

## **CHANGES IN THE LIVER DURING PREGNANCY**

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### **ABSTRACT**

The liver is the largest unpaired organ in the abdominal cavity and at the same time the largest gland in the human body. Pregnancy is a condition related with the implementation of numerous adaptive changes in the mother's organism which enable proper development of the foetus.

The objective of the study was to collect and present on the basis of available literature, information on changes in the mother's liver in the course of physiological pregnancy.

The liver's dimensions and histological structure remain unchanged during pregnancy, yet pregnancy may induce changes similar to those observed in various liver conditions. Pregnancy may influence the production and extraction of bile acids, and, due to high oestrogen levels, lead to mild cholestasis. Also, during the course of pregnancy, there is an observable increase in the level of proteins produced by the liver.

**Key words:** pregnancy, liver, patophysiology.

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## INTRODUCTION

The liver is the largest parenchymal organ in the body. It plays a major role in metabolism (approx. 500 functions). It is composed of a connective tissue holding numerous blood vessels, lymphatic vessels and nerves, as well as a parenchyma consisting of hepatic cells (hepatocytes), Browicz-Kupffer cells and perisinusoidal stellate cells (Ito).

The liver is characterised by several unique properties [1], including: its regenerative possibilities, rich dual vascularization and a homogenous structure that ensures the efficient functioning of the entire organ with its segment being excluded from physiological activity. Moreover, it participates in inflammatory processes mainly as a part of the innate immune response (acute phase, complement, heat shock proteins).

These characteristic features result from the properties of hepatocytes, i.e. cells forming in the liver. They have a unique proliferation and a high adhesive capability. Additionally, they are characterized by a broadly understood autonomy, enabling the fulfilment of their functions outside the liver in an ectopic manner.

Hepatocytes are polyhedral cells with the dimensions of 20x30  $\mu\text{m}$  and a round nucleus. From 30% to 80% hepatocytes contain polyploid nuclei and approx. 25% are characterised by having two nuclei. The average hepatocyte life span is a minimum of 150 days.

The cytoplasm is acidophilic. It contains 1-2 thousand mitochondria, whose biological half life lasts 10 days; ca. 50 thousand Golgi apparatus dictyosomes and a developed smooth and rough endoplasmic reticulum; ca. 400 peroxisomes and numerous glycogen granules (glycosomes), bile pigment granules and ribosome build-ups [2].

Hepatocytes are the major functional cells of the liver with 3 main surfaces: The sinusoidal surface constitutes 70% of hepatocyte area and is separated from the sinusoids by the Disse space. The intercellular surface covers 15% of the hepatocyte area and constitutes the place through which bile moves from the hepatocyte into the biliary canaliculus.

The basal-side surface comprises 15% of a hepatocyte and is located in the area between neighbouring hepatocytes where the hepatocyte is not in contact with a sinusoidal vessel or a biliary canaliculus.

Hepatocytes are organised as lamellae with sinusoidal capillary vessels situated between them (sinusoids). Sinusoids contain blood from further branches of the hepatic artery and the portal vein. Blood from the sinuses flows into central veins.

The gall produced by hepatocytes passes to cholangioles, and then to small bile ducts connected with circumlobular ducts. Hepatocytes fulfill the greatest number of functions as compared with all the remaining cells of the human organism.

For instance, they participate in glucose metabolism (take glucose from the blood and synthesize glycogen through glycogen synthase, perform glycogenolysis and gluconeogenesis); they participate in lipid metabolism (produce cholesterol, triglycerides and phospholipids and combine them with apolipoproteins to produce lipoproteins so that they can be transported in the aquatic environment); they take part in protein and peptide metabolism (e.g. they synthesize and break down: albumin, prothrombin, fibrinogen, haptoglobin, hemopexin, transferrin, alpha-fetoprotein, C-reactive protein, peptide-hepcidin); they participate in the extraction of gall which causes fat emulsification thus facilitating its digestion; they take part in detoxication and drug inactivation. Hepatocytes release peptide hormones (somatomedin C stimulating mitosis and synthesis of proteoglycans in chondrocytes, thus having an effect on body growth, as well as erythropoietin stimulating erythropoiesis) and, moreover, store and, whenever necessary, release into the blood vitamins A, D3, B2, B4, B12, K and conduct the vitamin D3 hydroxylation.

