Journal of Medical Sciences. 11 May, 2023 - Volume 11 | Issue 4. Electronic - ISSN: 2345-0592
Medical Sciences 2023 Vol. 11 (4), p. 35-45, https://doi.org/10.53453/ms.2023.5.4

e-ISSN: 2345-0592
Online issue
Indexed in *Index Copernicus*

Medical Sciences

Official website:
www.medicsciences.com

Autoimmune diseases of the digestive system during pregnancy

Kamilė Piesliakaitė[1], Živilė Sabonytė – Balšaitienė[2,3] , Diana Ramašauskaitė[2,3], Virginija Paliulytė[2,3]

[1]*Vilnius University, Faculty of Medicine, Vilnius, Lithuania*

[2]*Vilnius University, Faculty of Medicine, Clinic of Obstetrics and Gynecology, Vilnius, Lithuania*

[3]*Vilnius University Hospital Santaros Clinics, Center of Obstetrics and Gynecology, Vilnius, Lithuania*

Abstract

Background. Autoimmune diseases of the digestive tract are more prevalent in women and have a negative impact on maternal or fetal health. Most common of these diseases are celiac disease, inflammatory bowel disease, autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cholangitis. Even though they usually tend to go into remission, the underlying pathological pathways may cause complications. Most frequent pregnancy risks include preterm birth, miscarriage, cesarian section, or low birth weight newborn.

Aim: the aim of the study is to analyze and review the evidence-based scientific literature describing the relationship between autoimmune diseases and pregnancy, maternal or fetal complications.

Methods. International databases PubMed and Google Scholar were used for literature review. 53 scientific articles were selected for this literature review.

Results. Celiac disease poses a risk of cesarean section, recurrent miscarriages, low birth weight and preterm delivery, especially for untreated women. Inflammatory bowel disease may cause hemostatic complications in women, preterm birth, small for gestational age birth weight, or stillbirth. Autoimmune hepatitis could lead to fetal loss premature delivery. Primary sclerosing cholangitis and primary biliary cirrhosis increase the risk of cesarean section and preterm birth.

Conclusions. Autoimmune diseases of the digestive tract are not common in pregnancy and most cases will be in remission. Preterm birth, caesarean section or small for gestational age fetus are most common complications. Careful multidiscipline follow-up of obstetrician-gynecologist and gastroenterologist is crucial for reducing pregnancy, maternal, or fetal risks.

Keywords: pregnancy; celiac disease; inflammatory bowel disease; autoimmune hepatitis; primary sclerosing cholangitis; primary biliary cholangitis

Autoimuninių virškinamojo trakto ligų pasireiškimas nėštumo metu

Kamilė Piesliakaitė[1], Živilė Sabonytė – Balšaitienė[2,3] , Diana Ramašauskaitė[2,3], Virginija Paliulytė[2,3]

[1]*Vilniaus universitetas, Medicinos fakultetas, Vilnius, Lietuva*

[2]*Vilniaus universitetas, Medicinos fakultetas, Akušerijos ir ginekologijos klinika, Vilnius, Lietuva*

[3]*Vilniaus universiteto ligoninė Santaros klinikos, Akušerijos ir ginekologijos centras, Vilnius, Lietuva*

Santrauka

Įvadas. Autoimuninėmis virškinamojo trakto ligomis dažniau serga moterys. Jei serga nėščioji, šios ligos gali turėti neigiamą poveikį motinos ar vaisiaus sveikatai. Dažniausios autoimuninės virškinamojo trakto ligos yra celiakija, uždegiminė žarnų liga, autoimuninis hepatitas, pirminis sklerozuojantis cholangitas ir pirminis biliarinis cholangitas. Nors nėštumo metu paprastai pasiekiama remisiją, pagrindiniai patologiniai mechanizmai vis tik gali sukelti komplikacijų. Didžiausia yra priešlaikinio gimdymo, persileidimo, cezario pjūvio operacijos arba mažo svorio naujagimio rizika.

Tikslas. Išanalizuoti ir apžvelgti įrodymais pagrįstą mokslinę literatūrą, aprašančią autoimuninių ligų ir nėštumo ryšį, komplikacijas nėščiajai ar vaisiui.

Metodai. Literatūros apžvalgai naudotos tarptautinės duomenų bazės PubMed ir Google Scholar. Buvo atrinkti 53 moksliniai straipsniai šiai literatūros apžvalgai.

