: The association of PWVao values in Trim II and Trim III*

Group 2 Analysis

This part of the study included 100 healthy pregnant patients whose pregnancies progressed without complications. While the previous chapter highlighted significant differences between some variables, this section aims to determine whether associations exist among these variables.

To explore this hypothesis, we tested for associations between Aix brachial values and key cardiovascular parameters, including blood pressure (systolic and diastolic), pulse pressure (PP), central systolic blood pressure (SBPao), and heart rate (HR). The analysis revealed a strong, positive, and statistically significant correlation between Aix brachial values and all the tested variables (r>0.75r > 0.75, p<0.001p < 0.001).

The detailed results of this analysis are presented in Table 40, highlighting the robust relationships between Aix brachial values and cardiovascular parameters in healthy pregnant patients.

The analysis demonstrated a significant strong positive correlation (r>0.75r > 0.75, p<0.001p < 0.001) for all tested variables. These results indicate a robust association between the Aix brachial values and the analyzed cardiovascular parameters. Statistically significant findings are highlighted in blue.

Table 40*: Correlation Model for Tested Variables*

Variables↓	**Statistics↓**	**Sys [mmHg]**	**Dia [mmHg]**	**PP [mmHg]**	**SBPao [mmHg]**	**HR [1/min]**
Aix brachial: [%] TrimII	Pearson Correlation	.928**	.957**	.981**	.950**	.961**
	Sig. (2-tailed)	.000	.000	.000	.000	.000
	N	100	100	100	100	100
****. Correlation is significant at the 0.05 level (2-tailed).**						

Analysis of Aix Brachial Values and Pregnancy Outcomes

We further examined potential associations between Aix brachial values and key pregnancy outcomes, including gestational period, APGAR score, and fetal weight. The results of this analysis are summarized in Table 41.

The analysis revealed:

- A **positive, weak, but significant correlation** between Aix brachial values and the gestational period (r∈[−0.3;0.3]r \in [-0.3; 0.3], p=0.019<0.05p = 0.019 < 0.05).
- A **negative, weak, and statistically insignificant association** between Aix brachial values and the APGAR score and fetal weight (r∈[−0.3;0.3]r \in [-0.3; 0.3], p>0.05p > 0.05).

Statistically significant findings are highlighted in blue. These results suggest a limited but notable association between vascular stiffness and the gestational period, while no meaningful correlations were found for the other parameters.

***Table 41**: Correlation Model for Aix Brachial and Pregnancy Outcome Variables*

Variables↓	Statistics↓	Gestational Period [weeks]	APGAR score [1 min]	Fetus Weight [Grams]
Aix brachial: [%] TrimII	Pearson Correlation	.235	-.078	-.080
	Sig. (2-tailed)	.019	.440	.429
	N	100	100	100
*. Correlation is significant at the 0.05 level (2-tailed).				

Group 2 Correlation Analysis

For Group 2, the Aix brachial values in Trim II were found to be strongly and positively correlated with blood pressure parameters (systolic and diastolic), pulse pressure (PP), central systolic blood pressure (SBPao), and heart rate (HR), with results showing extreme statistical significance (r>0.75,p<0.001r > 0.75, p < 0.001). Additionally, a weak but significant positive correlation was observed between Aix brachial Trim II values and the gestational period (p<0.05p < 0.05). A positive correlation indicates that as one variable increases, the other also increases, while a negative correlation implies an inverse relationship between variables. The same conclusions were observed for Aix brachial values in Trim III.

Subsequently, the analysis tested associations between PWVao values and cardiovascular parameters, including blood pressure, PP, SBPao, and HR. Results revealed a strong, positive, and highly significant correlation (r>0.75,p<0.001r > 0.75, p < 0.001) across all tested variables.

The table presents the correlation model for PWVao values and cardiovascular parameters. In all cases, a strong, positive, and statistically significant correlation (r>0.75,p<0.001r > 0.75, p < 0.001) was observed. Significant results are highlighted in blue, underscoring robust relationships between PWVao and the analyzed parameters.

***Table 42**: Correlation Model for Tested Variables*

Variables↓	**Statistics↓**	**Sys [mmHg]**	**Dia [mmHg]**	**PP [mmHg]**	**SBPao [mmHg]**	**HR [1/min]**
PWVao [m/s] Trim II	Pearson Correlation	.969**	.964**	.987**	.969**	.983**
	Sig. (2-tailed)	.000	.000	.000	.000	.000
	N	100	100	100	100	100
****. Correlation is significant at the 0.05 level (2-tailed).**						

Analysis of PWVao Values and Pregnancy Outcomes

We also evaluated potential associations between PWVao values and key pregnancy outcomes, including the gestational period, APGAR score, and fetal weight. The results of this correlation analysis are summarized in Table 43.

- A **positive, weak, but significant correlation** was found between PWVao values and the gestational period (r∈[−0.3;0.3]r \in [-0.3; 0.3], p=0.019<0.05p = 0.019 < 0.05).
- A **negative, weak, and statistically insignificant association** was observed between PWVao values and both the APGAR score and fetal weight (r∈[−0.3;0.3]r \in [-0.3; 0.3], p>0.05p > 0.05).

Statistically significant results are highlighted in blue. These findings suggest a limited association between PWVao and the gestational period, while no meaningful correlations were identified with APGAR scores or fetal weight.

***Table 43**: Correlation Model for PWVao and Pregnancy Outcome Variables*

Variables↓	Statistics↓	Gestational Period [weeks]	APGAR score [1 min]	Fetus Weight [Grams]
PWVao [m/s] Trim II	Pearson Correlation	.241	-.050	-.071
	Sig. (2-tailed)	.016	.621	.482
	N	100	100	100
*. Correlation is significant at the 0.05 level (2-tailed).				

Group 2 Correlation and Regression Analysis

In Group 2, the PWVao values measured in Trim II showed a strong, positive, and extremely significant correlation with blood pressure parameters (systolic and diastolic), pulse pressure (PP), central systolic blood pressure (SBPao), and heart rate (HR) (r>0.75,p<0.001r > 0.75, p < 0.001). Additionally, a weak but significant positive correlation was observed between PWVao Trim II values and the gestational period measured in weeks (r∈[−0.3;0.3],p<0.05r \in [-0.3; 0.3], p < 0.05). A positive correlation indicates that as one variable increases, the other also increases, whereas a negative correlation implies an inverse relationship. Similar findings were observed for PWVao values in Trim III.

Regression Analysis: Aix Brachial and PWVao

To further explore these relationships, we tested a regression model to evaluate the association between values in Trim II (predictor) and Trim III (response) for Aix brachial and PWVao values. The results were as follows:

- For **Aix brachial values**, we found a strong, positive, and extremely significant correlation between Trim II and Trim III values (r=0.97,R2=0.94,p<0.001r = 0.97, R^2 = 0.94, p < 0.001).
- For **PWVao values**, a similarly strong, positive, and extremely significant correlation was observed between Trim II and Trim III values (r=0.895,R2=0.801,p<0.001r = 0.895, R^2 = 0.801, p < 0.001).

These findings confirm the predictive capacity of Trim II values for Trim III outcomes, highlighting the stability and progression of these vascular parameters during pregnancy. Both results are presented graphically in Figure 20, illustrating the strength and significance of these relationships.

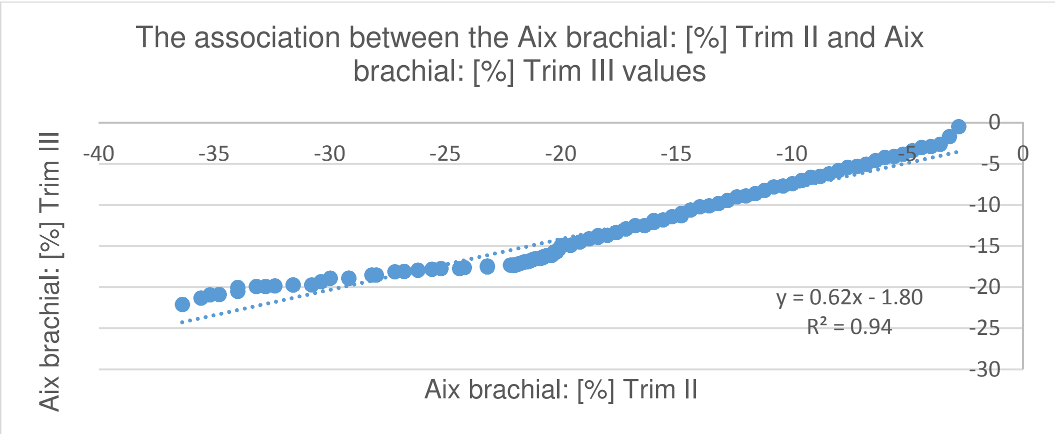


***Figure 20**: The association of Aix brachial values in Trim II and Trim III*

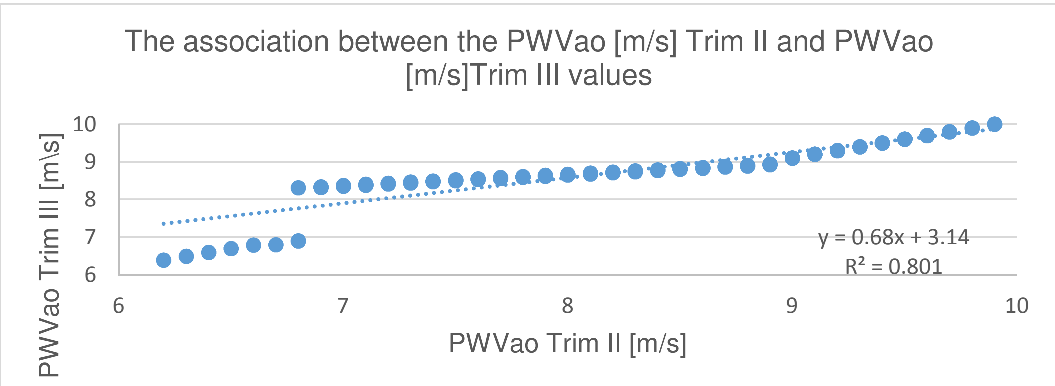


***Figure 21**: The association of PWVao values in Trim II and Trim III*

    - Between Group 1 and Group 2 and Group 3

Correlation Analysis of Aix Brachial and PWVao Values Across Groups

In this part of the study, we investigated potential associations between Aix brachial values and PWVao values across the three groups. A correlation model was applied to evaluate relationships between:

- **Aix brachial values**:
    - Group 1 (pregnant patients with hypertension or preeclampsia) and Group 2 (healthy pregnant patients).
    - Group 1 and Group 3 (healthy non-pregnant controls).
    - Group 2 and Group 3.

