Evaluation of physiological changes and therapeutic approaches of hypertension in pregnancy
Mohammed Safi Ur-Rahman1, Sumayya2, Ayesha Naseer1, Korapati Ramarao1, S P Srinivas Nayak1,2,5*

1,2,5Intern, PharmD, Aster Prime Hospital, Sultan-ul-Uloom College of Pharmacy, JNTUH, Hyderabad, Telangana, India
3Assistant Professor, Dept. of Pharmacology, Sultan-ul-Uloom College of Pharmacy, JNTU, Hyderabad, Telangana, India
4Assistant Professor, Dept. of Pharmacy Practice, Sultan-ul-Uloom College of Pharmacy, JNTUH, Aster Prime Hospital, Ameerpet, Hyderabad, Telangana, India

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Corresponding author: Dr. S P Srinivas Nayak
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Abstract:
There are various physiological and pharmacokinetic changes occur in pregnancy to nurture the developing foetus, avoid toxicities, resistance to infections and prepare the mother for labour and delivery. Some of these changes influence normal biochemical values while others may mimic symptoms of medical disease and alter the kinetic parameters of the drugs. It is important to differentiate between normal physiological changes and disease pathology. This article highlights the important changes that take place during normal pregnancy, development of common conditions and pharmacokinetic variations. This review also will describe basic concepts in pharmacokinetics and their clinical relevance and highlight the variations in pregnancy that may impact the pharmacokinetic properties of medications, different treatment approaches, contraindications and drugs used in pregnancy.

Key words: Physiological changes in pregnancy, Hypertension, pregnancy disorders.

Introduction
During pregnancy, the pregnant mother undergoes significant anatomical and physiological changes in order to nurture and accommodate the developing fetus. These changes begin after conception and affect every organ system in the body. For most women experiencing an uncomplicated pregnancy, these changes resolve after pregnancy with minimal residual effects. It is important to understand the normal physiological changes occurring in pregnancy as this will help differentiate from adaptations that are abnormal. [1] The female body goes through immense changes during a pregnancy that involve all organ systems in the body. These changes result in physiology that differs from that of a non-pregnant female. Additionally, abnormalities in the development of pregnancy can lead to further complications within both mother and fetus. [2]

1.1. The embryogenesis and development:

The fertilization of an egg with a sperm starts the process of embryogenesis. The fertilized egg goes through several divisions to form a blastocyst. This blastocyst then initiates implantation with the maternal endometrium. Implantation triggers the uterine stroma to undergo decidualization to accommodate the embryo. This decidual supports embryo survival and appears to act as a barrier against immunologic responses. Additionally, upon implantation, human chorionic gonadotropin (hCG) begins to be secreted, allowing the sustenance of pregnancy. The blastocyst then begins the process of forming three distinct germ layers, including the ectoderm, mesoderm, and endoderm. At this stage, the blastocyst then becomes an embryo. The embryo goes through a process known as organogenesis, in which the majority of the major organ systems develop.

2. Female reproductive system and its modification in pregnancy
To accommodate a growing fetus, the uterus must undergo extreme structural changes and cellular hypertrophy. During this time, the uterus must maintain a passive noncontractile state; this occurs through elevated levels of progesterone, which act to relax smooth muscle—growth of the placenta results in uterine tissue and vascular remodeling. Hormonal signals, primarily estrogen, are responsible for initiating the uterine growth
process during early pregnancy. The uterus increases from 70 g to 1100 g, with its volume capacity increasing from 10 ml to 5 L. Between weeks 12 and 16, the lower uterine corpus unfolds, allowing the uterus to become more spherical and giving room for amniotic sac expansion with minimal stretching of the uterus. When fetal growth rate begins to accelerate at 20 weeks, the uterus rapidly elongates, and the walls thin. The longitudinal diameter grows more rapidly than the left-right and anterior-posterior diameters, with the maximum rate of elongation happening between weeks 20 and 32. By 28 weeks, the maximum fetal growth rate has occurred, and the uterine tissue growth slows while continuing to stretch rapidly and become thin. Within several weeks of delivery, the uterus then returns to its pre-pregnancy structure. [6]