Rezultatai: celiakija didina cezario pjūvio operacijos, pasikartojančių persileidimų, mažo gimimo svorio ir priešlaikinio gimdymo riziką, ypač negydomoms moterims. Uždegiminė žarnyno liga moterims gali sukelti hemostazinių komplikacijų. Taip pat didėja priešlaikinio gimdymo, mažo gimimo svorio pagal gestacinį amžių naujagimio arba negyvagimio rizika. Autoimuninis hepatitas gali sukelti savaiminį persileidimą, priešlaikinį gimdymą. Pirminis sklerozuojantis cholangitas ir pirminis biliarinis cholangitas didina cezario pjūvio operacijos ir priešlaikinio gimdymo tikimybę.

Išvados. Autoimuninės virškinamojo trakto ligos nėštumo metu nėra dažnos ir daugeliu atvejų liga yra remisijos stadijoje. Priešlaikinis gimdymas, cezario pjūvio operacija arba mažas vaisius pagal gestacinį amžių yra dažniausios komplikacijos. Atidus multidisciplinis gydytojo akušerio – ginekologo ir gydytojo gastroenterologo stebėjimas yra labai svarbus, siekiant sumažinti nėštumo, motinos ar vaisiaus komplikacijų riziką.

Raktažodžiai: nėštumas; celiakija; uždegiminė žarnų liga; autoimuninis hepatitas; pirminis sklerozuojantis cholangitas; pirminis biliarinis cholangitas

1. Introduction

It is widely known that autoimmune diseases affect more women than men. This tendency may be explained due to influence of sex hormones (1). Hormones are an important part of pregnancy because they cause immunological changes in the uterus that help successful implantation and gestation (1). However, hormonal changes during pregnancy affect autoimmunity which has an immense impact on fertilization, pregnancy, adverse maternal and fetal outcomes (1). Autoimmunity is related to autoantibodies, which can damage different organ systems. It manifests differently in the digestive system, adversely affecting organs and causing clinical symptoms. Autoimmune diseases of the digestive system may be classified into three categories: associated with human leukocyte antigen (HLA), immunoglobulin G4-related diseases (IgG4-RD), and other autoimmune gastrointestinal diseases (2,3).

One of these diseases is celiac disease. The symptoms appear in only 0.2 % of patients and most of the symptomatic people are women (4). Untreated it can lead to infertility or cause adverse fetal outcomes (4). Inflammatory bowel disease (IBS) is divided into Crohn's disease and ulcerative colitis. The incidence of this disease is highest during reproductive years, and it can cause spontaneous abortion, preterm birth, or other complications (5). Autoimmune hepatitis occurs more frequently in women of young age (6). The flares of the disease occurring during pregnancy are related to adverse outcomes (6). Immune-mediated cholangiopathies – primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC) cause symptoms by the accumulation of activated T-lymphocytes in bile ducts (7). PBC is usually diagnosed in middle-aged females rather than males. PSC, however, affects more males (7). These autoimmune diseases can affect women of reproductive age and have unfavorable outcomes on their pregnancies. It is important to know outcomes and help women to treat these diseases.

2. Materials and methods

International databases PubMed and Google Scholar were used for literature review. 1016 articles based on the keywords or their combination. After reading abstracts and full texts 53 scientific articles were selected - meta-analyses, systematic reviews, literature reviews, clinical studies. Articles not in English were rejected.

3. Results

3.1 Celiac disease

Celiac disease is an immune-mediated gluten-sensitive enteropathy. Meaning that manifestation of celiac disease can include extra-digestive organs, sometimes gynecological-obstetric symptoms might be the only noticeable ones (menstrual cycle disorders, infertility, early miscarriages) (8). Tissue transglutaminase (tTG EC 2.3.2.13) is a specific autoantigen. The body produces antibodies against it. In pregnancy, tTG is present on the outer layer of the syncytiotrophoblast microvillous membrane, decidual cells, and mother-embryo interface (9). It has a high affinity to fibronectin (9). Cross-linked they both support cell adhesion in the uterus. This autoantigen on the syncytiotrophoblast microvillous membrane is directly exposed to maternal autoantibodies in the blood (9). The interaction between tTG and autoantibodies might cause obstetric complications. During peri-implantation period anti-tissue-transglutaminase (anti-tTG) reduces the proliferation and migration of trophoblast and might even cause its apoptosis (10). Moreover, the ineffective clearance of apoptotic cells might lead to uterine inflammation, which is usually seen in miscarriages (10).