This analysis was conducted for the Trim II and Trim III time points, noting that Group 3 only provided one set of values, which were compared with both time points from Group 1 and Group 2.

- **PWVao values**:
- The same hypothesis was tested for PWVao values, with comparisons made for Trim II and Trim III across the groups.

The correlation model was performed using SPSS v17, with a significance level set at α=0.05\alpha = 0.05. The detailed results of this analysis are summarized in Tables 44–47, and significant results are visualized for clarity in Figure 22.

The analysis explored potential associations of Aix brachial values in Trim II across the three groups. The correlation model revealed the following:

- A **weak positive, insignificant association** between Group 1 (pregnant patients with hypertension or preeclampsia) and Group 2 (healthy pregnant patients) (r=0.101,p=0.320r = 0.101, p = 0.320).
- A **weak negative, insignificant association** between Group 1 and Group 3 (healthy non-pregnant controls) (r=−0.086,p=0.394r = -0.086, p = 0.394).
- A **weak positive, insignificant association** between Group 2 and Group 3 (r=0.009,p=0.926r = 0.009, p = 0.926).

These results indicate no significant relationships between Aix brachial values across the three groups during Trim II.

***Table 44**: Correlation Analysis of Aix Brachial Values in Trim II Across the Three Groups*

Variables↓→	Statistics↓	Aix brachial: [%] TrimII Group 1	Aix brachial: [%] TrimII Group 2	Aix brachial: [%] Group 3
Aix brachial: [%] TrimII Sample 1	Pearson Correlation	----	.101	-.086
	Sig. (2-tailed)		.320	.394
	N		100	100
Aix brachial: [%] TrimII Sample 2	Pearson Correlation	.101	-----	.009
	Sig. (2-tailed)	.320		.926
	N	100		100

The analysis examined potential associations of Aix brachial values in Trim III across the groups.

The correlation model yielded the following results:

- A **weak negative, insignificant association** between Group 1 (pregnant patients with hypertension or preeclampsia) and Group 2 (healthy pregnant patients) (r=−0.147,p=0.139r = -0.147, p = 0.139).
- A **weak negative, insignificant association** between Group 1 and Group 3 (healthy non-pregnant controls) (r=−0.102,p=0.310r = -0.102, p = 0.310).
- A **weak positive, insignificant association** between Group 2 and Group 3 (r=0.044,p=0.661r = 0.044, p = 0.661).

These findings indicate no statistically significant correlations between Aix brachial values across the three groups in Trim III.

***Table 45**: Correlation Analysis of Aix Brachial Values in Trim III Across the Three Groups*

Variables↓→	Statistics↓	Aix brachial: [%] TrimIII Group 1	Aix brachial: [%] TrimIII Group 2	Aix brachial: [%] Group 3
Aix brachial: [%] TrimIII Sample 1	Pearson Correlation	----	-.149	-.102
	Sig. (2-tailed)		.139	.310
	N		100	100
Aix brachial: [%] TrimIII Sample 2	Pearson Correlation	-.149	-----	.044
	Sig. (2-tailed)	.139		.661
	N	100		100

This analysis evaluated potential associations of PWVao values in Trim II across the three groups.

The correlation model produced the following results:

- A **weak positive (direct) insignificant association** between Group 1 (pregnant patients with hypertension or preeclampsia) and Group 2 (healthy pregnant patients) (r=0.105,p=0.299r = 0.105, p = 0.299).
- A **weak negative (indirect) insignificant association** between Group 1 and Group 3 (healthy non-pregnant controls) (r=−0.010,p=0.921r = -0.010, p = 0.921).
- A **weak positive (direct) significant association** between Group 2 and Group 3 (r=0.250,r∈[−0.3;0.3],p=0.012<0.05r = 0.250, r \in [-0.3; 0.3], p = 0.012 < 0.05).

The statistically significant result is highlighted in blue. These findings suggest a limited but notable relationship between PWVao values in Trim II for Group 2 and Group 3, while other associations remain insignificant.

***Table 46**: Correlation Analysis of PWVao Values in Trim II Across the Three Groups*

Variables↓→	Statistics↓	PWVao [m/s] Trim II Group 1	PWVao [m/s] Trim II Group 2	PWVao [m/s] Group 3
PWVao [m/s] Trim II Sample 1	Pearson Correlation	-----	.105	-.010
	Sig. (2-tailed)		.299	.921
	N		100	100
PWVao [m/s] Trim II Sample 2	Pearson Correlation	.105	-----	.250*
	Sig. (2-tailed)	.299		.012
	N	100		100
*. Correlation is significant at the 0.05 level (2-tailed).				

The analysis assessed potential associations of PWVao values in Trim III across the three groups.

The correlation model yielded the following results:

- A **weak positive (direct) insignificant association** between Group 1 (pregnant patients with hypertension or preeclampsia) and Group 2 (healthy pregnant patients) (r=0.042,p=0.679r = 0.042, p = 0.679).

- A **weak negative (indirect) insignificant association** between Group 1 and Group 3 (healthy non-pregnant controls) (r=−0.027,p=0.789r = -0.027, p = 0.789).
- A **weak positive (direct) insignificant association** between Group 2 and Group 3 (r=0.162,p=0.107r = 0.162, p = 0.107).

These findings indicate no statistically significant correlations between PWVao values across the three groups during Trim III.

***Table 47**: Correlation Analysis of PWVao Values in Trim III Across the Three Groups*

Variables↓→	Statistics↓	PWVao [m/s] Trim II Group 1	PWVao [m/s] Trim II Group 2	PWVao [m/s] Group 3
PWVao [m/s] Trim II Sample 1	Pearson Correlation	-----	.042	-.027
	Sig. (2-tailed)		.679	.789
	N		100	100
PWVao [m/s] Trim II Sample 2	Pearson Correlation	.042	-----	.162
	Sig. (2-tailed)	.679		.107
	N	100		100

In all instances, the analysis revealed weak associations between the tested variables. The only statistically significant result was observed between the PWVao values from Group 2 in Trim II (healthy pregnant patients) and the PWVao values from Group 3 (healthy non-pregnant controls).

This finding can be medically explained by the fact that PWVao values are sensitive to changes in physical activity levels (as discussed in Chapter 4) and can be influenced by improvements in associated medical parameters. These factors underscore the dynamic nature of PWVao and its responsiveness to lifestyle and health interventions.

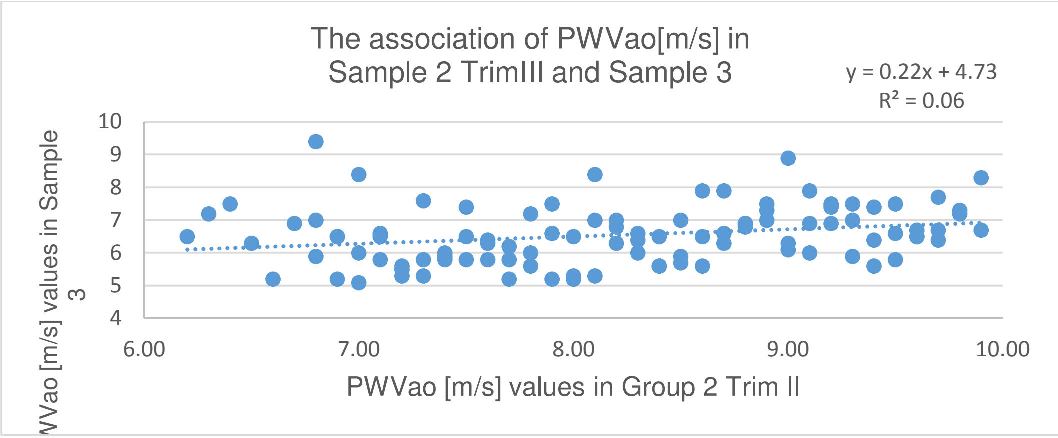


***Figure 22**: The association of PWVao values in Trim II from the patients who were included in Group 2, respectively the PWVao values from Group 3*

Follow-Up Study on Hypertension and Preeclampsia: Risk Analysis

This follow-up study analyzed 100 pregnant patients who developed hypertension or preeclampsia during pregnancy. The objective was to determine whether there is a correlation between elevated PWVao values and other medical parameters or habits.

To achieve this, we conducted a risk analysis by calculating the Risk Ratio (RR) and Odds Ratio (OR) for the sample, applying the χ^2 test, and estimating the 95% confidence interval for the RR and OR values for the entire population. A factor is considered a risk for the sample if the RR and OR values are greater than one. For the risk to be generalizable to the entire population, the pp-value must be less than 0.05.

Study Hypotheses

The analysis focused on three hypotheses:

1. To determine if smoking can be considered a risk factor for elevated PWVao values.
2. To assess whether high PWVao values serve as a risk factor for elevated cholesterol levels.
3. To evaluate if high PWVao values are a risk factor for elevated triglyceride levels.

The detailed results of the risk analysis are presented in Tables 48, 49, 50, and the associated findings are illustrated in Figures 23, 24, and 25.

This analysis assessed whether smoking could be considered a risk factor for PWVao values exceeding 9. The results indicate a significant risk factor within the group, which is generalizable to the entire population (RR=1.13RR = 1.13, OR=6.86OR = 6.86, p=0.042p = 0.042). These findings suggest that smoking contributes to the likelihood of elevated PWVao values.

