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Effect Study of Physiological changes of a Pregnant Woman

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Abstract

Understating these changes and their profound impact on the pharmacokinetic properties of drugs in pregnancy is essential to optimize maternal and fetal health. During normal pregnancy, the renin–angiotensin system (RAS) plays a vitally important role in salt balance and subsequent well-being of mother and fetus. In this balance, one must consider not only the classical renal RAS but also that of the uteroplacental unit, where both maternal and fetal tissues contribute to the signaling cascade. Many studies have shown that in normal pregnancy there is an increase in almost all of the components of the RAS. In derangements of pregnancy this delicate equilibrium can become unbalanced. Preeclampsia is one such case. It is a disorder of pregnancy characterized by hypertension, proteinuria and placental abnormalities associated with shallow trophoblast invasion and impaired spiral artery remodeling. Changes in the cardiovascular system in pregnancy are profound and begin early in pregnancy, such that by eight weeks' gestation, the cardiac output has already increased by 20%. The primary event is probably peripheral vasodilatation. This is mediated by endothelium-dependent factors, including nitric oxide synthesis, upregulated by oestradiol and possibly vasodilatory prostaglandins (PGI2). There is a significant increase in oxygen demand during normal pregnancy. This is due to a 15% increase in the metabolic rate and a 20% increased consumption of oxygen.

Keywords: Pharmacokinetic, vasodilatory, consumption, upregulated, proteinuria.

Introduction

Physiologic changes in pregnancy induce profound alterations to the pharmacokinetic properties of many medications. These changes affect distribution, absorption, metabolism, and excretion of drugs, and thus may impact their pharmacodynamic properties during pregnancy. Pregnant women undergo several adaptations in many organ systems. Some adaptations are secondary to hormonal changes in pregnancy, while others occur to support the gravid woman and her developing fetus. Some of the changes in maternal physiology during pregnancy include, for example, increased maternal fat and total body water, decreased plasma protein concentrations, especially albumin, increased maternal blood volume, cardiac output, and blood flow to the kidneys and uteroplacental unit, and decreased blood pressure. The maternal blood volume expansion occurs at a larger proportion than the increase in red blood cell mass, which results in physiologic anemia and hemodilution. Other physiologic changes include increased tidal volume, partially compensated respiratory alkalosis, delayed gastric emptying and gastrointestinal motility, and altered activity of hepatic drug metabolizing enzymes. Understating these changes and their profound impact on the pharmacokinetic properties of drugs in pregnancy is essential to optimize maternal and fetal health.[1]

1- Renal System

During normal pregnancy, the renin–angiotensin system (RAS) plays a vitally important role in salt balance and subsequent well-being of mother and fetus. In this balance, one must consider not only the classical renal RAS but also that of the uteroplacental unit, where both maternal and fetal tissues contribute to the signaling cascade. Many studies have shown

that in normal pregnancy there is an increase in almost all of the components of the RAS. In derangements of pregnancy this delicate equilibrium can become unbalanced. Preeclampsia is one such case. It is a disorder of pregnancy characterized by hypertension, proteinuria and placental abnormalities associated with shallow trophoblast invasion and impaired spiral artery remodeling. Despite being a leading cause of maternal death and a major contributor to maternal and perinatal morbidity, the mechanisms responsible for the pathogenesis of preeclampsia are poorly understood. Immunological mechanisms and the RAS have been long considered to be involved in the development of preeclampsia. Numerous recent studies demonstrate the presence of the angiotensin II type I receptor agonistic autoantibody (AT_1-AA). This autoantibody can induce many key features of the disorder and upregulate molecules involved in the pathogenesis of preeclampsia. Here we review the functional role of the RAS during pregnancy and the impact of AT_1-AA on preeclampsia.[2]

The kidneys are also mainly involved in water and sodium osmoregulation. Vasodilatory prostaglandins, atrial natriuretic factor, and progesterone favor natriuresis; whereas aldosterone and estrogen favor sodium retention Although elevated GFR leads to additional sodium wasting, the higher level of aldosterone, which reabsorbs sodium in the distal nephron, offsets this wasting The 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 womenAnother 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.[3]