One population-based cohort study has shown that cesarean section is increased by 30% for women with celiac disease (11). This number is also increasing as women age. Furthermore, the risk of assisted delivery is also greater. Miscarriages are slightly more common in women with celiac disease (11). Additionally, the preterm birth risk is increased for both treated and untreated women. However, treated women have a 20% lower risk compared to untreated women (12). Complications, such as intrauterine growth restriction, stillbirth, low birth weight and small for gestational age newborns are also more common (12). Up to 50 % of untreated patients might experience miscarriage or adverse pregnancy outcomes (13). Recurrent miscarriages (two or more consecutive spontaneous abortions of unknown origin) or intrauterine growth retardation might be signs of subclinical celiac disease (13). Spontaneous abortions might occur due to anti-tTG induced trophoblast apoptosis, immunity, and nutrient deficiency (for example zinc and folic acid) but many more pathogenetic mechanisms are being investigated (14). Moreover, normal development and function of the placenta depends on the extravillous trophoblast (EVT) invasion to the maternal decidua, followed by vascular growth (15). Trophoblasts produce some proteins and hormones involved in the maintenance of the pregnancy. Due to apoptosis of EVT, recurrent miscarriages or intrauterine growth retardation might occur (15,16). Furthermore, a study has showed an increased EVT apoptosis of women, non-compliant with a gluten-free diet. It also has been consistently linked to low birthweight of newborns (15). A population-based Swedish cohort study has found that women with undiagnosed celiac disease were more likely to have offspring with low birth weight and very low birth weight (17). Besides, the offspring of women with undiagnosed celiac disease had an increased risk for preterm and very preterm birth. Newborns of women with the diagnosed disease did not have a greater risk (17).

So far, the only treatment for celiac disease is a gluten-free diet. It is crucial to avoid barley, wheat, and rye to reduce symptoms, autoantibodies, and villous atrophy (18). Nevertheless, the diet has several disadvantages: high cost, vitamin and mineral deficiency, psychological impact, constipation, and cardiovascular disease risk (18). On the other hand, a gluten-free diet might not only improve the mother's health, and histological damage but also lower the risk of miscarriage or intrauterine fetal death (19). Women should be offered preconception counseling and supervision of a multidisciplinary team. A gluten-free diet should be advised and the anti-tTG levels should be monitored (4).

3.2 Inflammatory bowel disease

Inflammatory bowel disease (IBD) is categorized into Crohn's disease (CD) and ulcerative colitis (UC). Crohn's disease is more common in women and patients are most often diagnosed between 15 and 35 years (20). According to the Olmsted County study, the adjusted annual incidence of Crohn's disease from 2000-2010 was 10.7 cases per 100,000 person-years, while that of ulcerative colitis was 12.2 per 100,000 person-years (20). It is challenging to differentiate both diseases because the main symptom is chronic diarrhea (bloody stools are more common in UC). Abdominal pain, weight loss, and extraintestinal manifestations are also frequent. IBD manifests as flares or remissions, and treatment is indicated for those who have a complicated disease (21). A prospective European ECCO-EpiCom Study of 209 pregnant women found that pregnant patients with CD have more probability to remain in remission during pregnancy than patients with UC, respectively 81 % and 65 % (22). Additionally, women with UC are more likely to experience a

relapse during the first 6 months postpartum. When the disease was active at conception, 56% of CD and 33% of UC women had persistently active disease during pregnancy (22). Another study has found that in up to 45% of patients with ulcerative colitis who conceive during the active phase of the disease, the colitis worsens during pregnancy, 24% have stable disease, and 69% go into remission (23). Among patients with Crohn's disease one-third experiences remission, one-third is stably active, and one-third worsens (23).

Women with IBD might have fertility issues and negative pregnancy outcomes. Adverse outcomes such as preterm birth, small for gestational age birth weight, or stillbirth were reported in a meta-analysis (24). An indicated preterm delivery may be performed for fetal growth restriction or oligohydramnios that is the result of placental insufficiency or for non-reassuring fetal status (25). In addition, the stress response of a growth-restricted fetus may result in stimulation of the hypothalamic-pituitary-adrenal (HPA) axis, a key step in the cascade of events that results in spontaneous preterm birth (25). The odds of preterm birth are higher for those who have an unspecified form of IBD. UC and CD carry a similar risk of this pregnancy outcome (24). Some studies have found an increased risk of congenital anomalies, such as limb, urological and neurological defects, and UC to confer a greater risk than CD, but the results must be interpreted with caution due to methodological flaws (26). Moreover, IBD is associated with severe preeclampsia, preterm premature rupture of membranes, and medically indicated preterm delivery in women using systemic corticosteroids during pregnancy as well as with low 5-minute Apgar score in term infants (27). A population-based study has found that women with UC and CD have an increased chance of elective cesarean delivery. Besides women with UC have a 4-fold increased risk of venous thromboembolism during pregnancy, and with CD – a 2-fold increased risk of antepartum hemorrhage (28). Fortunately, no hypertensive disorders were associated with IBD (28). It is crucial to determine the mode of delivery in IBD. Vaginal delivery has risks for anal sphincter or perineal damage, which lead to worsening perianal disease in CD or pouch dysfunction in patients with IPAA prior to pregnancy. Cesarian section should be performed in women with active perianal disease, ileoanal pouch, and considered for inactive perianal disease (29,30).

