

## Particularities of associating viral hepatitis with pregnancy and mental disorders

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### Abstract

Pregnancy generates particular circumstances for all co-existent conditions. Associating pregnancy with liver diseases has distinct particularities. The authors will perform a presentation of the etiopathogenic, diagnosis and therapeutic conduct particularities regarding the association between pregnancy, chronic liver diseases and mental disorders. The three pathological entities are analyzed separately, followed by a study of a triple association. Associating pregnancy and mental disorders has been better studied due to a higher frequency of mental disorders, especially postpartum, but the triple association pregnancy, chronic hepatitis with viral etiology mainly, and mental disorders has been less analyzed. There is concluded that pregnancy, through the physiological changes it undergoes, as well as its pathology, represents a clearly influencing factor of the association with a chronic liver disease or with a mental disorder.

**Keywords:** mental illness, pregnancy, diagnostic screening, chronic liver diseases.

### ✉ Introduction

The particular context of pregnancy makes that its two-associated conditions influence one another. The particular reactivity of human body during pregnancy makes that any liver disease accompanied by mental disorders present surprising changes.

Acute hepatitis is the most frequent cause of jaundice during pregnancy. It seems that A, B, C and D viral hepatitis are aggravated by the pregnancy state, but E hepatitis is particularly serious, with a rate of mortality of the pregnant woman around 25% [1].

Gallbladder disorders during pregnancy have an incidence of 0.3–0.5%, but they represent the most frequent cause of non-obstetrical surgery in pregnant women. The risk factors for the development of gallstones are the pregnancy it-self, obesity, pre-existent gallbladder disorders, iron therapy and growth [1].

During pregnancy, there is a modulation of these painful symptoms. The pharmacological therapeutic options are limited during the first trimester [2].

Some of the women are having gastrointestinal (GI) disorders, which appear accidentally only during the pregnancy, meanwhile some are having chronic GI disorders that need full monitoring during the pregnancy [3].

Intrahepatic cholestasis can be responsible for early labor, fetal distress and *intra utero* death. The treatment with Ursodeoxycholic acid (UDCA) can reduce mother's symptoms, improve maternal biochemical abnormalities and also the outcome, but this is not confirmed in time or by relevant studies [4].

Intrahepatic cholestasis has an unknown cause. The acute fat liver during the pregnancy is associated with preeclampsia and HELLP (Hemolysis, Elevated Liver enzymes, Low Platelet count) syndrome [5].

All this associations regarding the pathology of the liver during pregnancy are different when they are associated with pre-existent or acquired during pregnancy, mental illness. In this case, there are difficulties in establishing diagnosis and also for treatment management.

On the other hand, the antidepressant treatment during pregnancy can reduce the recurrence of depression between 30–60% [6], but this is not free of teratogenic risks.

### ✉ Association of liver disease and pregnancy

Pregnancy determines functional changes of the digestive tract, in general, and of the liver, in particular.

The serum levels of sexual steroids in pregnancy clearly affect the liver function. The changes that appear include the decrease of gamma-glutamyltranspeptidase, increase of alkaline phosphatase and hypoalbuminemia, generated by the plasma volume increase. Serum transaminases alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) remain at normal values. Their increase, as well as of serum bilirubin concentration, during pregnancy requires further investigations because they exceed the normal physiological frame [1].

During pregnancy, there may be present some changes specific to liver diseases, such as angiomas, palmar

erythema, examples of conditions especially present in Caucasian white pregnant women. Moreover, there may appear some serum disorders, such as decrease of serum albumin, increase of serum alkaline phosphatase, increase of serum cholesterol levels, changes specific to liver disease that do not have the same diagnosed value of liver disease during pregnancy [2].

Preeclampsia is responsible in 50% of cases of liver enzyme increase during pregnancy. Liver damage in preeclampsia is generated by hepatic arterial and portal vasospasm, with fibrin periportal deposit, which leads to lobular ischemia and hepatocytarian necrosis [1].

In preeclampsia, transaminases increase up to five times, alkaline phosphatase is slightly increased, although liver function is not damaged. The HELLP syndrome, which is a complication of high blood pressure induced by pregnancy, is characterized by hemolysis, high levels of transaminases, decrease of thrombocytes [1].

Pregnancy generates favorable circumstances for bile stones. The risk of their appearance is higher in the second and third pregnancy trimester and during the postpartum period.

Their symptoms may be represented by epigastric or right hypochondrium pain, fever, vomiting, jaundice – symptoms that may be easily confused with an obstetrics condition or pancreatic complication [3].