2.1. Haematological changes

Plasma volume increases progressively throughout normal pregnancy. [6] Most of this 50% increase occurs by 34 weeks’ gestation and is proportional to the birthweight of the baby. Because the expansion in plasma volume is greater than the increase in red blood cell mass, there is a fall in haemoglobin concentration, haematocrit and red blood cell count. Despite this haemodilution, there is usually no change in mean corpuscular volume (MCV) or mean corpuscular haemoglobin concentration (MCHC). The platelet count tends to fall progressively during normal pregnancy, although it usually remains within normal limits. In a proportion of women (5–10%), the count will reach levels of 100–150 × 10⁹ cells/l by term and this occurs in the absence of any pathological process. In practice, therefore, a woman is not considered to be thrombocytopenic in pregnancy until the platelet count is less than 100 × 10⁹ cells/l. Pregnancy causes a two- to three-fold increase in the requirement for iron, not only for haemoglobin synthesis but also for for the foetus and the production of certain enzymes. There is a 10- to 20-fold increase in folate requirements and a two-fold increase in the requirement for iron, not only for haemoglobin synthesis but also for the foetus and the production of certain enzymes. Changes in the coagulation system during pregnancy produce a physiological hypercoagulable state (in preparation for haemostasis following delivery). [7] Pregnancy is a hypercoagulable state secondary to blood stasis as well as changes in the coagulation and fibrinolytic pathway such as increased plasma levels of clotting factors (VII, VIII, IX, X, XII), fibrinogen, and von Willebrand factor. Fibrinogen increases starting in the first trimester and peaks during the third trimester in anticipation of delivery. Prothrombin and factor V levels remain the same during pregnancy. Whereas, protein S decreases in pregnancy, protein C does not usually change and thus can be assayed if needed in pregnancy. Free antigen levels of the protein S above 30% in the second trimester and 24% in the third trimester are considered normal during pregnancy[8] Platelet function and routine coagulation screen panels remain normal. This hypercoagulable state may offer a survival advantage by minimizing blood loss after delivery, but it also predisposes pregnant women to higher risks for thromboembolism. [8][9]

2.2. Cardiovascular system in pregnancy

Pregnancy is associated with significant anatomic and physiologic remodeling of the cardiovascular system. Ventricular wall mass, myocardial contractility and cardiac compliance increase. [10] Both heart rate and stroke volume increase in pregnancy leading to a 30–50% increase in maternal cardiac output (CO) from 4 to 6 l/min, These changes occur primarily early in pregnancy, and 75% of the increase will occur by the end of the first trimester. The increase in total body water, blood volume, and capillary hydrostatic pressure increase significantly the volume of distribution of hydrophilic substrates. Clinically, a larger volume of distribution could necessitate a higher initial and maintenance dose of hydrophilic drugs to obtain therapeutic plasma concentrations. Additionally, because of the decrease in serum albumin concentrations and other drug-binding proteins during pregnancy; drugs, that are highly protein bound, may display higher free levels due to decreased protein binding availability, and thus higher bioactivity. For example, if a drug is highly (99%) bound to albumin in non-pregnant patients, a small drop in protein binding to 98% in pregnancy translates into doubling of the drug’s active fraction in pregnancy. Digoxin, midazolam, and phenytoin are examples of medications primarily bound to albumin. [8]

2.3. Gastrointestinal system

Elevated levels of estrogen, progesterone, and human chorionic gonadotropin (hCG) combine to bring about nausea and vomiting, commonly termed morning sickness. Hypoglycemia can be an additional cause of nausea. Morning sickness develops in over 70% of pregnancies and can occur at any time of day. It typically resolves by weeks 14 to 16 but persists beyond week 20 in about 10-20% of pregnant patients. If nausea and vomiting are severe enough to lead to ketosis and weight loss greater than or equal to 5% of pre-pregnancy weight, the term for this is hyperemesis gravidarum. In these patients, intravenous fluid and vitamin substitution may be necessary. Elevated progesterone levels induce smooth muscle relaxation, leading to prolonged gastric emptying time. When combined with decreased gastroesophageal sphincter tone and upwards displacement of the stomach, reflux often occurs. Progesterone-mediated smooth muscle relaxation also leads to decreased motility in the large bowel, resulting in increased water absorption and constipation. [11]

2.4. Urinary system

The renin-angiotensin-aldosterone system is activated in early pregnancy, consequently increasing sodium reabsorption. However, an increased glomerular filtration rate (GFR) acts to maintain sodium plasma levels. Additionally, elevated progesterone and prostacyclin,
along with angiotensin I receptor modification in pregnancy, leads to a relative resistance to angiotensin II. This state acts to balance the vasoconstrictive effect of angiotensin and allow for vasodilatation of the renal arteries mediated by relaxin stimulation of endothelin to synthesize nitric oxide. Due to renal vasodilation, both the GFR and renal plasma flow increase. The GFR increases 50% starting in early pregnancy, and this increase remains until delivery. The decrease in systemic vascular resistance results in both afferent and efferent arteriolar experiencing decreased vascular resistance, thus maintaining glomerular hydrostatic pressure—the resulting increased renal blood flow results in an increase in kidney size. Progesterone acts to reduce ureteral tone, peristalsis, and contraction pressure, thereby dilating the ureters. The elevation in GFR acts to decrease blood urea nitrogen and creatinine by 25%. The elevated GFR, combined with increased glomerular capillary permeability to albumin, results in an increase of fractional excretion of protein to as much as 300 mg/day. Less effective tubular reabsorption of both glucose and urea results in increased excretion rates. \[11\]