Table 48: *Risk Analysis for Smoking as a Potential Risk Factor for Elevated PWVao Values.*

Statistics	**PWVao [m/s] Trim II>9**	**PWVao [m/s] Trim II<=9**	**Total**	**p – values RR, OR 95% - RR,OR**
Smoker+	42	1	43	$p = 0.042$ $RR = 1.13$ $95\%\ RR \in (1.01; 1.27)$ $OR = 6.86$ $95\%\ RR \in (1.02; 57.09)$
Smoker-	49	8	57	
Total	91	9	100	

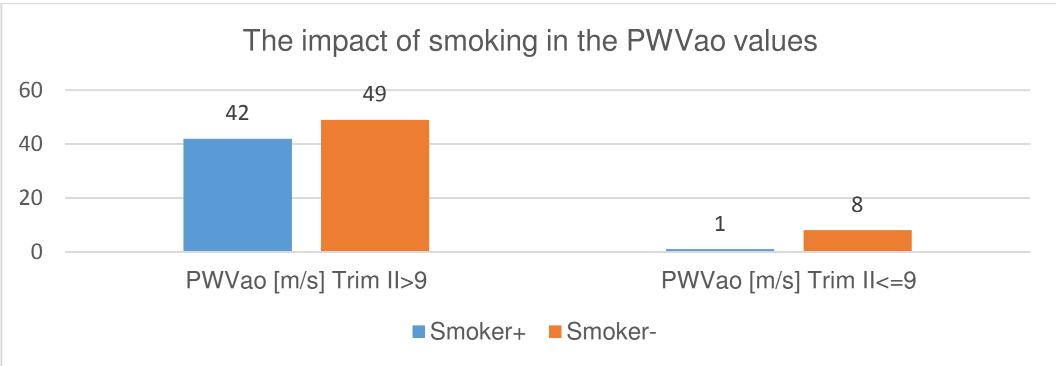


Figure 23: *Graphical Representation of the Impact of Smoking on PWVao Values*

Table 49: *Risk Analysis of Elevated PWVao Values as a Potential Risk Factor for High Cholesterol.*

Statistics	**Total cholesterol [mg/dl] >200**	**Total cholesterol [mg/dl] <=200**	**Total**	**p – values RR, OR 95% - RR,OR**
PWVao [m/s] Trim II>9	88	3	91	$p < 0.001$ $RR = 2.18$ $95\%\ RR \in (1.04; 4.52)$ $OR = 36.67$ $95\%\ RR \in (6.39; 210.42)$
PWVao [m/s] Trim II<=9	4	5	9	
Total	92	8	100	

This analysis evaluated whether PWVao values exceeding 9 could be considered a risk factor for elevated cholesterol levels (>200> 200). The results indicate a significant risk factor within the sample, which is generalizable to the entire population (RR=2.18RR = 2.18, OR=36.67OR = 36.67, p<0.001p < 0.001). These findings highlight the strong association between elevated PWVao values and high cholesterol levels

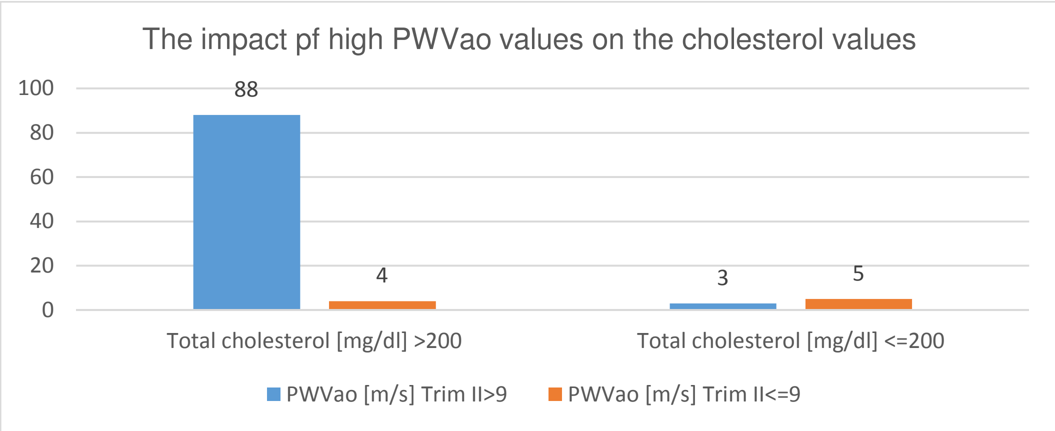


Figure 24: *Graphical Representation of the Impact of Elevated PWVao Values on Cholesterol Levels*

Table 50: *We assessed whether high PWVao values (> 9) could be considered a risk factor for elevated triglyceride levels (>160).*

Statistics	**Total triglyceride [mg/dl] >160**	**Total triglyceride [mg/dl] <=160**	**Total**	**p – values RR, OR 95% - RR,OR**
PWVao [m/s] Trim II>9	89	2	91	$p < 0.001$ $RR = 1.76$ $95\%\ RR \in (1.01; 3.16)$ $OR = 35.6$ $95\%\ RR \in (5.21; 243.22)$
PWVao [m/s] Trim II<=9	5	4	9	
Total	94	6	100	

The analysis revealed a significant risk factor within the sample, which can be generalized to the broader population (RR=1.76, OR=35.6, p<0.001).

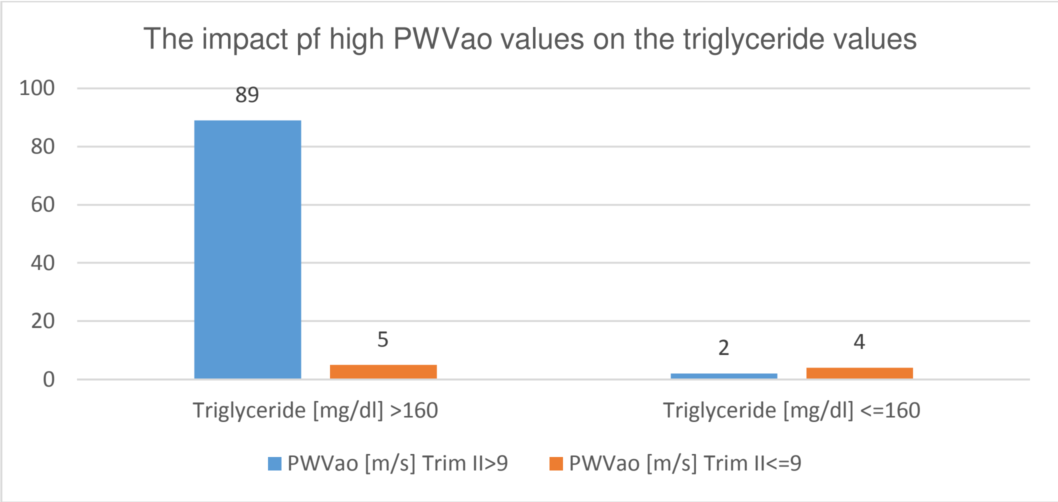


Figure 25: *The impact of high PWVao values on the triglyceride values*

After conducting the risk analysis, the following conclusions can be made: smoking is a significant risk factor influencing PWVao values (RR, OR > 1, $p < 0.05$). Smokers exhibited notably higher PWVao values. Additionally, elevated PWVao levels (PWVao > 9) are a highly significant risk factor for elevated cholesterol (>200) and triglyceride (>160) levels (RR, OR > 1, $p < 0.001$). Therefore, increased PWVao values are strongly associated with higher cholesterol and triglyceride levels. These factors—smoking, high PWVao, elevated cholesterol, and triglyceride levels—pose a toxic risk to pregnancy development.

At the conclusion of our study, we aimed to determine whether being over the age of 35 could be considered a risk factor for developing complications during pregnancy, such as hypertension, increased PWVao, PIGF, proteinuria, and elevated cholesterol or triglyceride levels. As demonstrated in the statistical test section, there were highly significant differences between these values in Group 1 (pregnant women who developed hypertension or preeclampsia) and Group 2 (healthy pregnant women). Following the risk analysis and the calculation of RR and OR values, we identified a significant risk factor (RR, OR > 1, $p < 0.05$).

All of these results are presented in Table 51 and illustrated in Figure 26.

Table 51: *We assessed whether being over the age of 35 could be considered a risk factor for complications that arise during pregnancy.*

Statistics	**Group 1**	**Group 2**	**Total**	**p – values** **RR, OR** **95% - RR,OR**
Age >=35	89	76	162	$p = 0.015$ $RR = 1.71$ $95\%\ RR \in (1.03; 2.85)$ $OR = 2.55$ $95\%\ RR \in (1.18; 5.55)$
Age< 35	11	24	38	
Total	100	100	200	

The analysis revealed a significant risk factor (RR = 1.71, OR = 2.55, p = 0.015 < 0.05).

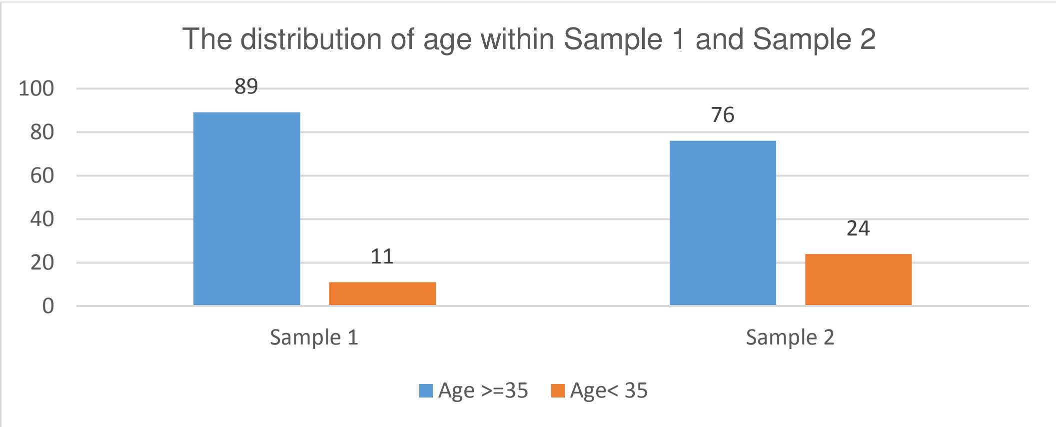


Figure 26: *We plotted the impact of a high age value in the pregnancy development, knowing that Sample 1 implies pregnancies with complication and Sample 2 a normal development in pregnancy.*

➢ Discussions

Arterial function can be altered in two ways: by affecting the function of the arterial duct (obstructed by an atheromatous plaque) and by altering its elastic function, such as increased arterial stiffness. The aim of this paper is to evaluate the impairment of arterial function, particularly its elastic component, by measuring arterial stiffness in pregnant women at risk.