Ca. 500 ml of blood from the hepatic artery of nutritional significance flows through the liver every minute, and nearly twice as much blood from the portal vein with functional significance, which constitutes almost 25% of heart capacity per minute. Such a dual supply system causes the area of exchange between the liver parenchyma and the vessels to reach ca. 400m<sup>2</sup>.

The basic morphological liver unit is a lobule with the shape of a multilateral pyramid whose periphery is marked out by the hepatic portal and bile areas. Inside each lobule there is a central vein collecting blood from the surrounding parenchyma. Lobule edges consist of connective tissue fibres surrounded by hepatocyte strips called trabeculae. Within the trabeculae, hepatocytes are organised in a single layer, connected to one another with specialised 'tight junctions' and desmosomes.

Recently it has been stipulated that the liver structure is better represented by a liver acinus which is smaller than the lobule. It consists of adherent parts of two neighbouring lobules supplied with blood through the branches of the portal vein and the hepatic artery.

Within the acinus we may distinguish three zones, depending on their distance from veins in the portal-bile area. The concept of the acinus being the basic liver structure is justified by the fact that the hepatocyte regeneration zone, the highest biological activity and their best nutrition, are all realized in the proximity of the most favourable blood and oxygen supply, i.e. near the portal-bile area.

In the course of the physiological development of the pregnancy, numerous adaptive changes occur in a woman's body aimed at ensuring the best conditions for foetus' development, but also changes resulting from the mother's own defence against the harmful invasion of the tissues of the ovum.

The said changes result from the activity of various hormones on a woman's organism disturbing the previous homeostasis and appearing in all organs.

The objective of the study was to present information on mothers' livers in the course of a physiological pregnancy. The work presents the most recent findings regarding the subject matter in question.

In the course of physiological pregnancy numerous adaptive changes occur in a woman's organism aimed at ensuring best conditions for foetal development, but also changes resulting from the mother's own defence against the harmful invasion of the tissues of the ovum. The said changes result from the activity of various hormones on a woman's organism disturbing the previous homeostasis and appearing in all organs.

Already in the first weeks of pregnancy there are visible changes in the functioning of the cardiovascular system. These are mainly caused by high progesterone concentrations produced by corpus luteum, and later also by the placenta and other placental hormones, i.e. estrogens, placental lactogen, prostaglandins [3] and relaxins produced by the ovaries [4].

A vital role in the functioning of the cardiovascular system during pregnancy is played by arachidonic acid derivatives: prostacyclin (PG12) and thromboxan A2 (TX A2). Prostacyclin has a vasodilating effect and inhibits uterine contractility. TX A2, on the other hand, has the opposite effect, i.e. it increases the blood platelets aggregation, is a powerful vessel constrictor [5] and stimulates uterine contractility.

During physiological pregnancy, PG12 generation is nearly twice as high as compared with TX A2. Consequently, by its impact on smooth muscle tissues, the peripheral vessels become dilated and the blood pressure is decreased. Prostaglandins reduce the vascular walls' sensitivity to angiotensin II pressor activity. Moreover, the blood pressure decrease experienced during pregnancy is also related to the activity of the relaxin hormone.

The stimulation of endothelial cells towards nitric oxide production enhances vascular diameter, which results in a better blood flow through the organs and a blood pressure decrease [4].

During pregnancy cardiac hypertrophy is a regular phenomenon leading to the shortening of the relaxation time of the myocardium and a diastolic heart dysfunction. Thus, cardiac activity becomes accelerated, whereas a growth of the volume of circulating blood results in an increase of cardiac minute output.

After the delivery the heart muscle returns to its former activity mode, i.e. from the period preceding pregnancy. During physiological pregnancy the volume of circulating blood plasma increases by ca. 1.5 litres. This process commences in the 12<sup>th</sup> week of pregnancy and reaches its peak around the 32<sup>nd</sup> week, after which it becomes gradually normalized.