### 2.5. Endocrine changes

#### A. Thyroid

There is an increase in the production of thyroxine-binding globulin (TBG) by the liver, resulting in increased levels of thyroxine (T4) and tri-iodothyronine (T3). Serum free T4 (fT4) and T3 (fT3) levels are slightly altered but are usually of no clinical significance. Levels of free T3 and T4 do however decrease slightly in the second and third trimesters of pregnancy and the normal ranges are reduced. \[12\] Free T3 and T4 are the physiologically important hormones and are the main determinants of whether a patient is euthyroid. Serum concentrations of TSH are decreased slightly in the first trimester in response to the thyrotropic effects of increased levels of human chorionic gonadotropin. Levels of TSH increase again at the end of the first trimester, and the upper limit in pregnancy is raised to 5.5 μmol/l compared with the level of 4.0 μmol/l in the non-pregnant state. Pregnancy is associated with a relative iodine deficiency. The causes for this are active transport of iodine from the mother to the foeto-placental unit and increased iodine excretion in the urine. The World Health Organisation recommends an increase in iodine intake in pregnancy from 100 to 150–200 mg/day. If iodine intake is maintained in pregnancy, the size of the thyroid gland remains unchanged and therefore the presence of goiter should always be investigated. The thyroid gland is 25% larger in patients who are iodine deficient. \[13\]

#### B. Adrenal gland

Three types of steroids are produced by the adrenal glands: mineralocorticoids, glucocorticoids and sex steroids. The RAA system is stimulated due to reductions in vascular resistance and blood pressure, causing a three-fold increase in aldosterone levels in the first trimester and a 10-fold increase in the third trimester. \[13\][14] Levels of angiotensin II are increased two- to four-fold and renin activity is increased three to four times that of non-pregnant values. During pregnancy there is also an increase in serum levels of deoxycorticosterone, corticosteroid-binding globulin (CBG), adrenocorticotropic hormone (ACTH), cortisol and free cortisol. These changes cause a state of physiological hypercortisolism and may be clinically manifested by the striae, facial plethora, rising blood pressure or impaired glucose tolerance. \[15\] Total cortisol levels increase at the end of the first trimester and are three times higher than non-pregnant values at the end of pregnancy. Hypercortisolism in late pregnancy is also the result of the production of corticotrophin releasing hormone by the placenta – one of the triggers for the onset of labour. Diurnal variations in ACTH and cortisol levels are maintained. The hypothalamic–pituitary axis response to exogenous glucocorticoids is blunted during pregnancy. \[15\]

### C. Pituitary gland

The pituitary gland enlarges in pregnancy and this is mainly due to proliferation of prolactin-producing cells in the anterior lobe. Serum prolactin levels increase in the first trimester and are 10 times higher at term. The increase in prolactin is most likely due to increasing serum oestradiol concentrations during pregnancy. Levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are undetectable during pregnancy due to the negative feedback from elevated levels of oestrogen, progesterone and inhibin. \[16\] Pituitary growth hormone production is decreased but serum growth hormone levels are increased due to growth hormone production from the placenta. The posterior pituitary produces oxytocin and arginine vasopressin (AVP). Oxytocin levels increase in pregnancy and peak at term. Levels of antidiuretic hormone (ADH) remain unchanged but the decrease in sodium concentration in pregnancy causes a decrease in osmolality. There is therefore a resetting of osmoreceptors for ADH release and thirst. \[17\]

### D. Female hormones

Plasma concentrations of female hormones, consisting of different estrogens and progesterone, rise steadily until they peak at term in pregnant women. Estradiol and progesterone levels reach 0.1 and 1 μM at term (100-fold higher as compared to pre-pregnancy levels), respectively. \[18\] In addition, estradiol up-regulates expression of CYP2A6, CYP2B6 and CYP3A4 and down-regulates CYP1A2 expression in human hepatocytes. These in vitro observations are in part similar to the reported clinical changes in pregnancy suggesting that for certain CYP enzymes female hormones are potentially responsible for the altered drug metabolism during pregnancy \[19\]. The rise in estrogen or progesterone concentrations in blood...
is less than 5-fold in rat pregnancy compared to the ~100-fold increase in humans [58][21]

2.6. Human placental lactogen and placental growth hormone

During pregnancy, levels of native GH decrease but those of other GH-like hormones, i.e., human placental lactogen (hPL) and placental growth hormone (PGH), rise dramatically (30 and 100-folds respectively for hPL and PGH) [22]

A. Prolactin

During pregnancy, the maternal plasma concentrations of prolactin increase gradually until they peak at term (10-fold increase as compared to pre-pregnancy levels). The higher prolactin level during pregnancy stimulates the mammary glands to produce milk. In addition, prolactin exerts biological functions in various organs and is involved in osmolegulation, growth, reproduction, immune regulation and behavior. After delivery, the prolactin concentrations remain elevated and fall gradually toward the pre-pregnancy levels during a 3- to 4-week interval in non-lactating mothers. In lactating mothers, however, prolactin levels remain elevated and increase with each nursing episode [23][24]