2 - cardiovascular system

Changes in the cardiovascular system in pregnancy are profound and begin early in pregnancy, such that by eight weeks' gestation, the cardiac output has already increased by 20%. The primary event is probably peripheral vasodilatation. This is mediated by endothelium-dependent factors, including nitric oxide synthesis, upregulated by oestradiol and possibly vasodilatory prostaglandins (PGI2). Peripheral vasodilation leads to a 25–30% fall in systemic vascular resistance, and to compensate for this, cardiac output increases by around 40% during pregnancy. This is achieved predominantly via an increase in stroke volume, but also to a lesser extent, an increase in heart rate. The maximum cardiac output is found at about 20–28 weeks' gestation. There is a minimal fall at term. [4]

Reduced cardiac output is associated with a reduction in uterine blood flow and therefore in placental perfusion, which could compromise the foetus. [5]

Pulmonary vascular resistance (PVR), like systemic vascular resistance (SVR), decreases significantly in normal pregnancy. Although there is no increase in pulmonary capillary wedge pressure (PCWP), serum colloid osmotic pressure is reduced by 10–15%. The colloid osmotic pressure/pulmonary capillary wedge pressure gradient is reduced by about 30%, making pregnant women particularly susceptible to pulmonary oedema. Pulmonary oedema will be precipitated if there is either an increase in cardiac pre-load (such as infusion of fluids) or increased pulmonary capillary permeability (such as in pre-eclampsia) or both.[6]

Labour is associated with further increases in cardiac output (15% in the first stage and 50% in the second stage) Uterine contractions lead to an auto-transfusion of 300–500 ml of blood back into the circulation and the sympathetic response to pain and anxiety further elevate the heart rate and blood pressure.

Cardiac output increases by 60–80%, followed by a rapid decline to pre-labour values within about one hour of delivery. Transfer of fluid from the extravascular space increases venous return and stroke volume further.[7]

The above physiological changes lead to changes on cardiovascular examination that may be misinterpreted as pathological by those unfamiliar with pregnancy. Changes may include a bounding or collapsing pulse and an ejection systolic murmur, present in over 90% of pregnant women. The murmur may be loud and audible all over the precordium, with

the first heart sound loud and possibly sometimes a third heart sound. There may be ectopic beats and peripheral oedema.[8]

Normal findings on ECG in pregnancy that may partly relate to changes in the position of the heart include:

- atrial and ventricular ectopics
- Q wave (small) and inverted T wave in lead III
- ST-segment depression and T-wave inversion in the inferior and lateral leads
- left-axis shift of QRS.

3 - Respiratory System

There is a significant increase in oxygen demand during normal pregnancy. This is due to a 15% increase in the metabolic rate and a 20% increased consumption of oxygen. There is a 40–50% increase in minute ventilation, mostly due to an increase in tidal volume, rather than in the respiratory rate. This maternal hyperventilation causes arterial pO2 to increase and arterial pCO_2 to fall, with a compensatory fall in serum bicarbonate to 18–22 mmol/l (see Table 1). A mild fully compensated respiratory alkalosis is therefore normal in pregnancy (arterial pH 7.44).[9]

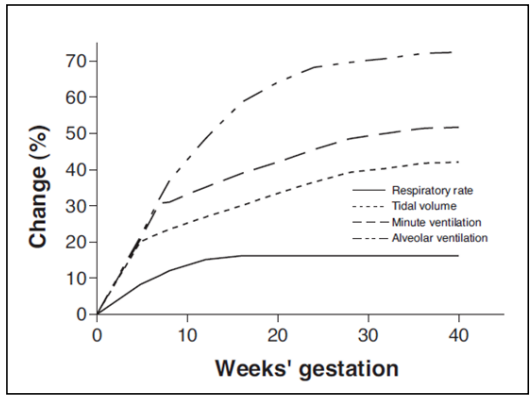
Table 1

1. Reference ranges for respiratory function in pregnancy

	Normal values	
Investigations	**Pregnant**	**Non-pregnant**
pH	7.40–7.47	7.35–7.45
pCO_2, mmHg (kPa)	≤ 30 (3.6–4.3)	35–40 (4.7–6.0)
pO_2, mmHg (kPa)	100–104 (12.6–14.0)	90–100 (10.6–14.0)
Base excess	No change	+2 to –2
Bicarbonate (mmol/l)	18–22	20–28

