Interactions Between Celiac Disease and Pregnancy: A Literature Review

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ABSTRACT Celiac disease (CD) is an immune-based reaction to dietary gluten. CD can present with a diverse array of symptoms. Many CD patients have no symptoms at all. Thus, a great number of atypical cases of CD remain undiagnosed, leading to a risk of long-term complications. Some atypical symptoms of CD such as pregnancy complications, infertility, recurrent abortions, intrauterine growth restriction, preterm delivery, and severe preeclampsia have been investigated in undiagnosed and diagnosed pregnant women with CD. Nutrient deficiency and autoimmune pathogenic mechanisms have been hypothesized to be the explanation of these adverse pregnancy outcomes. Recently, an association between obstetric complications and anti-tissue transglutaminase antibodies titers in women with CD has been reported. While the adverse effects of CD on the reproductive system are well investigated, there are only a few reports in the literature on the effect of pregnancy and puerperium on CD. We reviewed the published literature on the adverse effects and pathophysiology of CD in reproductive disorders and the effect of pregnancy and puerperium on the manifestation of CD.

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Celiac disease (CD) is an autoimmune-based reaction to dietary gluten that primarily affects the small intestine in those with a genetic predisposition. There has been a substantial increase in the rate of CD diagnosis in the last decades. CD occurs in adults and children at rates approaching 1% of the general population; however, only 20–50% of affected individuals have subjective symptoms. As CD is an autoimmune enteropathy characterized by circulating autoantibodies, several serological tests provide a noninvasive tool to screen both individuals at risk for the disease and the general population [1].

SCREENING FOR CELIAC DISEASE SHOULD BE CONSIDERED IN CASES OF UNEXPLAINED INFERTILITY OR RECURRENT MISCARRIAGE WITH NO EVIDENT EXPLANATION.

CD may present with a variety of symptoms, including typical gastrointestinal symptoms (e.g., diarrhea, steatorrhea, weight loss, bloating, flatulence, abdominal pain) as well as non-gastrointestinal abnormalities (e.g., abnormal liver function tests, iron deficiency anemia, bone disease, skin disorders, and reproductive disorders). Indeed, many individuals with celiac disease may have no symptoms at all [1].

Given the heterogeneity of clinical presentation, many atypical cases of CD remain undiagnosed, leading to a risk of long-term complications. Atypical non-gastrointestinal symptoms of CD may include disorders of fertility. Pregnancy complications have also been investigated [2-4].

Due to the autoimmune nature of this disease, several investigators have attempted to study the effect and pathophysiology of CD relating to perinatal outcomes and the effect of pregnancy on the disease.

In the current review, we describe the research on adverse pregnancy outcomes related to untreated CD as well as the presumed underlying pathophysiology. In addition, we focused on the effect of pregnancy and the related hypotheses concerning the activation of CD during pregnancy and the postpartum period.

PATIENTS AND METHODS

Electronic databases (MEDLINE, EMBASE, PubMed, Science direct, Web of Science, and the Cochrane Library) were searched from their inception until December 2022. The following terms were searched: celiac, celiac disease, coeliac, coeliac disease, pregnancy,

preterm birth, small for gestational age, miscarriage, premature, low birth weight, fertility, preeclampsia, recurrent, intrauterine growth restriction, stillbirth, obstetric complications, spontaneous preterm birth, puerperium, and postpartum. The search strategy consisted of the MESH terms celiac, and celiac disease as a major topic with a combination of the mentioned terms. Only human studies in English and Hebrew were included.

CD EFFECT ON REPRODUCTION AND PREGNANCY

Infertility

There have been several reports on the link between CD and fertility. Lasa et al. [5] described an association between women with a diagnosis of infertility and undiagnosed celiac disease (N=4471, odds ratio [OR] 3.09, 95% confidence interval [95%CI] 1.74–5.49). Interestingly, no difference was found when considering the occurrence of infertility in patients with CD compliant to gluten free diet (GFD) (N=33,636, OR 0.99, 95%CI 0.86–1.13) [5]. Similar results were found in a meta-analysis by Tersigni and colleagues [2] where the OR for CD was 5.06 (95%CI 2.13–11.35) in patients with unexplained infertility.