The total increase of the volume of circulating blood is estimated at 20%-25% in relation to the initial value, where at the end of pregnancy water retention may even reach 6 to 8.5 l. Hypervolemia is caused by a high activity of the antidiuretic hormone (ADH) as well as the renin-angiotensin-aldosterone system (RAA) responsible for sodium retention. Sodium inhibits water extraction and contributes to its retention in an organism [6].

Angiotensin and aldosterone activity during pregnancy is twice as high, whereas plasma renin activity grows by as much as 5-10 times [3].

Changes within the cardiovascular system constitute the main factor having an impact on the work and functioning of the remaining organs in a pregnant woman's body.

For example, a symptom observed during pregnancy is a reduction of protein concentration in the plasma. Depending on how advanced the pregnancy is, their level varies between 5 - 6g in 100 ml of blood, i.e. ca. by 1g less as compared with the period from before pregnancy.

This is related to an increase of circulating plasma and the thinning of blood components. The number of erythrocytes rises as a result of an increased secretion of erythropoietin by the kidneys, yet, despite a significantly increased plasma volume, a relative anaemia occurs with its escalation particularly around the 32<sup>nd</sup> week of pregnancy.

Erythropoietin secretion does not stem from hypoxaemia (hyperventilation) or anaemia but is a result of a violated hormonal balance (human placental lactogen HPL) [7].

During pregnancy there is a growth in the number of leukocytes and blood platelets.

Changes taking place within the respiratory system happen with the goal of providing the foetus with a proper amount of oxygen. With an increase in both the lung capacity and the number of breaths taken per minute, the organism of a pregnant woman increases its ventilation per minute by up to 40%. Such changes are induced for instance by an increased progesterone concentration.

The respiratory centre is more sensitive to higher carbon dioxide levels in the blood, which in ABG tests is revealed in a reduced CO<sub>2</sub> pressure and respiratory alkalosis, and clinically in hyperventilation of pregnant women.

This adaptive change, facilitating carbon dioxide diffusion from the foetus's blood to the mother, ensures optimal oxygen concentration in foetal circulation.

Every organism aims at maintaining proper parameters of the acid-base homeostasis, including the pH value of the blood. For the purpose of levelling respiratory alkalosis a compensatory metabolic acidosis is evoked in the organism of a pregnant woman. An excess of produced bicarbonates is secreted by the kidneys [3].

Also, pregnancy causes a change in the structure and functioning of the kidneys due to an increased blood flow. In the 34<sup>th</sup> week of pregnancy the blood flow increases by as much as 75% [7].

Kidney filtration rises to approx. 150-200 ml/min causing a reduction in creatinine concentration in the blood serum by ca. 0.4 mg/dl. This is crucial in test results interpretation since creatinine values recognised as regular in non-pregnant women may suggest renal failure during pregnancy.

Changes in the kidneys also have an impact on the functions of renal tubules, altering the filtration and excretion of numerous substances. During pregnancy we may also observe physiological proteinuria and glycosuria, though many researchers claim that proteinuria, albuminuria or microalbuminuria should not occur at all. However, commonly it is adopted that after the 20<sup>th</sup> week of pregnancy a slight proteinuria not exceeding 300 mg per day is a physiological condition, whose main cause is not to be sought in kidney dysfunction but in an increased glomerular filtration (GFR) [8]. Pregnancy-related adaptive changes occurring in kidneys recede several weeks after the delivery of the child.

The hormonal changes taking place during pregnancy and the growing and developing foetus also have an influence on the alimentary system of a pregnant woman. The growing uterus causes the intestines and stomach to be pushed up and to the sides.

Sex hormones have only a slight impact on intestinal absorption and secretion processes; however, they have a significant influence on the activity of the alimentary tract.

They cause an increased saliva production, which contributes to better digestion and flavour perception [9]. Other frequently observed changes include gingiva swelling, bleeding or gingivitis providing favourable conditions for dental caries. However, the immediate cause of dental caries connected with tooth demineralization during pregnancy has not been identified.