The high concentrations of bile acids may cause jaundice and itching. Up to 44% of women with intrahepatic cholestasis may have a premature delivery [1].

The fat liver syndrome during pregnancy is a rare, but serious, disease that appears in the last pregnancy trimester. It is caused by an abnormality of the fatty acids metabolism. Dehydrogenase may cause a high accumulation of fatty acids, in the fetal liver at first, and in the mother blood flow subsequently, which leads to hepatotoxicity [1].

Intrahepatic cholestasis during pregnancy is the most frequent liver disease specific to pregnancy. It is characterized by itchiness, especially at palm and sole level, generated by a high concentration of bile acids in the liver and blood. There may also be accompanied by jaundice in 5% of the cases. The determination of bile acids in the serum helps to confirm the diagnosis [4].

Intrahepatic cholestasis during pregnancy does not have a known cause, but it presents a marked geographical variation [5].

Intrahepatic cholestasis usually appears after the 30<sup>th</sup> week of pregnancy, it has unclear etiology and spontaneously regresses postpartum. It is more frequent in multiple pregnancies or in those with factors favoring intrahepatic cholestasis (oral birth control pills, family history of cholestasis). The pathogeny of intrahepatic cholestasis is multi-factorial, being generated by a hypersensitivity to the sexual steroid hormones characteristic to genetic transmission [6].

Nausea, with or without vomiting, a common symptom of liver diseases, appears in up to 90% of pregnancies, while vomiting is observed in 25–55% of pregnancies. Risk factors for nausea during pregnancy are given by the first gestation, obesity, smoking. It may also appear in subsequent pregnancies, but it has a shorter duration. Nausea specific to the first trimester has an inappropriately

known physiopathological mechanism. It is estimated that more factors would be involved, such as hormonal fluctuations, gastrointestinal motility disorders, as well as psychosocial factors.

The persistence of nausea and vomiting in other pregnancy trimesters involves the existence of different causes.

Other diseases responsible for nausea during pregnancy may be represented by infections of urinary tract, gastroenteritis, peptic ulcer, pancreatitis, acute and chronic hepatitis, appendicitis, suprarenal failure and intracranial high blood pressure [3].

These diseases interfere with some pregnancy conditions that appear in the second or third trimesters that may also generate nausea, besides other symptoms. These are represented by the excess of amniotic or hydramnios liquids, preeclampsia, labor start [3].

Severe liver diseases, such as autoimmune hepatitis, primary bile crisis and viral chronic hepatitis are rarer during pregnancy, because these women present an infertility syndrome generated by anovulation. Due to the improvement of chronic liver diseases treatment, pregnancies have become more frequent in these women, as well. In women with chronic viral hepatitis, the stable liver function favors a normal pregnancy. The treatment with Lamivudine, although risking, in pregnant women with B virus hepatitis, is accepted even from the first semester. This is a recommended drug only if its benefits are higher than its risks (C category, Food and Drug Administration – FDA classification) [1].

A quarter of pregnant women with chronic B virus hepatitis will develop phenomena of chronic liver inflammation after delivery. Women with Hbe antigen are twice more susceptible of presenting biological markers of inflammation.

There are studies suggesting the presence of certain postpartum exacerbations of liver abnormalities in pregnant women with B virus hepatitis [7].

The biomarkers presenting high levels were represented by alanine aminotransferase, with levels at least twice higher than normal limits, levels that returned to normal after 12 months since delivery [7].

These observations may confirm the hypothesis that the physiological immunodeficiency during pregnancy reduces the liver necroinflammatory activity, changes that may inverse after delivery [7].

Using a prenatal screening for chronic B virus hepatitis and performing a neonatal immunoprophylaxis in newborns of mothers infected with positive B virus hepatitis leads to a special efficiency in preventing neonatal transmission of this disease [8].

Immunoprophylaxis is quite efficient in women that do not present the “e” antigen of B virus hepatitis and those with viral loading.

Prenatal treatments with antiviral agents do not present an additional benefit and they may cause lesions, even if it is used on short periods of time [8].

The hepatic vaccine is recommended in women even during pregnancy, but, at the same time, the follow-up is not highlighted because it requires a period of six months, a time interval when delivery may occur. This is the reason for which in the United States there was visualized a

vaccination rate shorter than four months in pregnant women in whom the second dose is taken after four weeks, while the third dose after 16 weeks since the first one. This accelerated programme was tested on a group of 200 pregnant women with high risk of B virus hepatitis, meaning those pregnant women with an absent surface antigen [9].