3. Liver physiology in pregnancy:

Serum albumin concentration falls in normal pregnancy and is thought to relate to the increase in total plasma volume. This may persist for several months after delivery. Serum alkaline phosphatase (ALP) increases and may reach 2 to 4 times baseline level. This relates to placental production. In general, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and gamma-glutamyltransferase (GGT) concentrations remain normal, but elevations require further investigation. Ultrasound, if required, remains the preferred imaging modality. When further detailed images are needed, MRI without contrast is safe. [25]

3.1. Metabolism

The placenta produces human placental lactogen (hPL), which acts to supply nutrition to the fetus. It induces lipolysis to increase free fatty acids, which are preferentially used by the pregnant mother for fuel. It also acts as an insulin antagonist to induce a diabeticogenic state. This activity prompts hyperplasia of pancreatic beta-cells to create increased insulin levels and protein synthesis. In early pregnancy, maternal insulin sensitivity increases, followed by resistance in the second and third trimesters. Total serum cholesterol and triglyceride levels increase during pregnancy due to increased synthesis in the liver and decreased activity of lipoprotein lipase. LDL cholesterol increases throughout pregnancy, with a 50% increase by term. HDL cholesterol increases during the first half of pregnancy and then falls in the third trimester while still staying above non-pregnant levels. The increase in triglycerides is essential for supplying the mother’s energy while sparing glucose for the fetus. The increased LDL levels are crucial for placental steroidogenesis. There are increased caloric and nutritional requirements during pregnancy, including increased requirements for protein, iron, calcium, folate, and other vitamins and minerals. The protein requirement in pregnancy increases from 60 g/day to 70 to 75 g/day, as the amino acids are transported to the developing fetus. The calcium requirement increases to 1.5 g/day, due to the fetus requirement of 30 g of calcium. Maternal serum levels of calcium are maintained in pregnancy, with fetal needs being met by increased intestinal absorption starting at week 12. [11] Various factors (exogenously administered drugs or endogenous small molecules) that affect expression and/or activity levels of DMEs may alter CLint of drugs. Hepatic drug metabolism can be impaired by direct inhibition of enzyme activity, either by reversible or irreversible binding of inhibitors to the enzymes [29]. Altered drug metabolism during pregnancy Results from clinical pharmacokinetic studies suggest that pregnancy influences drug metabolism in a metabolic enzyme-specific manner. Elimination rates of drugs metabolized by UGT1A4, UGT2B7, CYP2A6, CYP2C9, CYP2D6 and CYP3A4 are increased, where as those of CYP1A2 and CYP2C19 substrate drugs are decreased. [30][31][32]

3.2. Calcium Metabolism

The average foetus requires about 30 g of calcium to maintain its physiological processes. Most of this calcium is transferred to the foetus during the third trimester and is derived from increased dietary absorption by the mother. [26] There is a decrease in total serum calcium concentration during pregnancy. This is mainly due to a decrease in serum albumin levels due to haemodilution, resulting in a decrease in the albumin-bound fraction of calcium. However the physiologically important fraction, serum ionized calcium, remains unchanged. [27] Therefore maternal serum levels of calcium are maintained during pregnancy and foetal needs are met by increased intestinal absorption, which doubles from 12 weeks’ gestation. However the peak demand for calcium is only in the third trimester. This early increase in calcium absorption may allow the maternal skeleton to store calcium in advance. [28] Serum levels of 25-hydroxyvitamin D increase and this is metabolised further into 1,25-dihydroxyvitamin D. The increase in 1,25-dihydroxyvitamin D is directly responsible for the increase in intestinal calcium absorption. [27] Increased calcium absorption is associated with an increase in calcium excretion in the urine and these changes begin from 12 weeks. During periods of fasting, urinary calcium values are low or normal, confirming that hypercalciiuria is the consequence of increased absorption. Pregnancy is therefore a risk factor for kidney stones. [26]
3.3. Respiratory System
During pregnancy, the diaphragm elevates, resulting in a 5% decrease in total lung capacity (TLC). However, the tidal volume (TV) increases by 30 to 40%, thereby decreasing the expiratory reserve volume by 20%. Minute ventilation is similarly increased by 30 to 40%, owing to the fact that TV becomes increased while a constant respiratory rate is maintained. The increase in minute ventilation that occurs during pregnancy allows for an increase in alveolar (PAO2) and arterial (PaO2) PO2 levels, and a decrease in PACO2 and PaCO2. PaCO2 decreases from a pre-pregnancy level of 40 mm Hg to 30 mm Hg by 20 weeks. This decrease in PaCO2 creates an increased CO2 gradient among the fetus and mother, thus enhancing oxygen delivery and carbon dioxide removal in the fetus. This gradient is created by elevated progesterone levels, which appear to act to either increase the responsiveness of the respiratory system to CO2 or to be a primary stimulant. These changes are needed to accommodate the 15% increase in metabolic rate and the 20% increase in oxygen consumption that occurs during pregnancy. Decreased PaCO2 levels, increased tidal volume, and decreased total lung capacity combine to result in dyspnea of pregnancy in approximately 60% to 70% of pregnant patients. This feeling is a subjective sensation of breathlessness with no hypoxia present. It is most common during the third trimester but can start at any time. [11]