As a result of progesterone activity, pregnancy also increases the risk of gallstone evoking cholestasis. Moreover, a decelerated motor activity of the alimentary tract leads to an impeded sphincter activity and causes chyme to move back to the oesophagus, which is the immediate cause of heartburn.

Pregnancy hormones also affect the work of internal secretion organs. In the thyroid the concentration of protein-related iodine as well as protein-transporting thyroxine become increased. The renal cortex increases glyocorticosteroid excretion by 100%, and the production of mineralcorticoids slightly grows as well.

Under the influence of estrogens the concentration of transcortin responsible for the number of thyroxine-transporting proteins is also elevated, which protects the pregnant woman from cortisol excess or deficiency. Cortisol stimulates endogenous glucose production and glycogen storage.

Moreover it reduces glucose utilization, thus having an effect on insulin efficacy. During pregnancy, especially at its late stage, there is an observable hyperplasia of Langerhans's islets and an increased insulin release due to high prolactin concentration in the blood serum. High estradiol and progesterone concentration during a healthy pregnancy contributes to the development of insulin resistance [10].

The typical physiological conditions observed during pregnancy are hyperinsulinemia and insulin resistance [11, 12].

Physiological hypoglycemia, characteristic of this period, is caused by a continuous glucose uptake by the foetus and, at the same time, by its reduced consumption by the muscle and adipose tissue of the pregnant woman's body due to insulin resistance. Quite often, due to metabolic disorders, the pregnant develop diabetes, which recedes after the delivery of the child.

Women that experienced diabetes should undergo periodic sugar level checks, as they are at a greater risk of suffering from this disease at an older age.

### LIVER DURING PREGNANCY

In the course of a pregnancy the liver reveals no specific structural changes. Despite an increased activity of the cardiovascular system, the flow of blood through the liver is preserved at the same unchanged level.

During pregnancy the liver's metabolism is significantly elevated because of progesterone and estradiol. At the beginning of the 1<sup>st</sup> trimester the albumin level decreases, which is connected with the hemodilution phenomenon resulting from an increased volume of circulating plasma.

The liver produces greater quantities of some proteins, for instance,  $\alpha$ -2 macroglobulin,  $\alpha$ -1 antitrypsin and ceruloplasmin. Also, there is a substantial increase in the production of coagulation factors, in particular: II, VIII, IX and XII, as well as a reduction in S protein levels, which leads to fibrinolysis inhibition.

This mechanism aims at protecting a woman from excess blood loss in labour, while at the same time, it may be the reason for thromboembolic complications during pregnancy [13, 14].

At the end of pregnancy the levels of cholesterol, triglycerides and phospholipids in the blood serum become elevated, which is a symptom of metabolic adjustment of a woman's body towards saving glucose for the developing foetus.

During the entire period of the pregnancy, the bilirubin level in the blood is lower as compared with that in non-pregnant women. This is partially due to hemodilution, which reduces the level of albumins, i.e. the main proteins transporting bilirubin.

What is significant in liver diagnostics is the determination of the level of alanine (ALAT) and aspartate (AST) aminotransferases. The impact of these enzymes on the pregnancy is somewhat controversial. Certain studies revealed an insignificant increase in the level of the said enzymes in the 3<sup>rd</sup> trimester; however, the majority of publications indicate that ALAT and AST concentrations do not change in the course of pregnancy and remain within normal limits during the entire period. An elevation in the aminotransferase level during pregnancy is a pathological symptom and requires medical diagnostics [15].

During pregnancy the liver also produces an increased quantity of alkaline phosphatase, in particular in the 3<sup>rd</sup> trimester, and such a high level is maintained even up to 6 weeks after the delivery. Determination of the level of this enzyme with the purpose of confirming or excluding cholestasis in late pregnancy seems groundless.

The level of - glutamylotransferase remains within normal limits during the entire pregnancy period, although when compared with the initial period, it becomes slightly reduced in the 3<sup>rd</sup> trimester. Moreover, during pregnancy the concentration of bile acids becomes elevated, though it is still maintained within normal limits. Their level increase, together with an accompanying itchy sensation, may be a symptom of cholestasis, in which case it is necessary to run additional diagnostics and treatment.