The association between liver transplant and pregnancy is generally rarely met, since women with liver failure that require a liver transplant are infertile. As there have been reported 14 000 births in women with organ transplants, it is also possible for liver-transplanted women to have pregnancies [10].

There is estimated that pregnancy does not seem to compromise the function of the liver graft if this was performed before pregnancy [10].

Fetal teratogenicity generated by the immunosuppressor treatment is not different from the one in the general population, a reason for which pregnant women should continue the immunosuppressor treatment during the whole pregnancy period [10].

### ☞ Association of mental disorders and pregnancy

Pregnancy is considered to be a period of emotional well-being for women, but, apart from this aspect, there is a high risk of developing mental disorders. The most common mental disorders manifesting during this distinct period in a woman's life are represented by emotional and anxiety disorders [11].

It is important to treat depression during pregnancy, because untreated depression is associated with premature delivery or intrauterine growth restriction.

It is recommended a differential treatment for pregnant women with depression. There should be taken into consideration both the patient's wish and the conduct imposed by the obstetrician [12].

Women prone to a high risk of postpartum mental disorders should be identified even before delivery. Pregnant women with depression episodes during pregnancy need to be considered as having a high risk for postpartum disorders.

The ones presenting a history of recurrent depression or with postpartum depression antecedents may benefit of prophylactic treatment with an antidepressive drug. Antidepressive medication is not recommended during pregnancy, but it may be initiated immediately after delivery [13].

Pregnant women aged less than 20-year-old have a higher risk of developing postpartum depression [14].

Postpartum depression is more persistent and more serious than the baby-blues syndrome. Untreated depression may be associated with obstetrical abnormalities, such as intrauterine growth restriction. Most frequently, it develops in the first four months of life and may affect 10–15% of women [13].

Postpartum depression does not essentially differ from any depression that may occur in any moment of the patient's life. The highest risk of postpartum depression belongs to those with depression antecedents, with episodes of postpartum depression in previous pregnancies or with depression during pregnancy. Moreover, a stressful life,

stress phenomena, lack of social support or an unwanted pregnancy may represent some risk factors [13].

Postpartum psychosis is the most severe form of mental disorder postpartum. It occurs in approximately 1–2 cases of 1000 women after delivery and the highest risk is presented by pregnant women with a personal history of bipolar disorder or with postpartum psychosis antecedents [13].

Postpartum psychosis has a sudden onset, in the first 48–72 hours after birth. The symptoms develop in the first two weeks after delivery and may take the form of a maniacal episode manifested by a state of anxiety, insomnia, irritability, mood change, disorganized behavior, delirious ideas regarding the baby.

Puerperal psychosis represents a psychiatric emergency and requires hospitalized treatment.

Pregnant women that receive treatment for a mental disorder with Selective Serotonin Reuptake Inhibitors (SSRIs) present an additional risk for miscarriage, a risk also found in those who received this medication before pregnancy.

It is difficult to establish a causative connection between SSRIs and miscarriage. It is possible that the factors associated with depression, as well as smoking and alcohol intake, might represent an additional risk for pregnant women that are treated with antidepressives. This is the reason for which interrupting medication before pregnancy is not beneficial. There was evaluated that the risk of pregnant women with mental disorders to present a miscarriage is approximately 25% higher than those who did not receive any medication [15].

Prenatal depression is itself a factor with obstetrical implications, such as prematurity, intrauterine growth restriction and preeclampsia. On the other side, antenatal depression is a risk factor for postpartum depression and implicitly a risk factor for suicidal, a reason for which antidepressive medication during pregnancy presents a risk that cannot be ignored [15].

A study performed in Denmark on a group of 1 279 840 pregnancies between 1997 and 2010 highlighted the fact that 142 093 of the pregnancies ended with a miscarriage, and 276 178 ended with induced abortion. Of these, 22 884 (1.8%) pregnant women received SSRIs medication at the beginning of pregnancy. 2 883 (12.6%) pregnant women presented miscarriage in comparison to 11.1% miscarriage found in pregnant women that have not been exposed to SSRIs [15].

The high risk of miscarriage in this study is explained by the additional risk generated by the pregnant woman's lifestyle, namely by alcohol intake, smoking and absence of folic acid administration during pregnancy.

The study presents important clinical indications regarding the counseling and guiding of women with anxiety that received SSRIs treatment during the pre-conception period [15].