4. Hypertension in pregnancy
Hypertension (HTN) has been identified by WHO, [33] as one of the most significant risk factors for morbidity and mortality worldwide and is responsible for the deaths of approximately 9 million people annually. [33] The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNCVI) and the World Health Organization/International Society of Hypertension guidelines subcommittees have agreed that both SBP and DBP should be used for the classification of hypertension. Systolic and diastolic hypertension is diagnosed when SBP is ≥140 mm Hg and DBP is ≥90 mm Hg. Isolated systolic hypertension (ISH) refers to an SBP of ≥140 with a DBP of <90 mm Hg. [34] [35] Treating hypertension results in significant reductions in risk of subsequent cardiovascular disease. [36] [37] Hypertension is a major public health issue, particularly in developing countries as whole. It’s now well established that over 80% of the burden of the disease is in low-income and middle income regions. [38] The prevalence of pregnancy-related hypertension in well-developed countries varies between 10-20% and it is the most important cause of maternal and fetal morbidity and mortality. [39] Hypertension in pregnancy includes a range of conditions, most notably preeclampsia, a form of hypertension unique to pregnancy that occurs de novo or may be superimposed on chronic hypertension. The other forms, chronic and gestational hypertension, usually have more benign courses. [40] In low-income and middle-income countries, preeclampsia and its convulsive form, eclampsia, are associated with 10–15% of direct maternal deaths. [41] Pregnant women with hypertension are at increased risk for experiencing numerous complications such as disseminated intravascular coagulation (DIC), cerebral hemorrhage, liver dysfunction and acute renal failure; while to the fetus, it may cause intrauterine growth retardation, prematurity and perinatal mortality. [42] Pathogenesis of preeclampsia (PE) is quite complex involving genetic, immunologic and environmental factors. The development of PE is categorized into 2 stages including abnormal placentation and maternal syndrome. [43] The classification of hypertension in pregnancy that has been commonly used is the one proposed by The National High Blood Pressure Education Program Working Group on Hypertension in Pregnancy (NHBPEP), in which hypertension is defined as blood pressure that is ≥140/90 mmHg [44] In the gestational period of pregnancy major hemodynamic changes is seen, it include an increase in the cardiac output during the first trimester, sodium and water retention leading to plasma volume expansion with a peak around week 30, and reductions in the systemic vascular resistance and systemic blood pressure. The reduction of the systemic vascular resistance is around 25% and is due to the increase in vasodilating agents, like nitric oxide and prostacyclin production, and the decrease in the sensitivity to norepinephrine and angiotensin. [45] The diastolic blood pressure begins to decrease from the 7th week of gestation, with a 10 mmHg decline between the 24th–26th gestation weeks, returning to normal values during the third trimester [46] [47]. These are some of the changes that can occur during pregnancy. Hypertension is the most prevalent maternal complication worldwide (several studies estimate that it affects 7–10% of all pregnancies) [48] [49] and it is associated with a significant morbidity and mortality of the mother and fetus. In fact, hypertension is the second largest cause of direct maternal death worldwide (14% of the total) [50] Pre-eclampsia and eclampsia are two hypertensive disorders of pregnancy, considered as major causes of maternal and perinatal morbidity and mortality [49] These diseases affect between 3% and 5% of all pregnancies and account for more than 60,000 maternal and 500,000 fetal deaths per year worldwide. It is known that pre-eclampsia and eclampsia are the hypertensive disorders that involve the most significant health risks for the pregnant woman and the fetus [51] Pre-eclampsia is a multisystemic disease characterized by the development of hypertension after 20 weeks of gestation in a previously normotensive woman, with the presence of proteinuria or, in its absence, of signs or symptoms indicative of target organ injury. The clinical signs involve multiple organs, including the liver, kidneys, heart, lungs, brain, and pancreas [52] These complications can result in maternal and fetal adverse outcomes that can lead to intrauterine growth restriction, placental hypoperfusion, premature
placental disruption or, in most serious situations, termination of pregnancy and fetal and maternal death [53][54]. This disease can be divided into mild and severe forms, according to the severity and type of the symptoms presented. The mild form of pre-eclampsia is characterized by systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg, and proteinuria >300 mg/24 h. The severe form of pre-eclampsia is characterized by severe hypertension (SBP > 160 mmHg or DBP > 110 mmHg), or severe proteinuria (>2 g/24 h), or signs and symptoms of target organ damage [55][56]. Women with severe pre-eclampsia may present headaches, visual disturbances (including blindness), epigastric pain, nausea and vomits, hepatic and renal insufficiency, and pulmonary edema [57]. Eclampsia represents the consequence of brain injuries caused by pre-eclampsia. It is defined as pre-eclampsia with the abrupt development of seizures or coma during the gestational period or post-partum, non-attributable to other neurologic diseases that can justify the convulsive state (namely epilepsy or cerebral stroke) [52]. Eclampsia is the rarest [58] and most severe [59] of all the hypertensive disorders of pregnancy, with a high maternal and fetal mortality [60]. Pre-eclampsia is associated with several complications not only during pregnancy but also in postpartum period. A broad diversity of studies has demonstrated that women who had pregnancies complicated with pre-eclampsia have, throughout live, a greater risk and incidence of cardiovascular diseases with an adjusted hazard ratio of 2.1 in a 95% confidence interval of 1.8–2.4 according to Ray and collaborators [61–63]. Major cardiovascular events, such as myocardial infarction (with an adjusted hazard ratio of 13.0 in a 95% confidence interval of 4.6–6.3), stroke (with an adjusted hazard ratio of 14.5 in a 95% confidence interval of 1.3–165.1), or heart failure (with an adjusted hazard ratio of 8.3 in a 95% confidence interval of 4.2–16.4) [64] and hospitalization related with cardiovascular events [65]. Children born from women who had pre-eclampsia during their pregnancies are also at a greater risk for cardiovascular events during their lifetime [66]. Other studies demonstrated an elevated blood pressure and body mass index in these children [67]. Therefore, pregnancy can be considered as a window for the future health of women and their children. It is known that, currently, the only definitive cure for pre-eclampsia is the delivery of the fetus, and available therapies for this disease only have symptom management purposes. For these reasons, it is of major importance that the pharmacological prophylaxis treatment is as effective and safe as possible to prevent severe forms of the disease and pre-eclampsia evolution to eclampsia, thus allowing the correct development and maturation of the fetus without risking the mother’s health and well-being. [49]