Although liver diseases during pregnancy have an occurrence rate of 1/1000 pregnant women [16], they still constitute an important clinical issue regarding the possible hazard borne in relation to the lives of the mother and the foetus. Incorrect results of liver function tests occur with regard to ca. 3-5% of pregnant women [17, 18].

A pregnancy during which liver diseases are revealed becomes a high risk pregnancy requiring intensive supervision by both an obstetrician and an internist. Not uncommonly it is ended prematurely with Cesarean section in order to save the lives of the mother and the child.

Liver diseases that are observed only during pregnancy, having a strict pathogenetic relation with this physiological state include [16] intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy, HELLP syndrome, preeclampsia and eclampsia.

Pregnancy is a particular period in a woman's life. When its course is regular it constitutes a physiological process conditioned mainly by hormonal changes. Still, despite this fact, during pregnancy the former homeostasis of a woman's organism becomes violated.

This adjustment of the mother's organism has the purpose of ensuring optimal conditions for proper development and growth of the foetus. The physiological course of pregnancy is inseparably connected with cell proliferation and differentiation on the one hand, and cell death processes on the other.

All of this allows proper tissue and organ development; however, it also means an additional energy supply requirement for the mother's organism.

The data of the US National Research Institute estimate additional energy requirements of a pregnant woman at ca. 300 kcal per day or 80,000 kcal for the entire pregnancy period. Such a large additional energy expenditure is to ensure proper functioning of a pregnant woman's organism as well as protecting the foetus in its development process [10].

Moreover, during pregnancy the development of diseases immediately related to or frequently accompanying this condition is possible. During this period there is a significant increase in the concentration of such hormones as: placental lactogen (its concentration rises particularly in the first trimester), prolactin, luteinizing hormone, human chorionic gonadotropin (hCG), progesterone, cortisol and glucagon.

In the initial period it is possible to observe a rise in the concentration of progesterone produced by corpus luteum and then by the placenta, as well as estradiol and estrone. Three estrogen types are produced in the course of pregnancy: estradiol, estrone and estriol. The greatest progesterone and estriol increase is observed in the third trimester. It has been found that progesterone concentration grows 100 or even 200 times, whereas estriol is increased 24 times [19].

It is also known that *in vitro* estrogens cause a reduction in the number of neutrophils, Th1 lymphocytes, as well as reducing chemokine synthesis for macrophages by keratinocytes. Moreover, estrogens have an inhibitory effect on the production of proinflammatory IL-2 and TNF- $\alpha$  but also increase the production of anti-inflammatory IL-10 by dendritic cells [20, 21]. Estrogens may also block IL-2 secretion via T and CD4+ lymphocytes. 17- $\beta$ -estradiol, on the other hand, is inhibited by IL-2 receptor expression,

Whereas progesterone displays an activity inhibiting the response of cytotoxic T cells and the synthesis of Th1-dependent cytokines. It stimulates the production of Th2-dependent cytokines and a transmitter protein known as progesterone-induced blocking factor (PIBF). This fact causes an additionally increased cytokine Th2 production by the lymphocytes present in the peripheral blood of the pregnant.

This leads to the reduction in NK cells activity (natural killers) and strengthens the Th2-dependent immunological response [22, 23]. Studies have confirmed that the lack of PIBF and a low progesterone concentration constitute one of the reasons behind a recurring miscarriage [22].

Changes in hormone concentrations during pregnancy have an impact on cellular metabolism as well as the functioning of numerous organs, mainly on the cardiovascular system, kidneys and the liver. Already during the first weeks of pregnancy the progesterone, estrogen, placental lactogen, prostaglandins produced by the placenta [3] and relaxin produced by the ovaries cause changes in the circulatory system [4].