Prenatal use of SSRIs seems to be a risk factor for the disorders of the autistic spectrum and developmental delays in children. Serotonin is essential in early brain development. Prenatal use of SSRIs was associated with autism and, to a lesser extent, to other developmental delays [16].

Dysfunctions of serum concentrations of oxytocin may

have bad effects upon maternal depression and upon the newborn development.

There was established that in mothers with depression, the determination of oxytocin in saliva presented lower levels.

There has been observed that this decrease of salivary oxytocin may be the consequence of abnormalities of oxytocin receptor gene, especially in the homozygotic genotype [17].

Abnormalities of oxytocin concentration are involved not only in maternal depression, but also in disorders involving social dysfunction, including autism, schizophrenia and social anxiety [17].

Extrapolating, we may state that variations of oxytocin concentration may shape the effects of maternal depression.

Girl exposure to preeclampsia *in utero* has been associated to a risk twice higher for developing autism and five times higher for developmental delay [18].

Preeclampsia may determine an abnormal neurodevelopment and may disturb fetal physiology mechanisms due to some placental abnormalities. Improving placental perfusion may be obtained by optimizing metabolic health before and during pregnancy [18].

Women that live in large urban areas have many more chances, in comparison to those living in more restricted areas, to develop postpartum depression. The risk is 40% higher than in those living in the rural area.

Thus, there has been highlighted that global prevalence of postpartum depression was 7.47% compared to 9.16% for women living in the urban area, and 6.07% for those living in the rural area [19].

More studies report fetal malformations in pregnant women exposed to antidepressant treatment in the first trimester, but there is no malformative defect specific to fetuses of mothers with an antidepressant treatment [20].

The association between Paroxetine and cardiac defects seems to have become more frequent. Using SSRIs in the first pregnancy trimester is associated with transient neonatal signs and with a high risk of persistent pulmonary hypertension in the newborn babies [20].

Using tricyclic antidepressants during pregnancy is more associated with structural malformations, but also with perinatal complications, such as agitation, irritability, convulsions in newborn babies [20].

There is estimated that the maximum theoretical risk of presenting a malformation is of one in 9000 pregnant women taking antidepressants. On the other hand, the antidepressant treatment during pregnancy may decrease depression recurrence between 30 and 80% [6].

Antidepressants may reversibly or permanently the development of fetal brain, according to the moment of exposure during pregnancy. Children of mothers exposed to antidepressants during the third pregnancy trimester presented motor deficiencies, they managed to stand 15.9 days later and walk 28.9 later. There have been identified associations between antidepressant exposure during the last pregnancy trimester and motor deficit, especially in boys [21].

#### ☞ Association of liver disease and mental disorder

This association has been well studied, a reason for which we will mention only a few therapeutic aspects.

In the etiological, symptomatological, clinical, paraclinical diagnosis and conduct polymorphism of viral chronic hepatitis, we may add the multitude of mental manifestations.

Among these, depression affects up to 50% of hepatitis C virus (HCV) patients receiving interferon treatment. Despite all these, mental changes in this situation may be transient and may not require any antidepressant treatment. Many times, the symptoms disappear spontaneously after ending the interferon treatment [22]. Patients with C hepatitis presenting mental disorders may benefit of integrated treatment.

A study performed on 1167 patients in three HCV clinics showed that 65% of the patients had risk factors for mental manifestations (Groessl – Reuters Health, 2013). Among these, 365 patients were randomized in order to receive integrated medical care. These patients had 1.6 times more chances of receiving antiviral treatment. Twice more patients had a sustained viral response in the integrated care group [23].

Around 40% of the patients with C virus hepatitis do not receive a correct and complete treatment. Identifying depression in patients with C virus hepatitis is influenced by the interferon treatment, and its treatment would optimize the treatment response.

There are studies showing that patients with chronic viral C hepatitis receive a treatment that is mostly addressed to virus suppression (80%), which may lead to the risk of increasing drug resistance and disease progression. The highest compliance rates have been observed in the patients also receiving antidepressant treatment at the same time [24].

#### ☞ Association of liver disease, mental disorder and pregnancy

Maternal prenatal anxiety and stress may have serious consequences upon the descendants. Among these negative consequences, we mention immune system deficiency, which may determine the excessive use of antibiotics in the first year of life.

Prenatal anxiety and stress have been suggestive for using excessive antibiotics treatment in the first year of life, especially for infections of the respiratory system, general infectious diseases, skin diseases, etc. and they have not been associated with diseases of the digestive tract [25].