4.1. Proposed Pharmacotherapy for Mild Pre-Eclampsia.

First, it is important to differentiate first-line and second-line therapies. The first-line therapy is the one accepted as the best treatment for the disease. This therapy can also be called induction therapy, primary therapy, and primary treatment. The second-line therapy is the treatment that is given when the primary treatment does not work or stops working. For this disease, oral alphamethyldopa, 250 mg (2–3 tablets/day) or oral nifedipine, 30–60 mg in slow-release forms (once daily) can be considered as first-line treatment. Nifedipine is a calcium channel blocker described as a safe, effective, and nonteratogenic drug [68][69]. Alpha-methyldopa is an _-adrenergic receptor agonist which is also an effective and safe drug in pregnancy, but the fact that it needs to be taken more than once daily is a disadvantage with respect to nifedipine. In Portugal, alpha-methyldopa is also used as a valid and safe alternative to the calcium channel blockers like nifedipine, being used as second-line therapy for mild pre-eclampsia [55]. The NICE (National Institute for Health and Care Excellence) and NHS (National Health Services) guidelines recommend oral labetalol for mild pre-eclampsia, since this drug is the only antihypertensive drug approved in United Kingdom for pregnancy. However, other consulted guidelines recommended intravenous labetalol only for the severe form of the disease. [70]

4.2. Proposed Pharmacotherapy for Severe Pre-Eclampsia

Because of the elevated risks that this form of the disease implies for the pregnant woman, it is recommended immediate hospital admission and continuous monitoring. The antihypertensive therapy should be started promptly, and the clinicians should check for signs of imminent eclampsia (if needed, they should start a prophylactic anticonvulsive therapy). [71] The recommended first-line therapy, which is agreed by the several national and international guidelines analyzed, is intravenous labetalol [55][70][72]. The infusion should start with a bolus of 20 mg in 2 min, followed by doses between 20–80 mg every 10 min (maximum cumulative dose: 300 mg) until the blood pressure is <150/100 mmHg. The normal maintenance dose is 6–8 mL/h. The objective is to maintain the blood pressure under the referred values. [70] Labetalol is an alpha 1 and beta-adrenergic antagonist, safe to use during pregnancy in situations of severe hypertension. This drug should not be used if the patient has asthma; alternatively, oral nifedipine, 10–20 mg in immediate-release forms, can be used. Intravenous hydralazine can also be used if the pregnant woman is refractory to either labetalol or nifedipine. [55]