DURING THE PREGNANCY OF A PATIENT WITH CELIAC DISEASE, CAREFUL SURVEILLANCE IS NEEDED FOR FETAL GROWTH AND SIGNS OF PRETERM DELIVERY. A GLUTEN FREE DIET MAY PREVENT THE OCCURRENCE OF INTRAUTERINE GROWTH RETARDATION, SMALL GESTATIONAL AGE, LOW BIRTH WEIGHT, STILLBIRTH, AND PRETERM BIRTH.

These studies show that undiagnosed CD is a risk factor for infertility, which may be the source for recommending screening such women evaluated for unexplained infertility. Moreover, adoption of a GFD may have a positive impact on fertility in this group of patients [2,5].

In contrast to these reports, Dhalwani and colleagues [6] studied the association between CD and infertility disorders with data from over 2 million women over a 20-year period. They found that rates of infertility among women without CD were similar to those of women with CD before and after diagnosis. The authors concluded that the majority of women with CD did not have a substantially greater likelihood of fertility disorders compared to women without CD.

A possible explanation for the differences observed in these studies may be that the former studies based their data on women who intentionally attended infertility clinics. Thus, only a selective group of women were included, since not all women who experience difficulties conceiving seek medical assistance.

Miscarriage

A significantly higher prevalence of spontaneous abortions (SA) was found among women with CD in a study conducted by Moleski and co-authors [7] (n=124/245 [50.6%] vs. n=198/488 [40.6%], P = 0.01). Their results also showed that most of the SA (85%) in women with CD occurred prior to initiation of a GFD.

In a meta-analysis by Arvanitakis et al. [8], a statistically significant positive correlation was also found between the risk for SA and CD (relative risk [RR] 1.35, 95%CI 1.10–1.65).

Interestingly, a prospective study by Chen et al. [9] showed a correlation between the presence of serum antibodies in patients undergoing in-vitro fertilization (IVF) and adverse outcomes, such as pregnancy failure and miscarriage.

These studies suggest that untreated CD might increase the risk of miscarriage. Furthermore, treatment of the condition may decrease the rate of early pregnancy loss. Thus, serologic screening for CD may be suggested in cases of unexplained infertility or recurrent miscarriage with no evident explanation.

Stillbirth

In a meta-analysis by Saccone and colleagues [10], which included 4,844,555 women, the risk of stillbirth in women with CD (both treated and untreated) was significantly higher (OR 4.84, 95%CI 1.08–21.75) than in women without CD. A statistically significant correlation was also found between stillbirth and CD (RR 1.57, 95%CI 1.17–2.10) in the meta-analysis by Arvanitakis and co-authors [8]. In contrast, no increased risk for stillbirth was found by the meta-analysis by Tersigni et al. [2]. These slight discrepancies may be the result of selection bias and lack of quality assessment for each individual study.

Intrauterine growth retardation, small gestational age, low birth weight

The meta-analysis by Saccone et al. [10] found that women with CD had a significantly higher risk of both developing intrauterine growth retardation (IUGR) (n=3773 vs. 2,963,065; OR 2.48, 95%CI 1.32–4.67) and delivering low birth weight (LBW) babies (OR 1.63, 95%CI 1.06–2.51). Similarly, the OR for pregnant women with CD was 8.73 for IUGR (n=234 vs. 400, 95%CI 3.23–23.58).

A significantly higher risk of LBW (OR 1.75, 95%CI 1.23–2.49) in CD patients was found in the meta-analysis by Tersigni and associates [2]. In addition, pregnancies of mothers with CD had a statistically significant correlation with lower mean birth weight (mean difference 176.08, 95%CI -265.79 to -86.38) in a meta-analysis by Arvanitakis and colleagues [8].

Interestingly, Kiefte-de Jong et al. [11], showed that fetuses of women with positive antithyroglobulin weighed approximately 20 grams less than women with negative antithyroglobulin (95%CI -32 to -1 gram) during the second trimester and about 80 grams less (95%CI, -140 to -8 grams) during the third trimester. Interestingly, the reduction in birth weight in offspring of mothers was twofold greater among mothers who carried HLA-DQ2 or -DQ8. They concluded that levels of antithyroglobulin in pregnant women are inversely associated with fetal growth, and that birth weight was further reduced in those carrying HLA-DQ2 and -DQ8.