Initially the capacity of the vascular bed is increased and the blood pressure is reduced. In the upcoming weeks the volume of circulating blood grows and the vascular flow through some of the organs, in particular the uterus, kidneys and skin, is increased. The volume of circulating bloods grows by 20-25%. Water retention in a pregnant woman increases to reach even as much as 6-8.5 litres, which, on the other hand, leads to a nearly 50% increase in the minute cardiac output.

Despite such extensive changes in the cardiovascular system no increased blood flow through the liver is observed. Still, hepatic metabolism becomes more intense. What is noted is a reduction in the total protein concentration, mainly caused by a 20%-40% albumin concentration decrease.

To some degree such a situation results from the blood serum dilution linked to an increase in the blood volume. In a healthy pregnancy on the other hand, there is a rise in the concentration of such proteins as: fibrinogen, ceruloplasmin, transferrin, thyroxine-binding and corticosteroids-binding globulin. Tests show no elevated bilirubin levels in the pregnant, although the level of alkaline phosphatase increases 2-4 times.

This is presumably caused by this enzyme's synthesis in the placenta. Other hepatic enzyme concentrations usually remain unchanged, though recent observations indicate lowering of the upper range of the correct values regarding alanine and aspartate aminotransferase.

Apart from the above biochemical changes occurring in the liver during pregnancy, it should be noted that certain symptoms, typical of chronic liver diseases, such as telangiectasias, hand erythema, may appear during this period; however, they are usually reversed after the delivery.

The relationship between pregnancy and liver diseases may vary. In this context we may enumerate: pregnancy-related liver diseases, pregnancy-unrelated liver diseases, and pregnancy in women with liver diseases.

## **PREGNANCY-RELATED LIVER DISEASES**

### **Hyperemesis gravidarum**

appearing at the initial stage of pregnancy (4-10 weeks), with the frequency of 3/1000 pregnant women [25]. This condition leads to a violation of water-electrolyte balance with an initial metabolic and then respiratory alkalosis.

The reasons for liver damage are not completely recognised. The contributing factors are believed to be the increased thyroxine and hCG concentrations. Microscopic images in such cases reveal hepatocyte steatosis and often an extensive necrosis of hepatic lobules. In this disease, the induced liver damage has the capability of self-limitation. Persistent vomiting usually stops naturally in the 18-20<sup>th</sup> week of pregnancy.

### **Gestosis (preeclampsia, eclampsia)**

occurs in 5-10% pregnant women, usually in the second and third trimester. It is manifested by arterial hypertension, proteinuria and peripheral oedema and may be responsible for circa 1% (or less) of fatalities resulting from pregnancy.

This condition is characterised by a fibrin deposit formation in hepatic sinusoidal vessels, blood extravasation into the liver, sometimes accompanied by necrosis. The said changes are induced by complementary activation and disorders in the coagulation system.

Moreover, histopathological tests reveal microvesicular liver steatosis.

#### **Intrahepatic cholestasis of pregnancy**

mainly occurs in the third trimester (usually in the 30<sup>th</sup> week) and more seldom at earlier pregnancy stages (around the 6<sup>th</sup> week). It was observed that in Araucanian Indians its rate of occurrence amounts to 24%, whereas in Chile to 14% [25].

In Europe the most numerous cases of this disease are reported in Sweden - ca. 2% of pregnancies. The probability of its occurrence is higher in multiple pregnancies and in multiparae. The cause of this disease is sought in genetic disorders, the main mutations of MDR-3 proteins (Multi Drug Resistance 3).

This protein is responsible for phospholipid transportation through a canalicular membrane. Other causes involve: BSEP (Bile Salt Export Pump) protein mutation, sulfotransferase deficits and estrogen or progesterone metabolism disorders [25, 26].

The symptoms involve itchy skin, mainly on the hands and feet, intensified at night, and jaundice. Histopathological studies show necrotic foci or hepatocyte apoptosis, most visible in the central lobule area. Hepatocyte atrophy occurs as a result of an accumulation of cytotoxic bile acids.

The condition may be accompanied by cholesterol gallstones. In such a case the risk of its occurrence is three times higher.