Changes in the respiratory system may be categorised as anatomical and physiological. Anatomical changes include capillary engorgement and oedema of the upper airway down to the pharynx, false cords, glottis and arytenoids. These changes are important to the anaesthetist as oedema in the air

Way makes upper airway obstruction and bleeding more likely during mask anaesthesia and may make tracheal intubation more difficult. A smaller diameter endotracheal tube may be required. The diaphragm is progressively displaced cranially by the gravid uterus. An increase in the diameter of the chest ensures that minute ventilation rises during pregnancy. However, diaphragmatic movement is reduced in late pregnancy, particularly in the supine position. Reports in the literature suggest failure to intubate the trachea is 7 times more common in the term parturient compared to non-pregnant patients. The reduced functional residual capacity causes airway closure in 50% of parturientsat term in the supine position. Thus, pre-oxygenation is less effective in the term parturient and desaturation is likely to occur much faster than in the non-pregnant patient. Apre-oxygenation period of 3–5 min is the standard recommendation. [10]



The increases in respiratory rate and tidal volumes result in increases in both alveolar and minute ventilation. Consequently, there is a fall in PaCO2 that plateaus at 4.1 kPa by the end of the first trimester. PaO2 rises to 14 kPaduring the third trimester but then falls to < 13.5 kPa at term because increased oxygen consumption is no longer full compensated for by the rise in cardiac output. Thus, the alveolar arterial oxygen gradient increases. In some parturients, this may be worsened by aortocaval compression and closure of dependent airways. At term, oxygen consumption and carbon dioxide production are increased by 60% above nonpregnantvalues.[11]

4 - Changes in the Ocular System

Pregnancy is often associated with ocular changes which may be more commonly transient but occasionally, permanent. The ocular effects of pregnancy may be physiological or pathological or may be modifications of pre-existing conditions. Physiological changes include increased pigmentation around the cheeks, ptosis, changes in

cornea and refractive status, decreased intraocular pressure. These usually resolve post partum. Pre-existing diseases such as Graves' disease, Retinitis pigmentosa, Optic neuritis, should be monitored due to their remission or relapses in pregnancy. There may be worsening of Diabetic retinopathy, and Central serous chorio-retinopathy with increased risk of Retinal detachment. Conditions like Glaucoma and Non infectiousuveal inflammatory disorders may even improve transiently. Pre-eclampsia and eclampsia could result in hypertensive retinopathy, exudative retinal detachment and cortical blindness. Neuro-ophthalmological disorders such as venous sinus thrombosis, benign intracranial hypertension, pituitary adenoma, meningioma and optic neuritis should be kept in mind as differential diagnosis in pregnant women presenting with visual acuity loss, visual field loss, persistent headaches or oculomotor palsies. Use of ophthalmic drugs can affect fetal health during pregnancy.[12]

Intraocular pressure has been shown to decrease during pregnancy;this is related to (1) increased progesterone levels,(2) the presence of relaxin, and (3) decreased production ofaqueous humor due to increased secretion of human chorionicgonadotropin. Changes in intraocular pressure in parturientsmay produce visual disturbances as well as contact lensintolerance.[13]