4.3. Proposed Pharmacotherapy for Eclampsia Prophylaxis.

The anticonvulsive therapy is the most important therapy for eclampsia. The recommended drug to use is intravenous magnesium sulfate. The infusion should start with a bolus of 4–6 g in 20 min, followed by a
maintenance dose of 2–3 g (rate of 50–75 mL/h of 50 mg/mL in a physiologic solution or glucose solution). The therapy must be maintained for 24 h after the last convulsive state, or post-partum. During the administration of this drug, it is important to control systemic magnesium levels to avoid any problems related to hypermagnesemia (in extreme cases, this can cause muscle paralysis and cardiorespiratory arrest), therefore, clinicians must constantly monitor the respiratory frequency, diuresis and patellar reflexes. Although not universally accepted, intravenous diazepam can be used as an alternative. This drug is related to greater fetal and maternal mortality and should only be used if the pregnant woman is refractory to magnesium sulfate. In Portugal, several hospitals follow this treatment with diazepam only when magnesium sulfate is contraindicated. It should be noted that, besides the anticonvulsive therapy, an antihypertensive therapy similar to the one recommended for severe pre-eclampsia is mandatory.

Table 1: Proposed Pharmacotherapy for severe pre-eclampsia.

| SEVERE PRE-ECLAMPSSIA | First Line | Second Line |
|-----------------------|------------|-------------|
|                       | Labetalol  | Nifedipine  | Hydralazine |
| • Initiate bolus 20 mg IV (2 min) | • 10–20 mg, immediate-release forms (never use sublingual administration) |
| • Repeat doses of 20–80 mg every 10 min (max cumulative dose: 300 mg) | • Bolus 5 mg IV (2 min) |
| • Maintenance dose: 6–8 mL/h (adjust between 2–12 mL/h according to patient’s evolution) from a concentration of 1 mg/mL | • Repeat doses every 20 min, until 20 mg total |
|                       |            |              | 2 mg/h |

5. Medications in pregnancy

Pregnancy can affect the effectiveness of medication. During pregnancy the blood volume increases and also the kidney and heart workload increases. Medication during pregnancy is important for reason like diabetes, seizures, depression, anxiety, and other medical conditions. Also some in common discomforts such as heartburn, morning sickness or headaches. During pregnancy the transfer of drugs occur through placenta via simple diffusion, facilitated diffusion, activated transport and pinocytosis and depends upon following factors:

5.1. Physicochemical nature of drug: Drugs having MW less than 400 cross the placental barrier faster and very easily.

5.2. Role of placental tissue: During pregnancy placental thickness decreases while surface area increases. However, the permeability is not affected.

5.3. Placental blood barrier: The rate of passage of drugs across the placenta depends upon the maternal and fetal placental flow.

6. Safer antihypertensive agents in pregnancy

The safer antihypertensive drugs are methyldopa, hydralazine and lidocaine. Methyldopa is an antihypertensive drugs of first choice in hypertension during pregnancy. It crosses the placenta but does not affect the uterine blood flow and fetus. It decreases the fetal wastage, increases the birth weight and length of gestation. Hydralazine is present in foxglove plant. It is used as a cardiac stimulant used to treat congestive heart failure. It has been found no adverse effect on the fetus so considered as a safe drug during pregnancy. Lidocaine is used in cardiac arrhythmia and it does not have any adverse effect on the fetus.

7. Antihypertensive drugs affiliated with some risk

Diazoxide is an antihypertensive agent and used as a vasodilator in an acute hypertension or malignant hypertension. It can cause the damage to the fetus by producing the sudden decrease in the blood pressure, Captopril is the first ACE inhibitor that was developed and used for the treatment of hypertension and congestive heart failure. It is given in the case when the other drug becomes ineffective. Reserpine has shown adverse effects during pregnancy and responsible for producing watery discharges and may even cause death of neonates. Nitroprusside can cause acute hypotension in fetus and may lead to death.

8. Choice of antihypertensive drug for use in pregnancy

The Food and Drug Administration reviews human and animal data to assign letter grades corresponding with risk of fetal exposure in pregnancy. Most antihypertensive agents used in pregnancy are designated as “category C,” which states that human studies are lacking, animal studies are either positive for fetal risk or are lacking, and the drug should be given only if
potential benefits justify potential risks to the fetus. [79] This category cannot be interpreted as no evidence of risk and is so broad to preclude usefulness in practice, leading some groups to suggest that the Food and Drug Administration classification be abandoned. Information is, thus, based on clinical cases, small studies, and meta-analyses. [80]-[81].

