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Review Article

Evaluation of Physiological Changes and Pharmacokinetic Variations in Pregnancy Condition

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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.

Keywords: Physiological Changes in Pregnancy; Pharmacokinetic; Pregnancy Disorders

Introduction

There are various changes in different organ system of a pregnant body experience due to hormonal imbalances. 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-glutamyl transpeptidase (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. [1]

Cardio Vascular 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. [2] 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 [3]

Respiratory System and Arterial Blood Gases

It is important to note that the arterial partial pressure of oxygen (PaO2) is normally increased to 101–105 mmHg and that of carbon dioxide (PaCO2) decreased to 28–31 mmHg. These changes are mainly driven by the increase in minute ventilation described above. The drop of PaCO2 in the maternal circulation creates a gradient between the PaCO2 of the mother and fetus, which allows CO2 to diffuse freely from the fetus, through the placenta, and into the mother, where it can be eliminated through the maternal lungs [3]. In addition, maternal arterial blood pH is slightly increased to 7.4–7.45 and consistent with mild respiratory alkalosis. This alkalosis is partially corrected by increased renal excretion of bicarbonate, leading to reduced serum bicarbonate level between

18 and 21 meq/L, and reduced buffering capacity[3][4]. This partially compensated respiratory alkalosis slightly shifts the oxy-hemoglobin dissociation curve rightward, thereby favoring dissociation of oxygen and facilitating its transfer across the placenta, but it also may affect protein binding of some drugs [5].

Excretory System

Both renal blood flow and glomerular filtration rate (GFR) increase by 50%, as early as 14 weeks of pregnancy[6] resulting outcome is one of significant water and sodium retention during pregnancy, leading to cumulative retention of almost a gram of sodium, and a hefty increase in total body water by 6–8 l including up to 1.5 l in plasma volume and 3.5 l in the fetus, placenta, and amniotic fluid. This "dilutional effect" leads to mildly reduced serum sodium (concentration of 135–138 meq/L compared with 135–145 meq/L in non-pregnant women) as well as serum osmolarity (normal value in pregnancy ~280 mOsm/L compared with 286–289 mOsm/L in non-pregnant women.[7]. Another consequence of this volume expansion is reduced in peak serum concentrations (Cmax) of many hydrophilic drugs, particularly if the drug has a relatively small volume of distribution. The increase in renal clearance can have significant increase (20–65%) in the elimination rates of renally cleared medications leading to shorter half-lives. For example, the clearance of lithium, which used to treat bipolar disorder, is doubled during the third trimester of pregnancy compared with the non-pregnant state, leading to sub-therapeutic drug concentrations [3][7]

Gastrointestinal System

In pregnancy, the rise in progesterone leads to delayed gastric emptying and prolonged small bowel transit time, by ~30–50%. Increased gastric pressure, caused by delayed emptying as well as compression from the gravid uterus, along with reduced resting muscle tone of the lower esophageal sphincter, sets the stage for gastro-esophageal reflux during pregnancy [8]. In addition, these changes alter bioavailability parameters like Cmax and time to maximum concentration (Tmax) of orally administered medications [9]. The decrease in Cmax and increase in Tmax are especially concerning for medications that are taken as a single dose, because a rapid onset of action is typically desired for these medications [10]. Drug absorption is also decreased by nausea and vomiting early in pregnancy. This results in lower plasma drug concentrations. For this reason, patients with nausea and vomiting of pregnancy (NVP) are routinely advised to take their medications when nausea is minimal. Moreover, the increased prevalence of constipation and the use of opiate medications to ease pain during labor slow gastrointestinal motility, and delay small intestine drug absorption. This may lead to elevated plasma drug levels postpartum [11]. The increase in gastric pH may increase ionization of weak acids, reducing their absorption. In addition, drug-drug interaction becomes important as antacids and iron may chelate co-administered drugs, which further decreases their already reduced absorption [12]. The increase in estrogen in pregnancy leads to increase in serum concentrations of cholesterol, ceruloplasmin, thyroid binding globulin, and cortisol binding globulin, fibrinogen and many other clotting factors [13]. Serum alkaline phosphatase is elevated during pregnancy as it is also produced by the placenta, and its levels in pregnant women may be two to four times those of non-pregnant individuals; therefore limiting its clinical utility when liver function or enzymes are assayed [3][13]. The rest of liver function tests such as serum transaminases (SGOT, SGPT), lactate dehydrogenase, bilirubin, and gamma-glutamyl transferase are not affected [13].