BINDING OF ANTITHYROGLOBULIN ON TROPHOBLAST WITH CONSEQUENT INFLAMMATORY ANTIANGIOGENIC PROCESS COULD BE A NOVEL PATHOGENIC MECHANISM CONTRIBUTING TO THE ADVERSE PREGNANCY OUTCOMES OCCURRING IN CELIAC DISEASE.

Preterm birth

Saccone et al. [10] found higher rates of preterm birth (PTB) among women with CD (OR 1.40, 95%CI 1.18–1.6). In addition, women with diagnosed and treated CD had a 20% significant decrease of PTB (OR 0.80, 95%CI 0.64–0.99). Tersigni et al. [2] also noted a significant relative risk (RR) for PTB among those patients (RR 1.37, 95%CI 1.19–1.57). Both studies found that after initiation of a GFD the risks of PTB were markedly reduced. Similarly, Arvanitakis et al. [8] found a statistically significant association between CD and PTB (RR 1.29, 95%CI 1.12–1.49).

During the pregnancy of a patient with CD, careful surveillance should be performed for evaluating fetal growth as well as signs for PTB. Moreover, physicians should consider screening for CD among patients presenting with IUGR of an unknown etiology. These studies also indicated that GFD in these patients may improve fetal nutritional support and growth. Further studies are necessary to evaluate the cost-effectiveness of screening for CD in these women.

Preeclampsia

Wolf and colleagues [12] investigated the prevalence of undiagnosed CD in patients with preeclampsia. Women with a history of preeclampsia were tested for antithyroglobulin and EMA seropositivity but an increased incidence of CD compared with controls was not found.

With this regard, no statistically significant difference in the incidence of preeclampsia was found in all mentioned meta-analyses [2,8,10].

CURRENT HYPOTHESES OF THE EFFECT OF CD ON PREGNANCY COMPLICATIONS

The pathogenesis of reproductive disorders in CD is unclear, but some hypotheses have been suggested. These hypotheses may be classified into two main categories: nutrient deficiency and autoimmune mechanisms. Recent research shed light on hypercoagulability in CD and the gut-uterus axis and their potential effect on reproduction.

Malabsorption and nutrient deficiency

In individuals with CD, the main nutrients that are often deficient include iron, calcium, vitamin D, vitamin B12, folate, and zinc. During pregnancy, these nutrient deficiencies can have significant effects on both maternal health and pregnancy outcomes. Iron deficiency can lead to anemia, which may increase the risk of preterm birth and low birth weight. Calcium and vitamin D deficiencies can contribute to bone health issues for the mother and may affect fetal skeletal development. Insufficient vitamin B12 and folate levels can lead to neural tube defects and other developmental problems in the baby. Zinc deficiency may impair immune function and hinder proper fetal growth [13,14].

Addressing and managing these nutrient deficiencies in pregnant women with celiac disease is crucial to promote better maternal and fetal health and improve pregnancy outcomes. Regular monitoring, appropriate supplementation, and a well-balanced gluten-free diet are essential measures to ensure optimal nutritional status during pregnancy in those with CD [1].

Autoimmune mechanisms

Studies have investigated the role of direct immune mediated impairment of the physiologic processes occurring during embryo implantation and placental development in women with CD.

Antithyroglobulin antibodies induce trophoblast apoptosis

The enzyme thyroglobulin is expressed intra- and extracellularly in endometrial, stromal, and trophoblast cells, with higher levels in late pregnancy [15]. Considering the role of thyroglobulin in extracellular matrix assembly and cell

adhesion, and in the spreading and migration of diverse tissues, thyroglobulin may play a critical role in the process of implantation.

Patients with untreated CD generally show increased levels of serum antithyroglobulin antibodies. Thus, it is plausible that the binding of circulating antithyroglobulin antibodies to trophoblasts could serve as an immunologic mechanism by which CD interferes with pregnancy. In addition, it is likely that the increased apoptosis of extravillous trophoblasts may contribute to the pathophysiology of human miscarriage and IUGR [16].