Crucial part of successfully delivering a healthy offspring is a preconception counseling for women with IBD. An important part of counseling is to assess and optimize disease activity, review medication safety, suggest folate supplementation, smoking cessation as well as education (26). Gastroenterologists should proactively initiate preconception counseling conversations with all men and women of childbearing age (26). Usually, amino salicylates, corticosteroids, immunomodulators, biologic therapy, or surgical treatment are offered for the patients (31). However, some medications have a negative impact on pregnancy or fetal outcomes. British Society of Gastroenterology consensus guidelines recommend women to discontinue methotrexate due to its teratogenic and embryotoxic effect 6 months prior to conception (strong recommendation) (31). If a patient becomes pregnant while on methotrexate, the usage should be immediately ceased, and high dose of folic acid (15 mg daily) provided for at least 6 weeks (31). It is an antimetabolite that interferes in purine synthesis by decreasing the availability of tetrahydrofolate (32). Growth deficiency, cranial abnormalities, microcephaly, meningomyelocele, hydrocephaly, micrognathia, and limb hypoplasia have been associated with "MTX embryopathy" (32). Recommendation guidelines also suggest continuing anti-TNF therapy for those with active

disease or a high risk of relapse but advise discontinuing therapy at the start of the third trimester, for those who wish to stop it (very low–quality evidence) (31). Anti-TNF medications may be safely discontinued in the second trimester in women with quiescent disease (31). A Danish study of 219 women treated in the third trimester with anti-TNF medications, revealed no increased risk of low birth weight or preterm birth, but 66% experienced moderate to severe disease, which was associated with low birth weight and preterm birth (33). The same council advises treating flares and controlling the disease as normal with 5-ASA, thiopurines, anti-TNF, nutrition, and steroids. Indications for surgery are the same as for non-pregnant patients (31).

3.3 Autoimmune hepatitis

Autoimmune hepatitis (AIH) is an immune-mediated chronic liver disease of unknown etiology (34). The prevalence is 16 to 18 cases per 100,000 people in Europe (35). If left untreated, AIH leads to chronic hepatitis, progressive fibrosis, eventually leading to liver cirrhosis and cancer. Women, especially those of childbearing age, are more affected by autoimmune hepatitis (36). One study showed that around 73% of pregnant women are in remission at conception and others experience a flare during their pregnancy (37). In this study, for 9 % of patients serious maternal complications occurred and high rate (52 %) of postpartum flares was observed (37). A higher risk complication was reported in patients with type 2 or 3 autoimmune hepatitis. The unexplained adverse pregnancy outcomes were associated with anti-SLA/LP and anti-Ro/SSA antibodies (37). Another study has reported that fetal loss rate is 29.4 %, usually before the 20th week (38). Also, premature delivery occurred in 11.8 % of patients (38). In the same study, 54.9 % of pregnant patients had elevated aminotransferases during pregnancy or in the postpartum period (38). 31.4 % of women experienced a relapse of autoimmune hepatitis and 13.7% had flares in the postpartum period, with a median time of 75 days after the delivery (38). There are not many studies, conducted with patients with autoimmune hepatitis, but overall good obstetric and maternal outcomes could be expected.

For the treatment of autoimmune hepatitis corticosteroids, azathioprine, mycophenolate mofetil, biological therapy or other immunosuppressive agents could be used (39). Regardless of remission, some patients still require treatment during pregnancy. Azathioprine (50 to 100 mg/d) does not increase the rate of birth defects, although it was associated with lower birthweight, lower gestational age, and prematurity (39). Breastfeeding during the treatment with azathioprine is usually not recommended, although only 1.2% is excreted in the breast milk (38). Prednisone is not associated with fetal teratogenicity and does not cross the placenta. Therefore, prednisone is the preferred treatment to control disease activity during pregnancy and is allowed during breastfeeding. Mycophenolate mofetil is contraindicated in pregnancy because it causes congenital malformations (6,40).

3.4 Primary sclerosing cholangitis and primary biliary cirrhosis

Primary sclerosing cholangitis (PSC) is a chronic liver disease when bile ducts are inflamed and scarred. When the disease progresses, they narrow and cause cholestasis. About 2/3 of the patients have coexistent IBD (75 % ulcerative colitis) (41). As mentioned, the disease is insidious, and abnormal liver function tests are usually the only sign of the disease. The most common symptoms are abdominal pain, pruritus, jaundice, or fatigue (42). PSC disrupts maternal-fetal bile salt metabolism as in obstetric cholestasis (43). Cholestasis may occur

due to hormonal influence on the bile salt export pump and the hepatocytes. Elevated bile acid levels may be toxic to the fetus, and it also affects myometrial contractility, which can cause vasoconstriction of chorionic veins in the placenta. This may lead to preterm delivery and fetal distress (43).