#### **Acute fatty liver of pregnancy**

is a disease occurring only during pregnancy in the third trimester (30-38<sup>th</sup> week), and seldom after the delivery. Its frequency is estimated at 1/7,000-1/16,000 deliveries. It usually occurs in the third and fourth decade of life in primiparae in the case of male fetuses and multiple pregnancies.

Acute liver steatosis constitutes one of the most severe pregnancy complications. Its cause is sought in the mutation of gene G1528C of chromosome 2, which in this case fails to code long-chain 3-hydroxy-acyl coenzyme A dehydrogenase (LCHAD).

The said enzyme is responsible for mitochondrial fatty acid  $\beta$ -oxidation (Bayless and others 2006). A mutated enzyme, in the case of foetus-homozygote and mother-heterozygote, is incapable of correct metabolism of long-chain fatty acids and triglycerides. This causes an accumulation of the above substances in hepatocytes, and hence their increased activity.

The main symptoms related to this condition include: nausea, vomiting, aversion to food, pain in the right hypochondrium, jaundice, and rarely, itchy skin. It may lead to acute multiple organ dysfunction and even death. Microscopic images show microvesicular hepatocyte steatosis, mainly in the central part of a hepatic lobule, and in 25% of cases also the features of bridging hepatic necrosis.

#### **HELLP Syndrome**

(an abbreviation of 'haemolysis, elevated liver enzymes and low platelets count') [27].

The condition occurs in 0.1-0.6% pregnant women, usually young primiparae, most frequently in the second or third trimester (24<sup>th</sup>-37<sup>th</sup> week of pregnancy), and in 30% also immediately after the delivery. It is characterised by a 25% mortality rate among mothers and ca. 7-60% mortality rate among fetuses. In 20-25% of sufferers, HELLP syndrome is accompanied by preeclampsia.

The main cause of this condition is sought in the stimulation of arterial endothelial cells and the violation in the production of endothelin and nitric oxide. Its symptoms include: arterial hypertension, headaches, vision impairment, general oedema and abdominal pain. It may also lead to severe multiple organ dysfunction.

#### **Hepatic rupture and intrahepatic haemorrhages**

are rare complications in late pregnancy in women with preeclampsia. It is characterised by a 50-60% mortality rate among mothers and fetuses.

### **PREGNANCY UNRELATED LIVER DISEASES AND PREGNANCY IN WOMEN WITH LIVER CONDITIONS**

The most common pregnancy unrelated liver conditions are viral hepatitis type A, B or C. If they are mild or moderately severe they are known to have no effect on pregnancy and do not constitute a contraindication towards breast feeding. The viruses do not reveal a teratogenic effect.

The symptomatology, clinical course and complications observed in those diseases are practically the same in non-pregnant women.

A particular type of the disease is a pregnancy-related type E hepatitis, whose mortality rate reaches 25% and occurs mainly in the third trimester of pregnancy. The reasons behind this condition in pregnant women remain unknown. Fortunately in Europe its occurrence is extremely rare.

Another liver disease that may be observed during pregnancy is Herpes Simplex (HSV) virus infection. It's usually mild form becomes particularly violent in pregnant women. Histopathological tests indicate focal haemorrhagic necrosis of the liver and an appearance of intranuclear inclusion bodies [28].

The most common prenatal infection is the infection with cytomegalovirus (CMV). It concerns 0.5-2% of live-born neonates. Approx. 90% of cytomegaly cases have an asymptomatic form.

In women in whom Wilson's disease is detected, it is important to introduce treatment modifications during pregnancy. In the case of an advanced autoimmune hepatitis, on the other hand, women should be advised against becoming pregnant, although in its initial period the condition is not a contraindication to procreation.

In the case of cirrhosis, becoming pregnant is impeded due to ovulation inhibition. Often, effective insemination is followed by foetus atrophy, and in the situation when the foetus survives it is characterised by a low birth weight. An increased bilirubin concentration in the mother may be the cause of kernicterus in the baby.

This constitutes an indication for the requirement of an exchange blood transfusion. Mothers, on the other hand, may experienced intensified symptoms related to oesophageal varices.

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