In support of these hypotheses, Di Simone et al. [17] observed that both commercial monoclonal antithyroglobulin IgG antibodies isolated from CD women were able to bind directly to trophoblasts and significantly reduce trophoblast invasion through apoptotic damage [17]. Furthermore, Sóñora et al. [18] evaluated the ability of autoantibodies against thyroglobulin present in sera from CD patients to display direct effects through their interaction with thyroglobulin expressed on trophoblast cells and phagocytes, inducing tissue damage and interfering with wound healing and the clearance of trophoblast apoptotic bodies by phagocytes. The results revealed a decrease in trophoblast migration and proliferation with an increase in apoptosis levels and a delay in injury healing and clearance of trophoblast apoptotic bodies. All were compared with those observed in control sera.

PHYSICIANS SHOULD BE AWARE OF LATENT CELIAC DISEASE ACTIVATION DURING PREGNANCY AND THE PUERPERIUM.

Antithyroglobulin antibodies affect human endometrial angiogenesis

Endometrial angiogenesis and decidualization, as well as trophoblast invasion, are fundamental preconditions for a successful implantation and a desirable pregnancy outcome.

Di Simone et al. [19] observed that both polyclonal immunoglobulins isolated from the sera of CD patients and commercial monoclonal antithyroglobulin directly bound human endometrial endothelial cells isolated from placental explants. This binding caused a consequent decrease in cellular thyroglobulin activity followed by a decrease of in-vitro angiogenesis was confirmed in-vivo, using a murine model of angiogenesis.

Binding of antithyroglobulin has subsequent functional inhibitory effects on trophoblast invasion and endometrial angiogenesis. These inflammatory, antiangiogenic processes might interfere with embryo implantation and can be considered a pathogenic mechanism contributing to the adverse pregnancy outcomes occurring in CD.

Hypercoagulability in CD

A newly explored area of CD is the existence of hypercoagulability and the resulting thromboembolic phenomena. There is an increased risk for thromboembolic events in adults as well as in children with CD. Even the onset of the disease's presentation may occur due to a thrombotic event, as is the case for other complications manifested in CD [20].

Many autoimmune conditions are associated with CD, some of which are known for their increased tendency to induce thromboembolic phenomenon. Two classical examples include systemic lupus erythematosus (SLE) and anti-phospholipid (aPL) syndrome. It is well known that aPL autoantibodies confer increased risk for thromboembolic events and poor outcomes in these diseases, including adverse pregnancy outcomes such as recurrent miscarriage, IUGR, and PTB. Interestingly, an autoantibody network associated with these two entities, composed of anti-phosphatidylserine prothrombin, aPL, and anti-prothrombin have been found in CD [21].

Further studies are necessary to confirm and establish a reliable connection between CD hypercoagulation and adverse pregnancy outcomes.

Dysbiosis and the gut–uterus axis

Medical research has shed light on the bidirectional communication between the gastrointestinal tract and distant organs, including the gut–uterus axis [22]. Emerging evidence suggests that luminal eco-events occurring within the gut, such as shifts in the gut microbiome, may impact the maternal–fetal interface, potentially contributing to adverse outcomes such as miscarriage, preterm birth, and low birth weight (LBW) [23]. The presence of dysbiosis, an alteration in the gut microbiome, has been identified in the pathogenesis of CD [24,25]. The presence of dysbiosis, an alteration in the gut microbiome, has been identified in the pathogenesis of CD and could potentially be the cause of various complications observed in pregnant women diagnosed with CD [24-26].