Haemopoitic System in pregnancy

White (WBC) and red blood cell (RBC) counts increase during pregnancy. The first is thought to be secondary to bone marrow granulopoiesis; whereas the 30% increase in RBC mass (250–450 mL) is mainly driven by the increase in erythropoietin production. The higher WBC count can sometimes make diagnosis of infection challenging; however normally the increase in WBC is not associated with significant increase in bands or other immature WBC forms [3]. Despite the increase in RBC mass, and as previously described, plasma volume increases significantly much higher (~45%), which leads to "physiologic anemia" of pregnancy. Anemia usually peaks early in the third trimester (30–32 weeks) and may become clinically significant in patients already anemic (iron deficiency, thalassemia, etc.) at entry to pregnancy [14][15] 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[3] 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[3][16]

Endocrine Changes in Pregnancy:

Plasma iodide concentration decreases in pregnancy because of fetal use and increase in maternal clearance of iodide. This predisposes the thyroid gland to increase in size and volume in almost 15% of women. In addition to anatomic changes, the thyroid gland increases production of thyroid hormones during pregnancy. This is due to the up-regulation of thyroid binding globulin, which is the major thyroid hormone binding protein, by almost 150% from a pre-pregnancy concentration of 15–16 mg/L to 30–40 mg/L in mid-gestation. This massive increase is driven by the hyper-estrogenic milieu in pregnancy and reduced hepatic clearance. The net result is increase in total tetra-iodothyronin andtri-iodothyronin hormones (TT4 and TT3) in pregnancy. Despite the increase in total T4 and T3, the free forms of the hormones (fT4and fT3) remain relatively stable

or slightly decreased but remain within normal values and these patients are clinically euthyroid [3][17-19] For patients with hypothyroidism and who require levothyroxine replacement in pregnancy, it is recommended that they increase their levothyroxine dose by30% early in pregnancy, be monitored during pregnancy, and to decrease the dose in the postpartum period. The offspring of diabetic mothers are prone to obesity in childhood [20] and diabetes later in life [21], but little is known about the underlying biological mechanisms.

Common Disorders Associated with Pregnancy

Hyperemesis Gravidarum. Hyperemesis gravidarum occurs in 0.3% to 2% of pregnancies, usually within the first trimester. Serum aminotransferases can be elevated by up to 20 times the upper limit of normal. Jaundice is rare. Liver function tests normalize after the resolution of vomiting. Treatment is supportive with thiamine supplements, fluid replacement, and antiemetics. [22] Preeclampsia and HELLP Syndrome. Approximately 10% of women with severe preeclampsia have hepatic involvement. [23] Women may have right upper-quadrant pain resultant from hepatic ischemia. Tight control of blood pressure is essential, but hepatic involvement signifies the development of severe preeclampsia, and delivery should be undertaken. Laboratory abnormalities may worsen before improving and usually normalize within 2 weeks of delivery. Five percent to 10% of women with preeclampsia develop HELLP syndrome (hemolysis, elevated liver enzymes, low platelets). [24][25]

Hepatic Drug Metabolism Changes

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[26] 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, whereas those of CYP1A2 and CYP2C19 substrate drugs are decreased [27][28][29]

Alterations in 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[30]. 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[31]. 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[32][33]

- **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)[34]

- **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 osmoregulation, growth, reproduction, immuno 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 [35, 36]

- **Cortisol**

Cortisol in plasma is mostly bound to corticosteroid-binding globulin (CBG) (75%) and to a lesser extent to albumin (15%). In pregnancy, plasma levels of CBG rise about 2-fold as compared to no pregnant women which increases concentrations of total cortisol. Concentrations of biologically active, free cortisol are also elevated to 20-30 μg/dL (0.5-0.8μM), partly due to marked increase in corticotropin-releasing hormone (CRH) during pregnancy. This free cortisol concentration is about 3-fold higher than that in non-pregnant women. [37-39]. In pregnant women, the higher concentrations of cortisol likely enhance activation of GR, leading to up-regulation of CAR and PXR expression. This may in turn potentiate the induction of CYP expression by other endogenous hormones such as GH-like hormones or female hormones (estrogen and progesterone). For example, CAR-mediated activation ofCYP2B6 by estrogens may be further enhanced by increased expression of CAR by the higher cortisol levels during pregnancy. Although further confirmatory studies are needed, this appears to provide additional potential mechanism underlying the increased elimination of substrates for PXR or CAR target genes, e.g., CYP2C9 and CYP3A4, in pregnant women [39].

Conclusion

Pregnancy is very important phase of life as utmost care should be taken. During pregnancy, many physiological changes take 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 The endocrine disorders are more prone in pregnancy such as diabetes, abnormal thyroid functions, cardiovascular changes, adrenal gland etc. Treating the underlying conditions with proper approaches in lifestyle modifications and pharmacological aids are very crucial for entire pregnancy.

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