With this device (TensioMedArteriograph), we can assess (through PWV) vascular (arterial) age which is independent of chronical age. Thus, although the pregnant woman is young, she may have (according to PWV) an advanced vascular age, which represents a cardiovascular risk factor.

The assessment of arterial rigidity as a marker of subclinical atherosclerosis has been analyzed in numerous studies and it was proven that it is correlated to cardiovascular and inflammatory risk factors involved in the mechanisms of developing clinical atherosclerosis.

Early detection of subclinical atherosclerosis is crucial for reducing cardiovascular risk in patients. However, current diagnostic strategies that focus on traditional risk factors or use risk scoring are not sufficient. Non-invasive imaging tools also have limitations, including high costs, time consumption, radiation exposure, renal toxicity, and the need for specialized techniques or equipment. (12)

Arterial stiffness and atherosclerosis are closely interconnected. Increased luminal pressure and shear stress caused by arterial stiffening lead to endothelial dysfunction, accelerate the formation of atheroma, and promote excessive collagen production and deposition in the arterial wall, contributing to the progression of atherosclerosis. (12)

Age is the major clinical determinant of aortic stiffness, a finding confirmed in several populations in different countries. (13) This is important because the age of women who become pregnant in constantly increasing. In developed countries, such as Finland and Sweden, childbearing later in life is a phenomenon which has become increasingly evident in the last three decades.

There have been many clinical studies and meta-analyses showing the association between PWV and coronary/cerebral/carotid atherosclerosis. More importantly, longitudinal studies have shown that PWV is a significant risk factor for future CVD independent of well-known cardiovascular risk factors. The measurement of PWV may be a useful tool to select subjects at high risk of developing subclinical atherosclerosis or CVD especially for mass screening. (12)

Yoav Ben-Schlomo et al. proved that aortic pulse wave velocity improves cardiovascular event prediction in an individual participant meta-analysis of prospective observational data from 17,635 subjects. (14)

Fears and anxieties typical of a high-risk pregnancy prevent the couple to live happily in the months of gestation. Effective communication, control and early detection are important tools that doctors must be able to ensure that women in order to plan the best treatment strategies and to minimize the risks of maternal and / or fetal. (15) Thus, it is essential to utilize all necessary tools, especially non-invasive methods to assess early and properly the complications of hypertensive pregnant women.

The optimal approach to cardiovascular disease screening and risk stratification remains controversial, with some favoring a strategy based on targeting high risk individuals (16) and others arguing for a population-based approach. (17) The former strategy focuses on measuring traditional risk factors and the relative cost effectiveness of such an approach has not been assessed in clinical practice. (16)

In recent years, great emphasis has been placed on the role of arterial stiffness in the development of cardiovascular diseases. Indeed, the assessment of arterial stiffness is increasingly used in the clinical assessment of patients. Although several papers have previously addressed this matter, very few focused on pregnant women.

In summary, aPWV predicts future cardiovascular risk and improves risk classification adjusting for established risk factors. As aPWV can now be reliably and easily measured (18) it may serve as a useful biomarker to improve cardiovascular risk prediction for patients at intermediate risk. However, before its adoption can be recommended, randomized-controlled trials using aPWV to guide risk stratification and/or treatment are required to provide convincing evidence that this method has clinical value.

Clinical conditions associated with increased arterial stiffness such as: ageing, obesity, low birth weight, smoking, menopausal status, hypertension, lack of physical activity, hypercholesterolemia, genetic background, impaired glucose tolerance, parental history of hypertension, metabolic syndrome, chronic kidney disease, parental history of diabetes, type 1 and 2 diabetes, systemic vasculitis.

In the literature it is mentioned that arterial stiffness in general (and PWV in particular) increases with blood pressure values, but this is not specifically described for pregnant women and especially not for pregnant women at risk. Moreover, the enhancement of the arterial stiffness is associated with elevated total cholesterol and LDL cholesterol, but this has not been yet demonstrated in pregnancy. (19, 20)

Smokers have diminished vascular elasticity due to the harmful effects. In this paper it was shown that smoking and arterial stiffness are correlated for pregnant women.

Arterial rigidity as a marker of altered arterial function and it can be correlated to multiple cardiovascular risk factors, but there is no data available until now to prove that cardiovascular risk factors are correlated to arterial compliance in pregnancy.

With TensioMedArteriograph, we can determine the vascular age (vascular aging assessed by PWV) of pregnant woman, independently of the chronological age. If the chronological age of the pregnant woman is increased and overlapped with higher vascular age is the equivalent of double risk. (21)

Arterial stiffness parameters were found to be elevated in hypertensive pregnant women. Furthermore, these parameters tended to increase more significantly in the third trimester compared to the second trimester, both in hypertensive and healthy pregnant women. In addition, arterial compliance was reduced in hypertensive patients when compared to their healthy counterparts. (22) This alteration in arterial function can lead to unfavorable changes in hemodynamic parameters. It was also observed that traditional cardiovascular risk factors, such as total cholesterol, LDL-cholesterol, and smoking, have a similar negative impact on vascular elasticity in pregnant women.

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CHAPTER 4

IMPACT OF A STRUCTURED PHYSICAL TRAINING PROGRAM ON HEMODYNAMIC PARAMETERS AND ARTERIAL STIFFNESS IN PREGNANT WOMEN: A LONGITUDINAL STUDY ACROSS TRIMESTERS

Study Aims:

- To assess hemodynamic parameters and arterial stiffness in pregnant women before and after a physical training program.
- To demonstrate that a structured training program improves hemodynamic parameters.

Objectives:

- To identify the group of patients suitable for an individualized physical training program.
- To evaluate blood pressure parameters after the physical training program in pregnant women.
- To demonstrate the potential of physical training in improving hemodynamic parameters during pregnancy.
- To study the incidence of hemodynamic parameters and the risk of arterial stiffness during pregnancy.

Materials and Methods:

This study was conducted in the Obstetrics and Gynecology Departments of the "Pius Brînzeu" Emergency Clinical Hospital Timișoara, under the guidance of an obstetrician, in collaboration with a cardiologist and physiotherapist. The patients participated daily in an individualized physical training program recommended by the kinetotherapist.(1)

Study Group Characteristics:

The following physical training exercises were part of the study:

1. Standing with circular head movements to the left and right (10 repetitions)
2. Standing with hands on shoulders, raise arms, inhale, exhale as hands return to shoulders (10 repetitions)
3. Standing with legs apart, hands on hips, rotate the trunk to the left, then to the right, exhaling (10 repetitions)
4. Standing, back straight, arms forward, heels on the floor, bend and extend knees while exhaling (10 repetitions, 2 sets, 1-minute break between sets)
5. Standing with 2 kg weights, perform alternating lunges (10 repetitions, 2 sets, 1-minute break between sets)
6. Standing with 2 kg weights, raise arms to 90 degrees, exhale slowly as arms return to starting position (10 repetitions, 2 sets, 1-minute break between sets)
7. Standing with 2 kg weights, flex forearms and exhale as arms return down (10 repetitions, 2 sets, 1-minute break between sets)
8. Standing with arms at 90 degrees and elbows bent, bring arms together in front, then back, exhaling (10 repetitions)
9. Standing with arms forward, lift each leg laterally, exhale (10 repetitions per leg)
10. Sitting on a fitness ball, 2 kg weights attached to ankles, lift each leg, inhale, exhale as leg returns (10 repetitions per leg)
11. Sitting on a fitness ball with a strap, extend leg backward, following with the eyes, return leg and exhale (10 repetitions per leg)
12. Sitting on a fitness ball, rotate trunk laterally (10 repetitions per side)

Warning Signs to Stop Physical Activity:

- Vaginal bleeding, shortness of breath, dizziness, headache, precordial chest pain, or easy fatigability.

Parameters Studied:

- Hemodynamic parameters and arterial stiffness (measured by the arteriograph) (2-5):
  - SBP (Systolic Blood Pressure)
  - DBP (Diastolic Blood Pressure)
  - PP (Pulse Pressure)
  - CF (Cardiac Frequency)
  - PWV (Pulse Wave Velocity)
  - Augmentation index (AIx), aortic augmentation index corrected for heart rate 75

Arteriograph: The arteriograph measures the increased stiffness of the arteries, which worsens with age, lifestyle, and family history. Arterial stiffness occurs when the elasticity of the arteries is lost, making the arteries more rigid. (6-8) Key parameters include:

- **Systolic Blood Pressure (SBP):** The highest pressure during a cardiac cycle, corresponding to ventricular systole. Optimal value: 120 mmHg.
- **Diastolic Blood Pressure (DBP):** The lowest pressure at the end of the cardiac cycle. Optimal value: 80 mmHg.
- **Pulse Pressure (PP):** The difference between SBP and DBP, used as a marker of cardiovascular risk, indicating higher risk for myocardial infarction and arterial stiffness.
- **Cardiac Frequency (CF):** The number of heartbeats per minute, essential for oxygenated blood distribution throughout the body.
- **Pulse Wave Velocity (PWV):** Measures arterial stiffness, with increased velocity indicating reduced arterial elasticity. PWV values above 12 m/s are considered pathological. (9,10)
- **Augmentation Index (AIx):** Used as a surrogate marker for arterial stiffness, predicting major cardiovascular events. It reflects the increase in arterial pressure due to peripheral resistance.(11-13)

This study aimed to investigate the effects of a physical training program on these hemodynamic and arterial stiffness parameters in pregnant women.