THE EFFECT OF PREGNANCY ON THE ACTIVATION OF CD

Several reports have described the effect of pregnancy on CD. The first case report on postnatal presentation of CD described two women who presented with CD in the postnatal period. The presenting symptom was diarrhea that started acutely at the end of the puerperium and was characterized by fat malabsorption, hypocalcemia,

and hypokalemia. In both cases, CD was diagnosed after jejunal biopsy [27]. Since then, only a few cases of CD have been diagnosed that could suggest a relation to pregnancy [28,29]. The descriptions of these reports suggest that physicians should be aware of the possible activation of undiagnosed CD and the varied clinical manifestations during pregnancy and the puerperium. A greater focus on refractory diarrhea with the concomitant finding of anemia, weight loss, and electrolyte imbalance, together with an emphasis on low calcium levels and isolated prolonged INR coupled with a low threshold for serological testing may uncover further cases of an otherwise submerged clinical iceberg and prevent the adverse outcomes of this easily treated disease.

The possible reason for an exacerbation of CD during pregnancy and the puerperium is unclear, but several possibilities exist. The appearance of a new autoimmune disease during pregnancy and the early postpartum period is not uncommon. Similar incidents have been described for rheumatoid arthritis (RA), inflammatory bowel disease, and SLE [28].

The reasons for the effect of pregnancy on the course of various autoimmune diseases are speculative. Sex hormones have a marked effect on the immune system. Estrogens have been shown to inhibit T suppressor cells and cause B cell release and the production of autoantibodies, whereas androgens have been shown to inhibit certain T cell subsets and cause an increase in the production of interleukin 2. Both T cells and B cells appear to be involved in the pathogenesis of CD, and their cooperation may be crucial for the generation of antibodies as well as for the amplification of the gluten reactive T-cell response [29].

Although androgens have opposing effects to estrogen, the relative concentration of these substrates and the amount of androgen that is converted to estrogen probably determine the net immune stimulation-immunosuppression ratio. In addition, progesterone has its own anti-inflammatory action that may differ from the other two. Female hormones may effect the expression of adult CD, as expressed by female predominance in CD [28].

Another immunomodulatory hormone that may play a role in the effect of pregnancy on the activation of CD is prolactin. It seems that prolactin is not only a pituitary hormone with an important role in reproduction, but also a cytokine involved in the immune response. In the last two decades, multi-organ and organ specific autoimmune diseases like SLE, RA, Sjogren's, Hashimoto's thyroiditis and active CD, were discussed to be associated with prolactin [30].

Studies revealed that many organs and cells, particularly lymphocytes, are affected by prolactin. Prolactin interferes specifically with B cell tolerance induction, enhances proliferative response to antigens and mitogens, and increases the production of immune globulins, cytokines, and autoantibodies [30]. Thus, excessive prolactin can shift the immune response toward higher activity and may account for a possible pathogenesis for the activation of CD during pregnancy and the postpartum period.

PROLACTIN MAY PLAY A PART IN IMMUNE MODULATION IN THE INTESTINAL DAMAGE OF CELIAC DISEASE

Further research on the effects of prolactin on the immune system in general and in CD patients specifically, may shed light on how to best utilize the hidden potential of prolactin in the activation of silent CD during pregnancy and the puerperium.

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Capsule

IL-1β+ macrophages fuel pathogenic inflammation in pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease with high resistance to therapies. Inflammatory and immunomodulatory signals co-exist in the pancreatic tumor microenvironment, leading to dysregulated repair and cytotoxic responses. Tumor-associated macrophages (TAMs) have key roles in PDAC2, but their diversity has prevented therapeutic exploitation. **Caronni** et al. combined single-cell and spatial genomics with functional experiments to unravel macrophage functions in pancreatic cancer. The authors uncovered an inflammatory loop between tumor cells and interleukin-1β (IL-1β)-expressing TAMs, a subset of macrophages elicited by a local synergy between prostaglandin E2 (PGE2) and tumor necrosis factor (TNF). Physical proximity with IL-1β+ TAMs was associated with inflammatory reprogramming and acquisition of pathogenic properties by a subset of PDAC cells. This occurrence was an early event in pancreatic tumorigenesis and led to persistent transcriptional changes associated with disease progression and poor outcomes for patients. Blocking PGE2 or IL-1β activity elicited TAM reprogramming and antagonized tumor cell-intrinsic and -extrinsic inflammation, leading to PDAC control in vivo. Targeting the PGE2–IL-1β axis may enable preventive or therapeutic strategies for reprogramming of immune dynamics in pancreatic cancer.

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