There is estimated that using antidepressant drugs during pregnancy, as well as prenatal exposure to antidepressants may lead to potential risks. All SSRIs are metabolized by the liver, they are dependent of the liver enzymes presence that, in their turn, present genetic variations. According to this genetic variation, these enzymes play a more or less important role in the catalytic activity. Their consequence is the variation of drug concentration during pregnancy, which may lead to higher drug plasma concentrations.

As metabolic activities are altered during pregnancy, there may appear decreases of SSRIs plasma concentrations [26].

*In utero* exposure to antidepressants may present additional risks for metabolic disorders, such as obesity

and type 2 diabetes mellitus. Also, research performed on animals that have been administered SSRIs highlighted the presence of liver inflammatory changes and adipose dystrophy in the newborn. The same mechanisms might be present in humans, as the Fluoxetine serum levels in animals are identical with serum levels identified in pregnant women [27].

Studies on experiment animals, which had an evaluation of the liver histology, liver lipid levels and inflammation markers, together with the SSRIs administering, highlighted a mild up to moderate hepatosteatosis in the fetuses [27].

There is estimated that a fat liver is associated with insulin resistance, and this is associated with a high risk of type 2 diabetes mellitus, insulin resistance alteration being also found during pregnancy. Also, in experiment animals that had been administered SSRIs there have been identified changes of hepatic triglycerides and cholesterol, as well as important increases of inflammation markers in the fetuses, regardless of their sex [27].

The increase of C-reactive protein (CRP) maternal levels, an inflammatory reaction marker, was associated with a high risk of almost 60% for children schizophrenia. This was established by excluding hereditocollateral antecedents of the mental disorder. There is more and more epidemiological and paraclinical proof suggesting that infection and activation of the immune system play an important part in the schizophrenia etiology [28].

There have been identified associations between high levels of maternal anti-*Haemophilus influenzae*, rubeola, toxoplasmosis and type 2 herpes simplex virus (HSV) antibodies and schizophrenia in the descendants [28].

Research has identified that every mg/L of increasing maternal CRP was correlated with an increase of the risk for schizophrenia by 28% [28]. Also, there has been observed that a significant increase of maternal CRP levels during pregnancy led to autism during childhood.

## ☐ Conclusions

The distinct analysis of the association between pregnancy, liver disease and mental disorder has revealed great aspects. However, the simultaneous study of the three entities has highlighted surprising changes. Thus, these significantly influence the evolution of a chronic liver disease, to which there may be associated mental changes. The associated analysis of the three entities is incomplete and does not present in its complexity the changes highlighted by their simultaneous analysis.

## Conflict of interests

The authors declare that they have no conflict of interests.