Primary biliary cirrhosis (PBC) is a chronic and slowly progressive autoimmune liver disease that may lead to liver cirrhosis (44). It affects more women than men (differently from PSC) and is thought to be triggered by environmental factors. PBC may overlap with autoimmune hepatitis (44). Even though there are not many studies done on the relation between pregnancy and PBC, one retrospective study of clinical case has found, that in 30 % of pregnancies flares occur (45). Clinical improvement or stabilization of disease activity was observed in 70 % of pregnancies. Postpartum flares were noted in 60 % of pregnancies (45). It may be due to decreasing estrogen concentrations in blood after delivery. This facilitates a cytokine shift to the inflammatory cytotoxic type 1 profile (46).

Considering, that these diseases are rare, there are not many studies published about their relation to pregnancy. But one study reported a higher cesarean section rate (47 %) in women with PSC compared to women with PBC (20 %) (47). Moreover, preterm delivery rate also increased (27 %) in women having PBC or PSC, compared to a healthy population (47). The rates of preterm birth correlated with higher serum bile acid levels and higher ALT concentration at booking also was associated with early delivery. Fortunately, no correlation was found between the MELD score in women with cirrhosis and preterm birth (47). A Swedish cohort has found that women with liver cirrhosis have an increased risk of cesarean delivery, low birth weight, and preterm birth (48). No risk of preeclampsia, small for gestational age fetus, gestational diabetes, stillbirth, or fetal malformations was noted (48). In another study, liver cirrhosis was associated with intrahepatic cholestasis in pregnancy, the induction of labor, puerperal infections, preterm birth, large for gestational age infants, and neonatal respiratory distress (49). PSC is associated with a higher miscarriage rate. In patients, who got diagnosed with PSC after they became pregnant, the miscarriage rate is 14 %, and 21 % when patients got pregnant with already established diagnosis (50).

Recommended treatment for PBC and PSC is ursodeoxycholic acid (UDCA) (51). It is usually continued throughout most of pregnancy and breastfeeding. The medication might lower maternal serum bile levels, reduce the passage of the bile to the fetus and decrease bile levels in colostrum (51). A Cochrane Review has found that UDCA has better outcomes in pruritus (52). Additionally, no significant differences in fetal distress and spontaneous preterm birth were observed. Less preterm deliveries were noted in UDCA-treated patients (52). UDCA is presumed to be safe during the second and third trimesters but safety data regarding UDCA during the first trimester and breastfeeding are scarce. However, one study reported no adverse fetal outcomes in PSC patients treated with UDCA throughout all gestational trimesters (53). It was also noted that liver enzymes remained stable in treated patients compared to untreated (53).

4. Conclusions

To sum up, autoimmune diseases such as celiac disease, inflammatory bowel disease, autoimmune hepatitis, primary sclerosing cholangitis, or primary biliary cholangitis are not common in pregnancy. Celiac disease poses a risk of cesarean section, recurrent miscarriages, low birth weight and preterm delivery, especially for untreated women and so far, the only treatment is a gluten-free diet.

Inflammatory bowel disease usually remains in remission during pregnancy but may cause hemostatic complications. Moreover, preterm birth, small for gestational age birth weight, or stillbirth may occur. Autoimmune hepatitis usually flares up during postpartum. Nevertheless, the disease may cause pregnancy complications: fetal loss and premature delivery. For inflammatory bowel disease and autoimmune hepatitis immunosuppressive therapy is recommended to avoid the relapse. Primary sclerosing cholangitis and primary biliary cirrhosis are not common diseases in young women. However, the higher risk of cesarean section, preterm birth is observed. The safe treatment during pregnancy is ursodeoxycholic acid. Even though these autoimmune diseases do not pose a high risk of negative outcomes, a careful multidiscipline follow-up by obstetricians and gastroenterologists is crucial for preventing pregnancy, maternal or fetal complications.

References:

1. Borchers AT, Naguwa SM, Keen CL, Gershwin ME. The implications of autoimmunity and pregnancy. J Autoimmun. 2010 May;34(3):J287–99. https://doi.org/10.1016/j.jaut.2009.11.015

2. Albert ED, Bodmer WF, Bontrop RE, Dupont B, Erlich HA, Geraghty DE, et al. Nomenclature for factors of the HLA system, 2002: Nomenclature for factors of the HLA system. Tissue Antigens. 2002 Nov;60(5):407–64. https://doi.org/10.1034/j.1399-0039.2002.600509.x

3. Cassinotti A, Birindelli S, Clerici M, Trabattoni D, Lazzaroni M, Ardizzone S, et al. HLA and Autoimmune Digestive Disease: A Clinically Oriented Review for Gastroenterologists. Am J Gastroenterol. 2009 Jan;104(1):195–217.