Forty female patients with the characteristics outlined in Table 1 were included in the study. In Table 1, we calculated the central tendency and dispersion parameters for the variables of age, height, weight, and BMI. The sample consists of relatively young subjects, with a mean age of approximately 25 years. Due to their regular physical activity, these participants remain fit despite being pregnant. All the details of these variables are presented in the table below.

Table 1: *Central tendency and dispersion parameters for the age, height, weight and BMI variables*

Statistics ↓	*Age (years)*	*Height [cm]-3 month*	*Weight [kg]-3 month*	*BMI (Kg/m2) - 3 month*
Mean	24.95	165.03	71.64	26.31
Standard Error	1.10	1.05	2.20	0.79
Median	22	165	69	25.91
Mode	21	168	75	25
Standard Deviation	6.95	6.65	13.92	5.03
Sample Variance	48.31	44.18	193.79	25.28
Range	27	34	61	21.63
Minimum	18	151	40	16.65
Maximum	45	185	101	38.28
Count	40	40	40	40

The average age of 25 and the appropriate physical condition of the participants allowed for the use of exercise sets with medium intensity on the Borg scale.

The evolution of hemodynamic parameters and arterial stiffness was studied at the beginning and end of a 12-week physical exercise program.

Inclusion Criteria:

- Patients aged between 18 and 45 years
- Gestational age in the 2nd trimester of pregnancy
- First or second pregnancy
- Stable clinical and hemodynamic conditions
- Patients willing to participate in physical therapy exercises

Exclusion Criteria:

- Family history of cardiovascular disease
- Patients younger than 18 or older than 45 years
- Multiparous patients (more than 3 pregnancies)
- Patients with cardiovascular disease
- Pregnancy-induced hypertension or other conditions
- High-risk pregnancy
- Other pregnancy complications
- Patient refusal to participate

Table 2: *Absolute and relative contraindications to exercise*

Absolute contraindications to exercise	**Relative contraindications to exercise**
Cervical insufficiency	Underweight (BMI <12) or maternal food disorder
Intrauterine growth restriction	Maternal arrhythmia or cardiovascular disorder
Multiple gestations	Mild to moderate respiratory distress
Persistent bleeding in the second or third trimester	Previous spontaneous abortion
Placenta praevia after 25-28 weeks of gestation	Severe anaemia
Preeclampsia	Twin pregnancy after 28 weeks of gestation
Pregnancy induced hypertension	Decreased blood pressure
Preterm labor during current or previous pregnancy	Type I diabetes poorly controlled
Premature rupture of membranes	A history of highly sedentary lifestyle
Preterm delivery risk	Orthopedic limitations Morbid obesity Convulsions or hypothyroidism Other significant medical conditions

For this study, we collected data from 40 pregnant patients who regularly engage in sports. The database was compiled using Microsoft Excel, and statistical analysis was conducted using both Microsoft Excel and SPSSv17. We calculated several descriptive statistical parameters, plotted the key results, performed a normality test, and applied the most suitable statistical tests, including the paired t-test and regression analysis. A confidence level of $\alpha = 0.05$ was used for all analyses.

In this study, we analyzed data from 40 pregnant patients who lead an active lifestyle and regularly practice sports. Information was collected on the subjects' age, height, weight, body mass index (BMI), brachial augmentation index (AIx), PWVao values, systolic (Sys) and diastolic (Dia) blood pressure, and heart rate (HR) during the second and third trimesters of pregnancy (Trim II, Trim III). The database consists solely of numerical variables, allowing us to calculate the central tendency and dispersion parameters for the entire dataset. To present the data in the descriptive analysis, we used line charts and histograms.

Table 3: *We calculated the central tendency and dispersion parameters for the brachial augmentation index (AIx), SD PWVao values, systolic and diastolic blood pressure values, and heart rate values during the second trimester of pregnancy (Trim II). All the characteristics of these variables are presented in the following table.*

Statistics ↓	*Aix brachial: [%]-Trim II*	*SD PWVao [m/s]-Trim II*	*Sys [mmHg]-Trim II*	*Dia [mmHg]-Trim II*	*HR [1/min]-Trim II*
Mean	-53.94	8.54	120.55	72.18	72.63
Standard Error	2.33	0.12	2.16	1.66	1.42
Median	-56	8.55	123	69.5	72.5
Mode	-61.3	7.9	124	66	75
Standard Deviation	14.77	0.77	13.65	10.52	9.01
Sample Variance	218.01	0.59	186.41	110.76	81.11
Range	49.3	2.9	52	45	36
Minimum	-78.7	6.9	96	53	57
Maximum	-29.4	9.8	148	98	93
Count	40	40	40	40	40

Table 4: *We calculated the central tendency and dispersion parameters for the brachial augmentation index (AIx), SD PWVao values, systolic and diastolic blood pressure values, and heart rate values during the third trimester of pregnancy (Trim III). All the characteristics of these variables are presented in the following table.*

Statistics ↓	*Aix brachial: [%]-Trim III*	*SD PWVao [m/s]- Trim III*	*Sys [mmHg]- Trim III*	*Dia [mmHg]- Trim III*	*HR [1/min]- Trim III*
Mean	-52.66	7.62	117.80	70.33	71.55
Standard Error	2.37	0.11	1.79	1.61	1.27
Median	-55.75	7.5	120	68.5	71
Mode	-30	6.8	120	60	62
Standard Deviation	14.98	0.69	11.30	10.20	8.03
Sample Variance	224.48	0.48	127.75	104.02	64.41
Range	58.7	2.6	45	35	33
Minimum	-78.7	6.5	100	55	57
Maximum	-20	9.1	145	90	90
Count	40	40	40	40	40

The mean values of hemodynamic parameters, specifically SBP and DBP, in both the second and third trimesters of pregnancy, indicated that the patient group maintained normal levels within the ESC guidelines. Additionally, the mean values for arterial stiffness parameters, namely Aix brachial and PWVao, were within the optimal ranges as per the guidelines.

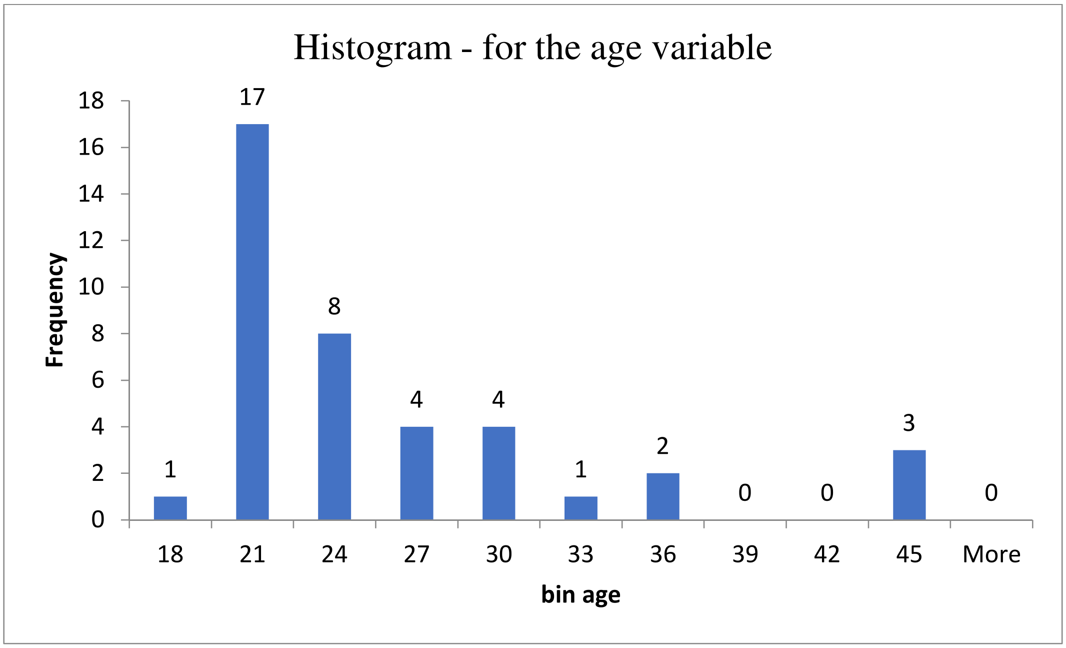

Figure 1: *Histogram for the age variable*

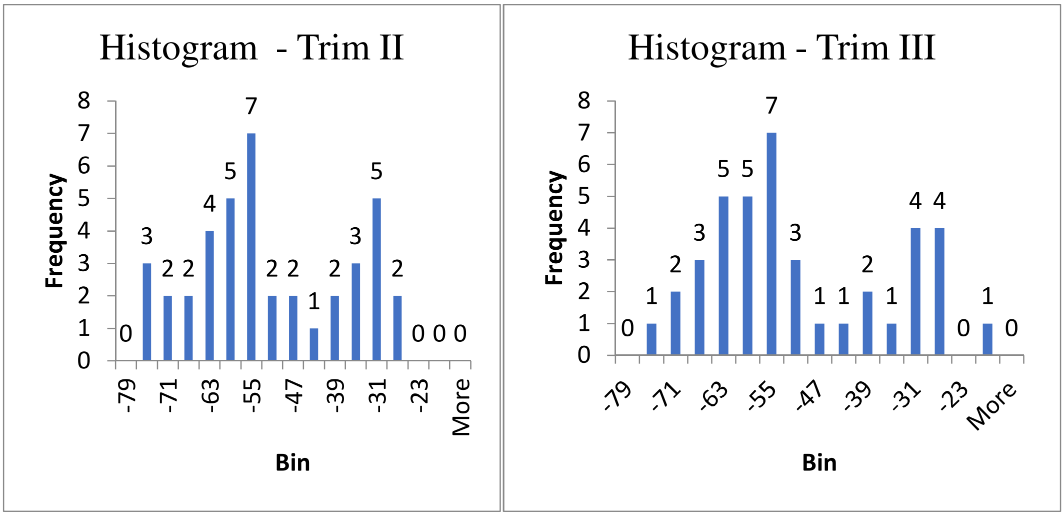

Figure 2: *We present the histograms for the Aix brachial values in the second and third trimester of pregnancy.*