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## References

- [1] Keller J, Frederking D, Layer P. The spectrum and treatment of gastrointestinal disorders during pregnancy. *Nat Clin Pract Gastroenterol Hepatol*, 2008, 5(8):430–443.
- [2] Rigby FB. Common pregnancy complaints and questions. Medscape Reference 2011, WebMD, LLC, Updated: Dec 19, 2014, <http://emedicine.medscape.com/article/259724overview#showall>.
- [3] Roy PK. Gastrointestinal disease and pregnancy. Medscape Reference 2011, WebMD, LLC, Updated: Jan 05, 2016, <http://emedicine.medscape.com/article/186225-overview>.
- [4] Frise CJ, Williamson C. Gastrointestinal and liver disease in pregnancy. *Clin Med (Lond)*, 2013, 13(3):269–274.
- [5] Gimson A. Liver and gastrointestinal diseases in pregnancy. In: Warrell DA, Cox TM, Firth JD (eds). *Oxford textbook of medicine*. 5<sup>th</sup> edition, Oxford University Press, 2014.
- [6] Furukawa TA. Adverse effects of antidepressants during pregnancy. *Evid Based Ment Health*, 2014, 17(4):103–104.
- [7] Reuters Staff. Hepatitis B virus flares common in postpartum period. Reuters Health Information, Last updated: December 05, 2014, <http://bit.ly/1vWmJhc>.
- [8] Kubo A, Shlager L, Marks AR, Lakritz D, Beaumont C, Gabellini K, Corley DA. Prevention of vertical transmission of hepatitis B: an observational study. *Ann Intern Med*, 2014, 160(12):828–835.
- [9] Sheffield JS, Hickman A, Tang J, Moss K, Kourosh A, Crawford NM, Wendel GD Jr. Efficacy of an accelerated hepatitis B vaccination program during pregnancy. *Obstet Gynecol*, 2011, 117(5):1130–1135.
- [10] Wakim-Fleming J, Zein NN. Liver diseases in pregnancy. In: \*\*\*. *Pregnancy in gastrointestinal disorders*. 2<sup>nd</sup> edition, American College of Gastroenterology, 2011, 32–47.
- [11] Gheorman VV, Pana RC, Chirita AL, Berceanu C, Gheorman V. Considerations regarding pregnancy associated with mental illness. *Curr Health Sci J*, 2014, 40(Suppl 8):6–9.
- [12] Moyer P. Pregnant women with depression are inadequately treated. American Psychiatric Association (APA) 157<sup>th</sup> Annual Meeting: Abstract NR266, Presented: May 3, 2004, <http://www.medscape.com/viewarticle/475013>.
- [13] Joy S. Postpartum depression. Medscape, WebMD, LLC, Updated: Apr 17, 2014, <http://reference.medscape.com/article/271662-overview>.
- [14] Harding A. Quick screening tools identify postpartum depression in teen moms. Reuters Health Information, Pediatrics, December 19, 2013, <http://bit.ly/JLIRqo>.
- [15] Andersen JT, Andersen NL, Horwitz H, Poulsen HE, Jimenez-Solem E. Exposure to selective serotonin reuptake inhibitors in early pregnancy and the risk of miscarriage. *Obstet Gynecol*, 2014, 124(4):655–661.
- [16] Hand L. More mothers depressed at 4 years than shortly after births. *BJOG*, 2015, 122(3):312–321, Medscape Medical News, <http://www.medscape.com/viewarticle/825547>.
- [17] Brooks M. Oxytocin dysfunction seen in both depressed moms and kids. *Am J Psychiatry*, 2013, 170(10):1086–1089, 1161–1168, Medscape Medical News, <http://www.medscape.com/viewarticle/812686>.
- [18] Walker CK, Krakowiak P, Baker A, Hansen RL, Ozonoff S, Hertz-Picciotto I. Preeclampsia, placental insufficiency, and autism spectrum disorder or developmental delay. *JAMA Pediatr*, 2015, 169(2):154–162.
- [19] Vigod SN, Tarasoff LA, Bryja B, Dennis CL, Yudin MH, Ross LE. Relation between place of residence and postpartum depression. *CMAJ*, 2013, 185(13):1129–1135.
- [20] Brauser D. Depression and pregnancy: new report weighs treatment options. *Gen Hosp Psychiatry*, 2009, 31(5):403–413; *Obstet Gynecol*, 2009, 114(3):703–713, Medscape Medical News, <http://www.medscape.com/viewarticle/707811>.
- [21] Barclay L. Antidepressants may permanently or reversibly affect fetal brain development. Medscape Medical News, Pediatrics, Published online: February 22, 2010, <http://www.medscape.com/viewarticle/717784>.
- [22] Keller DM. Depression in HCV often resolves after interferon treatment. EPA 2013: 21<sup>st</sup> European Congress of Psychiatry: Abstract 1680, Presented: April 7, 2013, Medscape Medical News, <http://www.medscape.com/viewarticle/782355>.
- [23] Goodier R. Integrated psych care for high-risk hep C patients may increase antiviral treatment. Reuters Health Information, Mar 26, 2013.

- [24] Brooks M. Depression may complicate hepatitis C therapy. International Conference on Viral Hepatitis (ICVH) 2011: Oral Abstract 70921, Presented: April 11, 2011, Medscape Medical News, <http://www.medscape.com/viewarticle/741301>.
- [25] Beijers R, Jansen J, Riksen-Walraven M, de Weerth C. Maternal prenatal anxiety and stress predict infant illnesses and health complaints. *Pediatrics*, 2010, 126(2):e401–e409.
- [26] Harrison P. Managing depression in pregnancy: the debate continues. *Can J Psychiatry*, 2012, 57(9):519–522, 523–529, 530–536, Medscape Medical News, September 28, 2012, <http://www.medscape.com/viewarticle/771784>.
- [27] Anderson P. *In utero* exposure to SSRI may up obesity, diabetes risk. Joint Meeting of the International Society of Endocrinology and the Endocrine Society – ICE/ENDO 2014, June 22, 2014: Abstract SUN-0910, Medscape Medical News, <http://www.medscape.com/viewarticle/827751>.
- [28] Cassels C. Inflammation in pregnancy strongly linked to schizophrenia. *Am J Psychiatry*, 2014, 171(9):901–905, 960–968, Medscape Medical News, September 04, 2014, <http://www.medscape.com/viewarticle/831135>.

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