4. Boers K, Vlasveld T, van der Waart R. Pregnancy and coeliac disease. BMJ Case Rep. 2019 Dec;12(12):e233226.

5. Mahadevan U, Long MD, Kane SV, Roy A, Dubinsky MC, Sands BE, et al. Pregnancy and Neonatal Outcomes After Fetal Exposure to Biologics and Thiopurines Among Women With Inflammatory Bowel Disease. Gastroenterology. 2021 Mar;160(4):1131–9. https://doi.org/10.1053/j.gastro.2020.11.038

6. Kothadia JP, Shah JM. Autoimmune Hepatitis and Pregnancy. In: StatPearls (Internet). Treasure Island (FL): StatPearls Publishing; 2022 (). Available from: http://www.ncbi.nlm.nih.gov/books/NBK544270/

7. Sarcognato S, Sacchi D, Grillo F, Cazzagon N, Fabris L, Cadamuro M, et al. Autoimmune biliary diseases: primary biliary cholangitis and primary sclerosing cholangitis. Pathologica. 2021 Jun;113(3):170–84.

8. Casella G, Orfanotti G, Giacomantonio L, Bella CD, Crisafulli V, Villanacci V, et al. Celiac disease and obstetrical-gynecological contribution. Gastroenterol Hepatol Bed Bench. 2016;9(4):241–9.

9. Robinson NJ, Glazier JD, Greenwood SL, Baker PN, Aplin JD. Tissue Transglutaminase Expression and Activity in Placenta. Placenta. 2006 Feb;27(2–3):148–57. https://doi.org/10.1016/j.placenta.2005.01.008

10. Sóñora C, Calo G, Fraccaroli L, Pérez-Leirós C, Hernández A, Ramhorst R. Tissue Transglutaminase on Trophoblast Cells as a Possible Target of Autoantibodies Contributing to Pregnancy Complications in Celiac Patients. Am J Reprod Immunol. 2014 Nov;72(5):485–95. https://doi.org/10.1111/aji.12290

11. Tata LJ, Card TR, Logan RFA, Hubbard RB, Smith CJP, West J. Fertility and pregnancy-related events in women with celiac disease: A population-based cohort study. Gastroenterology. 2005 Apr;128(4):849–55. https://doi.org/10.1053/j.gastro.2005.02.017

12. Saccone G, Berghella V, Sarno L, Maruotti GM, Cetin I, Greco L, et al. Celiac disease and obstetric complications: a systematic review and metaanalysis. Am J Obstet Gynecol. 2016 Feb;214(2):225–34. https://doi.org/10.1016/j.ajog.2015.09.080

13. Gasbarrini A, Torre ES, Trivellini C, De Carolis S, Caruso A, Gasbarrini G. Recurrent spontaneous abortion and intrauterine fetal growth retardation as symptoms of coeliac disease. The Lancet. 2000 Jul;356(9227):399–400. https://doi.org/10.1016/S0140-6736(00)02535-6

14. Tersigni C, Castellani R, de Waure C, Fattorossi A, De Spirito M, Gasbarrini A, et al. Celiac disease and reproductive disorders: meta-analysis of epidemiologic associations and potential pathogenic mechanisms. Hum Reprod Update. 2014 Jul 1;20(4):582–93. https://doi.org/10.1093/humupd/dmu007

15. Hadziselimovic F, Geneto R, Buser M. Celiac Disease, Pregnancy, Small For Gestational Age: Role Of Extravillous Trophoblast. Fetal Pediatr Pathol. 2007 Jan;26(3):125–34. https://doi.org/10.1080/15513810701563637

16. Minas V, Jeschke U, Kalantaridou SN, Richter DU, Reimer T, Mylonas I, et al. Abortion is associated with increased expression of FasL in decidual leukocytes and apoptosis of extravillous trophoblasts: a role for CRH and urocortin. Mol Hum Reprod. 2007 Jun 26;13(9):663–73. https://doi.org/10.1093/molehr/gam054

17. Ludvigsson JF, Montgomery SM, Ekbom A. Celiac Disease and Risk of Adverse Fetal Outcome: A Population-Based Cohort Study. Gastroenterology. 2005 Aug;129(2):454–63. https://doi.org/10.1053/j.gastro.2005.05.065

18. Tarar ZI, Zafar MU, Farooq U, Basar O, Tahan V, Daglilar E. The Progression of Celiac Disease, Diagnostic Modalities, and Treatment Options. J Investig Med High Impact Case Rep. 2021 Jan;9:232470962110537. https://doi.org/10.1177/2324709621105370

19. Tursi A, Giorgetti G, Brandimarte G, Elisei W. Effect of Gluten-Free Diet on Pregnancy Outcome in Celiac Disease Patients with Recurrent Miscarriages. Dig Dis Sci. 2008 Nov;53(11):2925–8. https://doi.org/10.1007/s10620-008-0242-x

20. Shivashankar R, Tremaine WJ, Harmsen WS, Loftus EV. Incidence and Prevalence of Crohn's Disease and Ulcerative Colitis in Olmsted County, Minnesota From 1970 Through 2010. Clin Gastroenterol Hepatol. 2017 Jun;15(6):857–63.