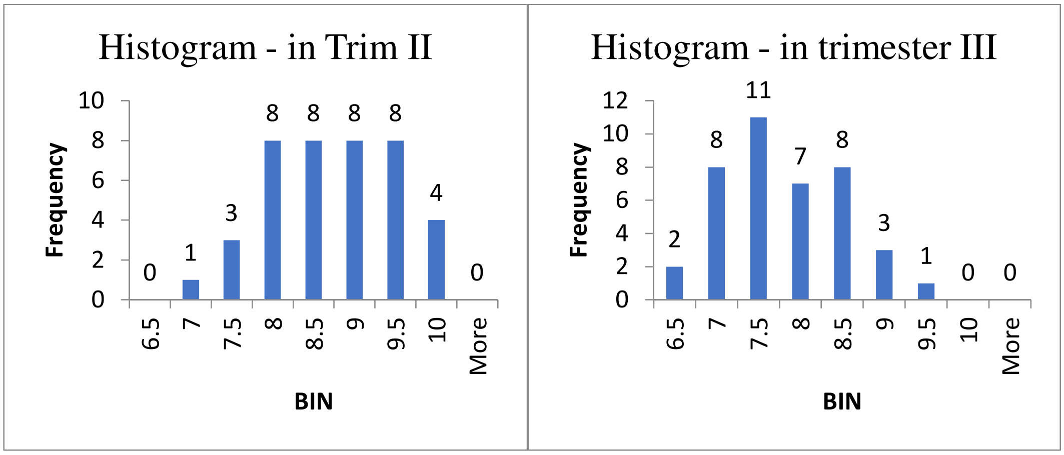

Figure 3: *We present the histograms for the PWVao values in the second and third trimester of pregnancy.*

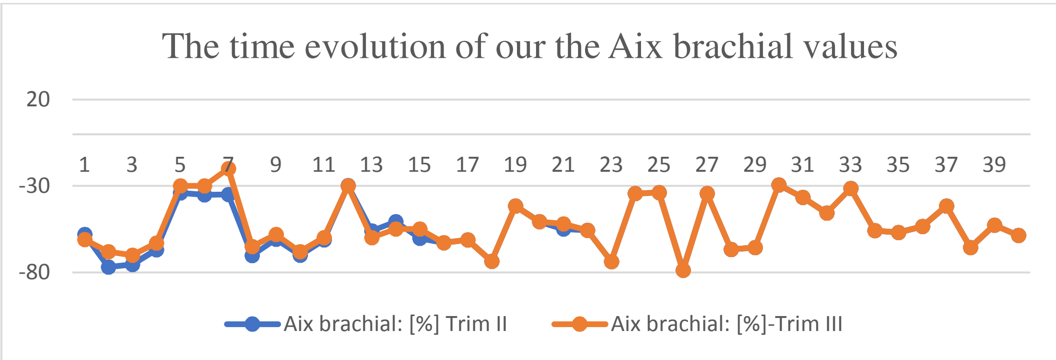

Figure 4: *The evolution of the Aix brachial values in the second and third trimester of pregnancy.*

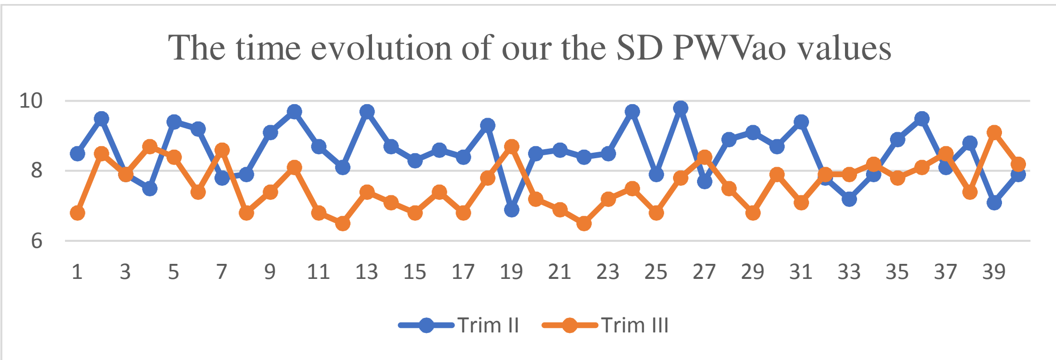

Figure 5: *The evolution of the PWVao values in the second and third trimester of pregnancy.*

In the initial part of our analysis, we tested the distribution of our data by applying the Shapiro-Wilk test, as the sample size is less than 50 (N=40). As shown in Table 5, all p-values are greater than 0.05, indicating that we can assume our data follows a normal distribution.

Table 5: *Normality test for our sample. For sample sizes greater than 50, the Kolmogorov-Smirnov test is used; otherwise, the Shapiro-Wilk test is applied. If the p-value from our test is greater than 0.05, we can conclude that the data follows a normal distribution.*

Variables	**Kolmogorov-Smirnov**			**Shapiro-Wilk**		
	Statistic	df	Sig.	Statistic	df	Sig.
Height [cm]-Trim II	.127	40	.103	.961	40	.185
Weight [kg]-Trim II	.129	40	.089	.960	40	.169
BMI (Kg/m2)- Trim II	.101	40	.200	.963	40	.217
Aix brachial: [%]-Trim II	.128	40	.095	.939	40	.053
SD PWVao [m/s]- Trim II	.098	40	.200	.969	40	.344
Sys [mmHg]- Trim II	.113	40	.200	.971	40	.396
Dia [mmHg]- Trim II	.169	40	.065	.940	40	.054
HR [1/min]- Trim II	.129	40	.092	.952	40	.086
Aix brachial: [%]-Trim III	.137	40	.057	.942	40	.041
SD PWVao [m/s]- Trim III	.105	40	.200	.956	40	.125
Sys [mmHg]- Trim III	.152	40	.020	.951	40	.081
Dia [mmHg]- Trim III	.149	40	.055	.913	40	.065
HR [1/min]- Trim III	.090	40	.20^{0}	.964	40	.229

Next, we tested for differences between the brachial augmentation index (AIx), PWVao values, systolic (Sys) and diastolic (Dia) blood pressure, and heart rate (HR) in Trim II and Trim III. To do so, we applied a paired t-test with a confidence level of $\alpha = 0.05$. Significant differences ($p < 0.05$) were found in all five cases, with some showing highly significant differences ($p < 0.001$). All the results are presented and discussed in Table 6.

Table 6: *The results from the paired t-test for the brachial augmentation index (AIx) values in Trim II and Trim III of pregnancy are presented*

Statistics↓	Aix brachial: [%] Trim II	Aix brachial: [%]-Trim III
Mean	-53.94	-52.66
Variance	218.01	224.48
Observations	40	40
Pearson Correlation	0.97	
Hypothesized Mean Difference	0	
df	39	
t Stat	-2.37	
P(T<=t) one-tail	0.01	
t Critical one-tail	1.68	
P(T<=t) two-tail	0.02	
t Critical two-tail	2.02	

As shown, the values decrease from one trimester to the next (the mean AIx value in Trim II is -53.94, compared to -52.66 in Trim III). The p-value of the test is 0.02, which is less than 0.05, indicating that the observed differences are statistically significant. The association between these two variables is very strong, with a Pearson correlation coefficient (r) of 0.97.

Table 7: *The results from the paired t-test for the SD PWVao values in Trim II and Trim III of pregnancy are presented.*

Statistics↓	SD PWVao [m/s]- Trim II	SD PWVao [m/s]- Trim III
Mean	8.54	7.62
Variance	0.59	0.48
Observations	40	40
Pearson Correlation	-0.25	
Hypothesized Mean Difference	0	
df	39	
t Stat	5.07	
P(T<=t) one-tail	5.06E-06	
t Critical one-tail	1.68	
P(T<=t) two-tail	1.01E-05<0.001	
t Critical two-tail	2.02	

As observed, the values decrease from one trimester to the next (the mean PWVao value in Trim II is -8.54, compared to -7.62 in Trim III). The p-value of the test is 0.00, which is less than 0.001, indicating that the observed differences are extremely significant statistically. However, the association between these two variables is weak, with a Pearson correlation coefficient (r) close to zero (r = -0.25).

Table 8 The results from the paired t-test for systolic blood pressure values in Trim II and Trim III of pregnancy are presented. As shown, the values decrease from one trimester to the next (the mean systolic blood pressure in Trim II is 120.55 mmHg, compared to 117.8 mmHg in Trim III). The p-value of the test is 0.00, which is less than 0.001, indicating that the observed differences are extremely significant statistically. The association between these two variables is very strong, with a Pearson correlation coefficient (r) of 0.96.

In our study, physical training led to a significant reduction in PWV values (as indicated by the p-value of the test), as well as a reduction in the Aortic Augmentation Index adjusted for heart rate (AIx-75).