8.1. Peripherally Acting Adrenergic Receptor Antagonists

β-Blockers have been used extensively in pregnancy. Although several randomized trials comparing β-blockers with either placebo or other agents have been conducted, [82]-[83],[84]-[85] there are still some unresolved issues regarding their use in pregnancy, largely a result of a few small studies that suggest an association with lower birth weight infants. None of the β-blockers have been associated with teratogenicity. In meta-analysis and Cochrane review [86] individual agents were not distinguishable in their perinatal effects with the exception of atenolol, which in 1 small study was started at 12 to 24 weeks’ gestation and resulted in clinically significant fetal growth restriction and decreased placental weight compared with placebo. [87] This observation was supported in a subsequent retrospective review comparing atenolol with alternative therapies. [88] Given differences in β-blockers with respect to lipid solubility and receptor specificity, the potential for clinically relevant differences between agents exists but has not been investigated in pregnancy. Oral β-blockade had been associated with nonclinically significant neonatal bradycardia, [89],[90] although in a systematic review of trials, labetalol does not (along with oral methyldopa, nifedipine, or hydralazine) seem to cause neonatal heart rate effects. [91] Parenteral therapy has been found to increase the risk of neonatal bradycardia, requiring intervention in 1 of 6 newborns. [92] Further reassurance is derived from a 1-year postpartum follow-up study, which showed normal development of infants exposed to atenolol in utero. [93] Maternal outcomes are improved with the use of β-blockers, with effective control of maternal BP, decreased incidence of severe hypertension, and decreased rate of preterm admission to hospital [89]; they have been found in a recent Cochrane analysis to be more effective in lowering BP compared with methyldopa in 10 trials. [94] Labetalol, a nonselective β-blocker with vascular α1-receptor blocking capabilities, has gained wide acceptance in pregnancy. When administered orally to women with chronic hypertension, it seems as safe [94],[95],[96],[97] and effective as methyldopa, although neonatal hypoglycemia with higher doses has been reported. [98] Of some concern, 1 placebo controlled study reported an association with fetal growth restriction in the management of preeclampsia remote from term. [97] Parenterally it is used to treat severe hypertension, and because of a lower incidence of maternal hypotension and other adverse effects, its use now supplants that of hydralazine. [99] Adverse effects may be predicted as consequences of β-receptor blockade. Fatigue, lethargy, exercise intolerance (because of β2-blocking effects in skeletal muscle vasculature), peripheral vasoconstriction, sleep disturbance (with use of more lipid-soluble drugs), and bronchoconstriction may be seen; however, discontinuation because of adverse effects is uncommon. [93] Peripherally acting α-adrenergic antagonists are second-line antihypertensive drugs in non-pregnant adults. These are indicated during pregnancy in the management of hypertension because of suspected pheochromocytoma, and both prazosin and phenoxybenzamine have been used, with β-blockers used as adjunctive agents after α-blockade is accomplished. Because there is but limited experience with these agents in pregnancy, their routine use cannot be advocated. [100]-[101].

8.2. Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Antagonists

Angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blocking agents are contraindicated in the second or third trimesters because of toxicity associated with reduced perfusion of the fetal kidneys; use is associated with a fetopathy similar to that observed in Potter’s syndrome (ie, bilateral renal agenesis), including renal dysgenesis, oligohydramnios as a result of fetal oliguria, calvarial and pulmonary hypoplasia, intrauterine growth restriction, and neonatal anuric renal failure, leading to death of the fetus. [102]-[103] Angiotensin receptor blocker use in pregnancy has also caused fetal demise, attributed primarily to renal failure. [104]-[105],[106]

First-trimester exposure to ACE-I has been associated recently with a greater incidence of malformations of the cardiovascular and central nervous systems. Of 29 096 pregnancies analyzed, 209 were exposed to ACE-I in the first trimester alone, associated with a risk ratio of congenital malformation of 2.71 when compared with no antihypertensive medication or other types of antihypertensive medication. [107] Whether adverse outcomes are because of a hemodynamic effect in the fetus or specific (non-hemodynamic) requirements for angiotensin II as a fetal growth factor is unknown. As such, first-trimester use of ACE-I and angiotensin receptor blocker agent medications should be avoided. Because exposure to ACE inhibitors during the first trimester cannot be considered safe, it may be best to counsel women to switch to alternate agents while attempting to conceive. However, in those who inadvertently become pregnant while taking ACE-I or angiotensin receptor blocking agents, the risk of birth defects rises from 3% to 7%. [107]

9. Conclusion:

During pregnancy, many physiological changes takes place in terms of pharmacokinetic parameters of drugs and physiological changes. Pharmacodynamic properties of drugs are altered with great extent and effects during the period of pregnancy. Hence the administration of drugs and their dosage is closely monitored. The unique nature of physiology of pregnancy presents challenges for pharmaceutical treatment of chronic and acute
disorders and for symptom management of many complaints associated with pregnancy. It is the responsibility of all clinicians including pharmacists to counsel patients with complete, accurate and current information on the risks and benefits of using medications during pregnancy. ACEIs, Reserpine, Nitroprusside are strictly contraindicated in pregnancy. Few beta blockers, calcium channel blockers, methyldopa and some vasodilators are used in Pregnancy. However all drugs are used carefully and Adverse drug reactions are monitored time to time till delivery.

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