21. Wehkamp J, Götz M, Herrlinger K, Steurer W, Stange EF. Inflammatory Bowel Disease: Crohn's disease and ulcerative colitis. Dtsch Ärztebl Int (Internet). 2016 Feb 5; Available from: https://www.aerzteblatt.de/10.3238/arztebl.2016.0072

22. Pedersen N, Bortoli A, Duricova D, D'Inca R, Panelli MR, Gisbert JP, et al. The course of inflammatory bowel disease during pregnancy and postpartum: a prospective European ECCO-EpiCom Study of 209 pregnant women. Aliment Pharmacol Ther. 2013 Sep;38(5):501–12. https://doi.org/10.1111/apt.12412

23. Miller JP. Inflammatory Bowel Disease in Pregnancy: A Review. J R Soc Med. 1986 Apr;79(4):221–5.

24. O'Toole A, Nwanne O, Tomlinson T. Inflammatory Bowel Disease Increases Risk of Adverse Pregnancy Outcomes: A Meta-Analysis. Dig Dis Sci. 2015 Sep;60(9):2750–61. https://doi.org/10.1007/s10620-015-3677-x

25. Romero R, Espinoza J, Kusanovic J, Gotsch F, Hassan S, Erez O, et al. The preterm parturition syndrome. BJOG Int J Obstet Gynaecol. 2006 Dec;113:17–42. https://doi.org/10.1111/j.1471-0528.2006.01120.x

26. Laube R, Paramsothy S, Leong RW. Review of pregnancy in Crohn's disease and ulcerative colitis.

Ther Adv Gastroenterol. 2021 Jan;14:175628482110162. https://doi.org/10.1177/175628482110162

27. Boyd HA, Basit S, Harpsøe MC, Wohlfahrt J, Jess T. Inflammatory Bowel Disease and Risk of Adverse Pregnancy Outcomes. Siegmund B, editor. PLOS ONE. 2015 Jun 17;10(6):e0129567. https://doi.org/10.1371/journal.pone.0129567

28. Bröms G, Granath F, Linder M, Stephansson O, Elmberg M, Kieler H. Complications From Inflammatory Bowel Disease During Pregnancy and Delivery. Clin Gastroenterol Hepatol. 2012 Nov;10(11):1246–52.

29. Caprilli R. European evidence based consensus on the diagnosis and management of Crohn's disease: special situations. Gut. 2006 Mar 1;55(suppl_1):i36–58. http://dx.doi.org/10.1136/gut.2005.081950c

30. Fahad Ali M. Inflammatory bowel disease and pregnancy: fertility, complications and treatment. Ann Gastroenterol (Internet). 2020; Available from: http://www.annalsgastro.gr/files/journals/1/earlyview/2020/ev-10-2020-01-AG_5357-0536.pdf

31. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019 Dec;68(Suppl 3):s1–106. http://dx.doi.org/10.1136/ gutjnl-2019-318484

32. Hyoun SC, Običan SG, Scialli AR. Teratogen update: Methotrexate. Birt Defects Res A Clin Mol Teratol. 2012 Apr;94(4):187–207. https://doi.org/10.1002/bdra.23003

33. Kammerlander H, Nielsen J, Kjeldsen J, Knudsen T, Friedman S, Nørgård B. The Effect of Disease Activity on Birth Outcomes in a Nationwide Cohort of Women with Moderate to Severe Inflammatory Bowel Disease: Inflamm Bowel Dis. 2017 Jun;23(6):1011–8. https://doi.org/10.1097/MIB.0000000000001102

34. Oo YH, Hubscher SG, Adams DH. Autoimmune hepatitis: new paradigms in the pathogenesis, diagnosis, and management. Hepatol Int. 2010 Jun;4(2):475–93.

35. Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, et al. Diagnosis and management of autoimmune hepatitis. Hepatology. 2010 Jun;51(6):2193–213. https://doi.org/10.1002/hep.23584

36. Bozward AG, Wootton GE, Podstawka O, Oo YH. Autoimmune Hepatitis: Tolerogenic Immunological State During Pregnancy and Immune Escape in Post-partum. Front Immunol. 2020 Sep 24;11:591380. https://doi.org/10.3389/fimmu.2020.591380

37. Schramm C, Herkel J, Beuers U, Kanzler S, Galle PR, Lohse AW. Pregnancy in Autoimmune Hepatitis: Outcome and Risk Factors. Am J Gastroenterol. 2006 Mar;101(3):556–60.