„In normal pregnancy, there is a significant reduction in unadjusted aortic PWV from preconception to the second trimester (although the reduction is not significant for MAP-adjusted PWV)". (14)

„Unadjusted aortic PWV remains low or increases slightly in the third trimester and returns to baseline in the postpartum period. Aortic Aix adjusted for heart rate (i.e. AIx-75) in normal pregnancy follows a pattern similar to that of aortic PWV, with the most significant changes occurring between pre-pregnancy and the early first trimester. FMD increases in pregnancy until 32 weeks' gestation, then decreases significantly from 36 weeks." (15)

Studies of arterial stiffness in complicated pregnancies have focused largely on pre-eclampsia, intrauterine growth restriction, preterm birth and gestational diabetes , disorders that are associated with a greater risk of a future cardiovascular event in the mother (15)

Table 8: *The results from the t – paired test for the Systolic blood pressure values in Trim II and Trim III of pregnancy*

Statistics↓	*Sys [mmHg]-Trim II*	*Sys [mmHg]-Trim III*
Mean	120.55	117.8
Variance	186.41	127.75
Observations	40	40
Pearson Correlation	0.96	
Hypothesized Mean Difference	0	
df	39	
t Stat	4.07	
P(T<=t) one-tail	0.00	
t Critical one-tail	1.68	
P(T<=t) two-tail	0.00<0.001	
t Critical two-tail	2.02	

Table 9*: We present the results from the t – paired test for the Diastolic blood pressure values in Trim II and Trim III of pregnancy.*

Statistics↓	*Dia [mmHg]-Trim II*	*Dia [mmHg]-Trim III*
Mean	72.18	70.33
Variance	110.76	104.02
Observations	40	40
Pearson Correlation	0.94	
Hypothesized Mean Difference	0	
df	39	
t Stat	3.27	
P(T<=t) one-tail	0.00	
t Critical one-tail	1.68	
P(T<=t) two-tail	0.00	
t Critical two-tail	2.02	

As we can see the values are decreasing from one trimester to another (the mean value of Diastolic blood pressure in Trim II is -72.18 compared with the mean value of Diastolic blood pressure in Trim III which is -70.33). The p – value of the test is $0.00 < 0.001$, so, we can say that the observed differences are extremely significant from the statistical point of view. The association between this two variables is very strong, the Pearson coefficient (r) is close to one$(r = 0.94)$.

Table 10: *We present the results from the t – paired test for the Hear rate values in Trim II and Trim III of pregnancy.*

Statistics↓	*HR [1/min]-Trim II*	*HR [1/min]-Trim III*
Mean	72.63	71.55
Variance	81.11	64.41
Observations	40	40
Pearson Correlation	0.96	
Hypothesized Mean Difference	0	
df	39	
t Stat	2.54	
P(T<=t) one-tail	0.01	
t Critical one-tail	1.68	
P(T<=t) two-tail	0.02	
t Critical two-tail	2.02	

As we can see the values are decreasing from one trimester to another (the mean value of heart rate in Trim II is – 72.63 compared with mean value of heart rate in Trim III which is -71.55). The p – value of the test is $0.02 < 0.05$, so, we can say that the observed differences are significant from the statistical point of view. The association between this two variables is very strong, the Pearson coefficient (r) is close to one $(r = 0.94)$.

In the final part of our study, we conducted a regression analysis on the Aix brachial values and SD PWVao values from Trim II and Trim III. We observed significant differences between these two time points and sought to test if a relationship exists between these variables. For this, we performed a regression analysis, using the values from Trim II as predictors and those from Trim III as the response. The association within the sample was evaluated using the Pearson correlation coefficient. The results showed the following: the association between the Aix brachial values in the second and third trimesters of pregnancy is a strong, positive, and extremely significant relationship ($r = 0.97$, $R^2 = 0.95$, $p < 0.001$); whereas the association between the SD PWVao values in the second and third trimesters is a weak, negative, and insignificant relationship ($r = -0.25$, $R^2 = 0.06$, $p = 0.12 > 0.05$).

From a statistical perspective, we can conclude that the Aix brachial values consistently decrease across the entire sample. However, for the SD PWVao values, the decrease does not follow the same pattern throughout the sample. The relationship between these two variables is illustrated in Figure 6 and Figure 7.

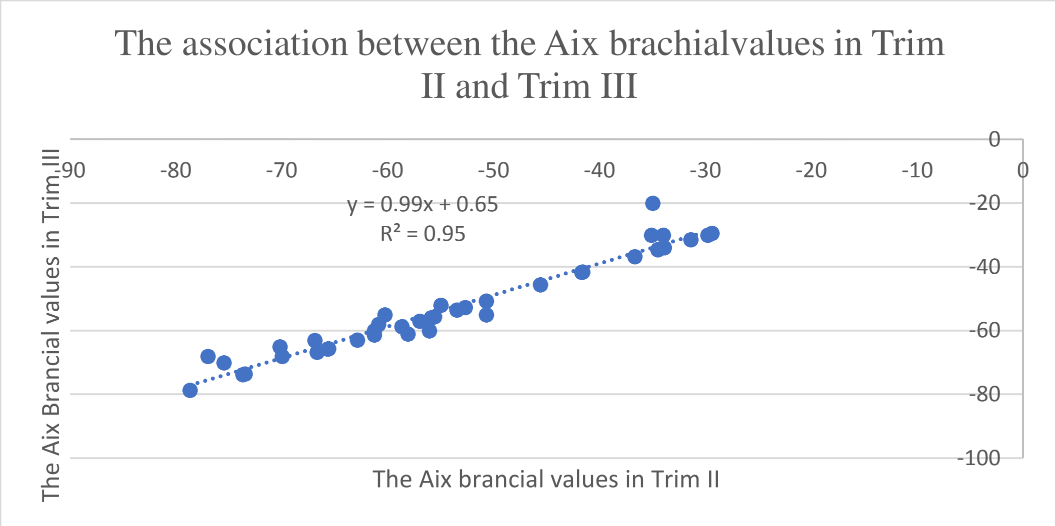

Figure 6: *The association between the Aix brachial values in Trim II and Trim III*

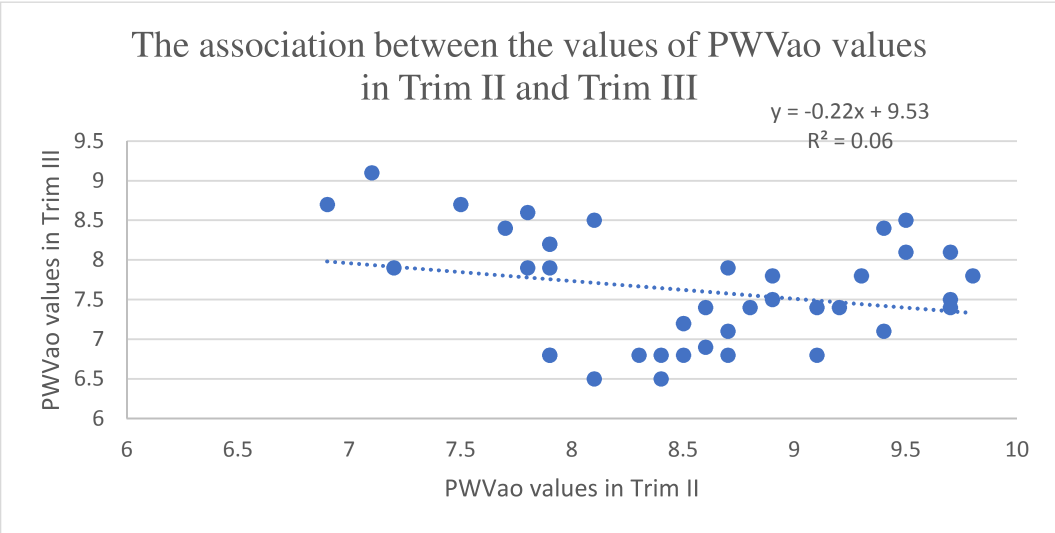

Figure 7: *The association between the SD PWVao values in Trim II and Trim III*

➢ Perspectives

Pregnancy is a physiological condition for women, during which physical activity typically decreases. Over this period, lifestyle changes often occur and tend to persist over time. As a result, the progressive development of chronic metabolic diseases is often inevitable. The onset of these conditions is associated with risks for both the mother and the fetus.

Specialized studies have shown that physical activity has been extensively researched and emphasized during pregnancy, highlighting its importance in promoting a healthy status. Engaging in an appropriate level of physical activity or following an exercise program during pregnancy is highly beneficial. Maintaining and continuing this healthy status has become a recent focus in maternal and child health research, with pregnant women having the option to choose different levels of physical activity. (16)

Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure. Our patient group falls within this definition. It is important to distinguish physical activity from sports activity, which is characterized by competition, performance, and the optimization of athletic movement (17).

The concept of physical activity encompasses both leisure activities and high-intensity structured exercises. While there is a distinction between low-intensity and moderate physical activity, it is important to establish a comprehensive set of basic exercises to achieve a certain level of fitness before beginning a more specific program. This is particularly crucial during pregnancy.

All basic daily physical activities require energy expenditure, which is measured in MET (metabolic equivalents). This is typically assessed using a simple survey that relates physical activity to energy consumption based on a well-known scale. The Borg scale, an easy-to-use tool for measuring physical effort intensity, was also employed in our study. The intensity level practiced by our patients was classified as light to moderate according to the Borg rating scale. It is important to note that the intensity of daily spontaneous physical activity is generally limited to less than 2 MET (18).

A moderate level of physical activity is also recommended by the American College of Obstetricians and Gynecologists (ACOG) and the United States Department of Health and Human Services (DHHS).

Additionally, the American College of Sports Medicine (ACSM) advises pregnant women to engage in moderate physical activity on a weekly basis throughout pregnancy. They also recommend maintaining a normal level of physical activity during the postpartum period (19).

Studies support the notion that all pregnant women should participate in physical activity throughout their pregnancy (19).

In the absence of critical clinical evidence, such as bleeding, anemia, severe hypertension, membrane rupture or the presence of cardiovascular disease, pregnant women should begin or maintain a sustained physical activity during pregnancy and continue with it throughout the postpartum period. (20)

Physical activity during pregnancy is recommended due to numerous lifelong health benefits. Physical activity during pregnancy is associated with a reduced risk of preeclampsia, gestational diabetes and premature delivery. (21)

Physical activity during pregnancy can also have implications for psychological health, including mood and self-esteem. (22)

In 2002, the American College of Obstetricians and Gynaecologists (ACOG) published their latest data and recommendations on physical activity during pregnancy. The American College of Obstetricians and Gynaecologists recommend that in the absence of medical or obstetric complications, pregnant women should do 30 minutes or more of moderate intensity exercise. It is also advisable to perform a complete clinical exam for each pregnant woman prior to physical exercise recommendations. In the absence of contraindications, regular exercises of moderate intensity are recommended. Pregnant women should be informed of the signs of stopping physical training (23).