5 - Changes in the Gastrointestinal System

The enlarging uterus displaces and disrupts the lower esophageal sphincter, and progesterone relaxes this highpressurezone, causing a progressive increase in the incidence of heartburn (up to 80% at term). An increase in gastric pressure due to mechanical compression also contributes to heartburn. Despite the prevalence of this symptom, total acid production is decreased (although placental production of gastrin increases the total concentration of this hormone). Opioids administered by any route will further increase the gastric emptying time. Studies demonstrate solid food in the stomachs of laboring women even after 18 h of fasting. 17 Gastric emptying remains abnormal on the first postpartum day but returns to normal on the second day. Hepatic transaminases, bilirubin, and LDH are increased slightly in pregnancy. Alkaline phosphatase is markedly increased (2–4 fold), but due to placental production, not hepatic changes. Serum cholinesterase activity is reduced 24%before delivery and reaches a nadir (33% reduction) on thethird postpartum day14 (Fig. 1-3). Approximately 11% of post[14]

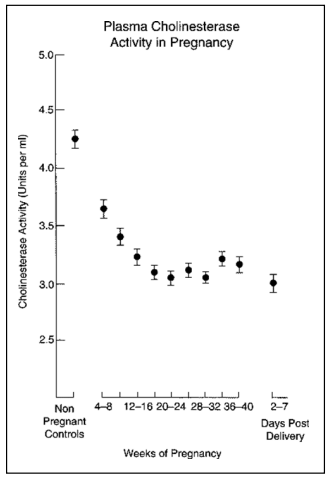


Figure. Plasma cholinesterase activity in pregnancy. (From Cohen.18 Used with permission from Elsevier.) partum women exhibit clinically deficient activity, manifest as an exaggerated response to normal doses of succinylcholine.[15]

Even with this lower activity, normal dosing of succinylcholine for intubation is recommended when general anesthesia is required, though use of a peripheral nerve stimulator seems prudent.

Gallbladder function and emptying are impaired during pregnancy, and there is evidence that pregnant women may be more prone to gallstones.[16]

6 - Changes in the Central and PeripheralNervous Systems

The central and peripheral nervous systems undergo significantchanges during pregnancy. MAC is decreased by 25–40% duringnpregnancy.Increased progesterone and endorphin concentrationsduring pregnancy have been implicated as a causeof this change. However, a few studies have shown that endorphinconcentrations do not increase until the onset of activelabor,21 so this cannot explain early decreases in MAC. Byinjecting exogenous progesterone in oophorectomized rabbits,a decrease in MAC was observed when compared with controlanimals. The factors suggested werecompensated respiratory alkalosis of pregnancy, reducedplasma and cerebrospinal fluid (CSF) protein levels duringpregnancy, leading to increased free local anesthetic, andpregnancy hormones. The latter

is the most likely explanation,based on animal studies. An increased sensitivity tobupivacaine in isolated nerve fibers has been demonstrated. [17] It is possible that progesterone or one of its activemetabolites is responsible for the observed increased sensitivityof the peripheral nervous system to anesthetics inparturients. This increased sensitivity was also observed innerves from oophorectomized rabbits treated chronically withexogenous progesterone. Interestingly, this phenomenon wasnot observed following acute exposure to progesterone. Inhumans, enhanced sensitivity of peripheral nerves to localanesthetic has also been documented.[18]

7 - Hematologic and Coagulation Systems

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 [19]. 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 [20]. This physiologic hemodilution may provide survival advantage to women during pregnancy and childbirth, since the less viscous blood improves uterine and intervillous perfusion, while the increased red cell mass, coupled with increased uterine blood flow, optimizes oxygen transport to the fetus, and at the same time the blood lost during delivery will be more dilute [21]. The increase in RBC mass is accompanied by increased in maternal demand of iron by an additional 500 mg during pregnancy. This is coupled with an additional 300 mg of iron that is transferred to the fetus and 200 mg that is required for normal daily iron losses, making the total iron requirement in pregnancy around 1 g [22].

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 [23]. Anti-thrombin III levels do not change, however, plasminogen activator levels are decreased and those of plasminogen activator inhibitor (PAI-1) levels increased by 2–3 fold, leading to suppressed fibrinolytic state in pregnancy. 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 [24].

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Ethical Clearance: This study is ethically approved by the Institutional ethical Committee.

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