38. Terrabuio DRB, Abrantes-Lemos CP, Carrilho FJ, Cançado ELR. Follow-up of Pregnant Women With Autoimmune Hepatitis: The Disease Behavior Along With Maternal and Fetal Outcomes. J Clin Gastroenterol. 2009 Apr;43(4):350–6.

39. Goldstein LH, Dolinsky G, Greenberg R, Schaefer C, Cohen-Kerem R, Diav-Citrin Orna, et al. Pregnancy outcome of women exposed to azathioprine during pregnancy. Birt Defects Res A Clin Mol Teratol. 2007 Oct;79(10):696–701. https://doi.org/10.1002/bdra.20399

40. Peters MG. Management of Autoimmune Hepatitis in Pregnant Women. Gastroenterol Hepatol. 2017 Aug;13(8):504–6.

41. Hirschfield GM, Karlsen TH, Lindor KD, Adams DH. Primary sclerosing cholangitis. The Lancet. 2013 Nov;382(9904):1587–99. https://doi.org/10.1016/S0140-6736(13)60096-3

42. Lazaridis KN, LaRusso NF. Primary Sclerosing Cholangitis. Ingelfinger JR, editor. N Engl J Med. 2016 Sep 22;375(12):1161–70.

43. Kammeijer CQ, De Man RA, De Groot CJM. Primary Sclerosing Cholangitis and Pregnancy. Clin Pract. 2011 Aug 26;1(3):e55.

44. Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis: a Review Featuring a Women's Health Perspective. J Clin Transl Hepatol (Internet). 2014 Dec 15;2(4). Available from: http://www.xiahepublishing.com/ArticleFullText.aspx?sid=2&jid=1&id=10.14218%2fJCTH.2014.00024

45. Efe C, Kahramanoğlu-Aksoy E, Yılmaz B, Ozseker B, Takcı S, Roach EC, et al. Pregnancy in women with primary biliary cirrhosis. Autoimmun Rev. 2014 Sep;13(9):931–5. https://doi.org/10.1016/j.autrev.2014.05.008

46. Ostensen M, Brucato A, Carp H, Chambers C, Dolhain RJEM, Doria A, et al. Pregnancy and reproduction in autoimmune rheumatic diseases. Rheumatology. 2011 Apr 1;50(4):657–64. https://doi.org/10.1093/rheumatology/keq350

47. Cauldwell M, Mackie F, Steer P, Henehghan M, Baalman J, Brennand J, et al. Pregnancy outcomes in women with primary biliary cholangitis and primary sclerosing cholangitis: a retrospective cohort study. BJOG Int J Obstet Gynaecol. 2020 Jun;127(7):876–84. https://doi.org/10.1111/1471-0528.16119

48. Hagström H, Höijer J, Marschall H, Williamson C, Heneghan MA, Westbrook RH, et al. Outcomes of Pregnancy in Mothers With Cirrhosis: A National Population-Based Cohort Study of 1.3 Million Pregnancies. Hepatol Commun. 2018 Nov;2(11):1299–305.

49. Flemming JA, Mullin M, Lu J, Sarkar MA, Djerboua M, Velez MP, et al. Outcomes of Pregnant Women With Cirrhosis and Their Infants in a Population-Based Study. Gastroenterology. 2020 Nov;159(5):1752-1762.e10. https://doi.org/10.1053/j.gastro.2020.07.052

50. Wronka KM, Bik E, Milkiewicz P. Outcome of pregnancy in patients with primary sclerosing cholangitis. Dig Liver Dis. 2022 Apr;54(4):509–14. https://doi.org/10.1016/j.dld.2021.08.015

51. Brites D, Rodriguez CMP. Elevated levels of bile acids in colostrum of patients with cholestasis of pregnancy are decreased following ursodeoxycholic acid therapy. J Hepatol. 1998 Nov;29(5):743–51. https://doi.org/10.1016/S0168-8278(98)80255-9

52. Gurung V, Stokes M, Middleton P, Milan SJ, Hague W, Thornton JG. Interventions for treating cholestasis in pregnancy. Cochrane Pregnancy and Childbirth Group, editor. Cochrane Database Syst Rev (Internet). 2013 Jun 24 (cited 2022 Nov 6); Available from: https://doi.wiley.com/10.1002/14651858.CD000493.pub2

53. Wellge BE, Sterneck M, Teufel A, Rust C, Franke A, Schreiber S, et al. Pregnancy in primary sclerosing cholangitis. Gut. 2011 Aug 1;60(8):1117–21. http://dx.doi.org/10.1136/gut.2010.228924