When prescribing a physical exercise program, the type and intensity of the exercise must be taken into account. (24) Women should consider avoiding activities with a high risk of falling or injury (25).

Examples of low-risk sports: swimming, running, jogging, dancing, mobile or stationary bicycles, Nordic walking, skiing, Pilates, exercising with light weights.

Several theoretical complications may result from exercise during pregnancy. These can lead to foetal malformations or poor results in women or foetuses. Complications may occur due to increased maternal body temperature, change in uterine blood flow and foetal nutrient supply, hormonal impact on ligament laxity, soft tissue swelling, or premature labour induction. The treatment of these complications must balance the risks and benefits for both the woman and the foetus.

We must also note that the incidence of meconium, of abnormal foetal heart rates, the crossing of the umbilical cord around the foetus, and the fall in the Apgar score are all reduced with women who continue to do physical exercise during pregnancy. (26)

Following the obtained results, we recommend the following sports activities that would fit into the type of exercises previously studied and useful during normal pregnancy

- ***Upright stationary cycling*** is a low-impact, low-difficulty sport recommended by the Society of Obstetricians and Gynaecologists of Canada (SOGC) and by the American College of Sports Medicine (ACSM). Studies show that foetal heart rate and maternal temperature are not adversely affected. However, there may be greater variability in the foetal heart rate and maternal temperature with higher intensity and longer duration exercises. No negative foetal outcomes have been reported. Data have shown that cycling for 30 minutes at a maternal heart rate of approximately 140 BPM or physical exercise for 15 minutes at a rate of 155 BPM have not adversely affected the woman or foetus. (27)

- ***Swimming,*** an optimal exercise during pregnancy due to floating effects and thermal conductive properties of water, has been recommended by the American College of Obstetrics and Gynaecology and the American College of Sports Medicine. Studies have shown that baseline foetal heart rate may be less affected by swimming than cycling (28).

- ***Walking*** is considered by many women as the main exercise during pregnancy. It is recommended during pregnancy by the American College of Obstetricians and Gynaecologists and the American College of Sports Medicine. Walking has proven to be safe and increases the maternal feeling of well-being. In addition, it has not been shown that walking has a negative effect on maternal weight gain (29)

- ***Running*** and other weight-bearing activities can effectively increase placental growth, indicating a healthy pregnancy. (30)

Clapp found that women who continued to exercise during pregnancy maintained their training regimens and their fitness levels well above the cardiovascular risk index and their level of risk is well below those present in both the general population and the number of women who temporarily interrupted their exercise during pregnancy. (31)

Conditioning and physical therapy exercises to help maintain posture and prevent back pain have been recommended by the American College of Obstetricians and Gynaecologists. No adverse effects in light to moderate weight training have been reported. Some studies have indicated that strength and flexibility are actually improved with these activities. Moreover, moderate resistance conditioning has been shown to be safe in a healthy pregnancy, without obvious positive or negative effects. Minimal changes in foetal heart rate have been found as opposed to their initial value and that there is an increase in the foetal state of waking. (32) Physical training, when carefully coordinated by a multidisciplinary team including an obstetrician and a cardiologist, has been shown to significantly improve critical hemodynamic parameters in pregnant women. These parameters include systolic blood pressure (SBP), pulse pressure (PP), and heart rate (HR). By maintaining optimal hemodynamic function, physical training plays a pivotal role in enhancing maternal cardiovascular health during pregnancy.

Arterial elasticity, assessed using pulse wave velocity (PWV) — the gold standard for measuring vascular stiffness — shows marked improvement following structured physical training programs. These programs, designed and supervised by a collaborative medical team comprising an obstetrician, physiotherapist, and cardiologist, emphasize safe and effective exercises tailored to the unique needs of pregnant women. The reduction in arterial stiffness reflects the vital role of exercise in promoting vascular health and preventing long-term complications. Closely monitored physical training has the potential to mitigate pregnancy-induced hypertension, a condition associated with significant maternal and fetal risks. By lowering blood pressure and preventing the development of arterial rigidity, these exercise programs offer a non-pharmacological strategy for managing hypertensive disorders during pregnancy. Designing training regimens that specifically target these outcomes can significantly benefit high-risk populations.

Demonstrating the measurable improvements in hemodynamic parameters achieved through physical training serves as a powerful motivator for pregnant women to engage in structured exercise programs. These "medical gymnastics" sessions not only address immediate pregnancy-related challenges but also promote overall health and well-being. Empowering women with evidence-based insights about these benefits fosters adherence and long-term commitment to a healthy lifestyle.

Individualized physical training programs also contribute to optimizing the augmentation index, another key marker of arterial function. Improvements in this parameter underscore the effectiveness of tailored exercise regimens in enhancing cardiovascular performance and reducing the physiological burden of pregnancy on the maternal body.

Physical training during pregnancy offers a wide range of benefits that extend beyond cardiovascular health. These include:

- **Improved Muscle Tone:** Regular exercise strengthens muscles, preparing the body for the demands of labor and delivery.
- **Lower Blood Pressure:** Controlled physical activity helps maintain healthier pressure values, reducing the risk of hypertensive complications.
- **Faster Postnatal Recovery:** Exercise facilitates quicker recovery after childbirth, enabling new mothers to regain their strength and energy more rapidly.
- **Shorter and Less Painful Labor:** Women who engage in prenatal physical training often experience shorter labor durations and reduced labor pain, contributing to a more positive birthing experience.
- **Holistic Approach to Prenatal Exercise**
- To maximize the benefits of physical training during pregnancy, programs should be carefully designed to address individual needs, with input from obstetricians, cardiologists, and physiotherapists. Such an approach ensures that exercises are safe, effective, and adaptable to the changing physical demands of pregnancy. By incorporating physical training into standard prenatal care, we can empower pregnant women to achieve better health outcomes for themselves and their babies.

Hypertensive disorders during pregnancy are associated with significant increases in arterial stiffness, highlighting the altered vascular function in affected individuals. This emphasizes the importance of early detection and continuous monitoring to reduce associated risks. Arterial stiffness parameters progressively increase as pregnancy advances, with a more pronounced enhancement in the third trimester for both hypertensive and healthy pregnant women. This suggests the need for trimester-specific monitoring and timely interventions. Pregnant women with hypertension exhibit reduced arterial compliance compared to their healthy counterparts, reflecting the compromised vascular health that accompanies hypertensive states.

Well-established cardiovascular risk factors, such as elevated total cholesterol, LDL cholesterol, and smoking, negatively impact vascular elasticity in pregnant women. These findings underscore the importance of managing these risk factors during pregnancy. Supervised physical training programs significantly improve key hemodynamic parameters such as systolic blood pressure, pulse pressure, and heart rate. Structured exercise also enhances arterial elasticity, as shown by improvements in pulse wave velocity (PWV), the gold standard for measuring arterial stiffness.

Closely supervised physical training has been proven to reduce pregnancy-induced hypertension by lowering blood pressure and preventing the progression of arterial rigidity, highlighting the therapeutic potential of exercise in high-risk pregnancies. By demonstrating the tangible benefits of physical training on hemodynamic parameters, this research encourages pregnant women to participate in medically supervised exercise programs. These programs not only improve cardiovascular health but also enhance overall maternal well-being.

Individualized physical training effectively optimizes the augmentation index, further supporting the role of tailored exercise regimens in promoting vascular health during pregnancy. In addition to cardiovascular improvements, regular physical activity during pregnancy contributes to better muscle tone, reduced pregnancy-related pressure values, faster postpartum recovery, and shorter, less painful labor. These benefits make exercise a cornerstone of prenatal care.

Counseling should focus on personalized care, addressing medical, psychological, and socio-cultural factors. For women with high cardiovascular risk or potential pregnancy contraindications, discussions should begin early, ideally in adolescence or young adulthood. Counseling sessions should emphasize lifestyle modifications, such as smoking cessation, maintaining a healthy weight, and adopting a balanced diet, to optimize both maternal and fetal outcomes. A collaborative approach involving obstetricians, cardiologists, physiotherapists, and psychologists is crucial for managing high-risk pregnancies. A personalized care plan should be developed, addressing the unique needs of each patient.

Pregnancy is a critical time to encourage healthier habits, such as regular physical activity, balanced nutrition, and the avoidance of harmful substances like tobacco and alcohol. Programs should emphasize addressing obesity and its associated risks. In the initial obstetrics-gynecology office assessment, detailed family and personal medical history should be collected, and smoking habits, dietary patterns, and physical activity levels should be assessed. Laboratory investigations should measure lipid profiles and glucose levels as needed. Anthropometric data should be recorded, and hemodynamic parameters, including blood pressure, pulse pressure, and heart rate, should be monitored. Arterial stiffness should be assessed using aortic PWV and the augmentation index (Aix). The patient's cardiovascular risk category should be established based on this collected data. Ongoing monitoring across trimesters should reassess risk factors, anthropometric data, and hemodynamic parameters, performing arterial stiffness measurements and updating risk classification as necessary.

Exercise regimens should be designed for different risk categories, ensuring they are safe, effective, and adaptable to individual needs. These regimens should focus on cardiovascular and muscular health, such as low-impact aerobic activities and resistance training. Long-term cardiovascular and metabolic benefits of prenatal physical training should be investigated, with a focus on reducing the risk of chronic conditions like hypertension and diabetes later in life. The use of wearable devices to monitor hemodynamic changes and physical activity levels in real-time should be explored, along with the use of telemedicine to provide remote guidance and support for pregnant women participating in exercise programs.

This research underscores the critical role of arterial health and physical training in managing high-risk pregnancies. By integrating structured exercise programs and comprehensive assessments into prenatal care, maternal and fetal outcomes can be improved, while also promoting lifelong health benefits. Future efforts should focus on developing multidisciplinary approaches and leveraging technology to advance care for women with cardiovascular risk during pregnancy.

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