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Histological Changes of Female Reproductive Tract and Milk Breast Composition in Patients with Celiac Disease:

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ABSTRACT: Celiac disease (CD) is an autoimmune disturbance that occurs in genetically susceptible people who consume dietary gluten which causes intestinal mucosal atrophy , diarrhea and weight loss along with architectural alterations of the crypts and villi or one of them , a raise in cell density of the lamina propria, an increase in the in intra epithelial lymphocyte(IEL) and nutrient malabsorption. Female reproductive organs is affect in patients with CD which lead to infertility , endometriosis , polycystic ovary syndrome (PCOS) , miscarriage and menstrual cycle pattern changes for example oligomenorrhea, hypomenorrhea, dysmenorrhea , metrorrhagia, gestation and puerperal disorders which caused from nutrient deficiency or immune-mediated mechanisms . There is a reduction in immunoglobulin A (IgA) and IgM and immune-protective compounds transforming growth factor (TGF-β1) in CD patients milk. Conclusion: There is a lot of changes in reproductive life cycle and milk breast composition in CD women .

Celiac Disease (CD):

CD is a genetic inflammatory disease in a small bowel caused by extremism to gluten/gliadin protein **(Al-Saleem,2018; Al-Saleem ,2020)** which stores in barley, wheat and rye**(Al-Saleem,2019)**. The small bowel in CD patients have a wide shadow of histological changes from a raise of intraepithelial lymphocytes (IEL)in normal architecture mucosa, to the change of villi and crypts or one of them and raise of the cell density in lamina propria to the most severe is the traditional flat mucosa. **(Oberhuber,2000)** CD is diagnosed by traditional clinical symptoms, malabsorption characteristics , anti-transglutaminase antibodies positive reaction , also the decreasing iron level , endoscopic submission and histologic changes based on Marsh scores that an important for diagnosis of CD **(Freeman,2009)**. The deamidation of transglutaminase form a prolamine negative charge that made a complex with HLA which diagnosed by T helper cells, that induce other intestinal mucosa lymphocytes causing an inflammatory response by the production of interferon-gamma ,interleukins, and tumor necrosis factor and inflammatory reaction **(Farrell and Kelly,2002)**.

CD and Infertility :

Infertility is an inability to conceive after a year (in female under 30–35 years old) or six months (in a female over thirty-five years old) of regular, frequent (3 or 4 times per week), unprotected copulation and also inability to become pregnant to term and birth a healthy baby. Secondary or primary infertility may be caused by the female, the male, or both It affects approximately 13% of women and 10% of men**(Kasna and Agrawal,2022)**, The major causes of female infertility are an ovulation, fallopian tube disease(e.g., adhesions), pelvic adhesions, endometriosis, unexplained infertility caused by cervix diseases , uterus abnormalities, as well as ovarian failure**(Jerome et al.,2019; Holmes,1882)**,which appear with the age**(Kovanci and Schutt,2015)**. Reductions in antioxidants, vitamin B12 and folate, which are commonly noticed in patients with CD, have been explained to decrease mitochondrial function and raised oocytes oxidative stress, potentially reducing their evolution capacity**(Bianchi,2024)** .Another study confirm that undiagnosed CD have infertility risk factor**(Lasa ,2014)**.Also approximately of(4 %) infertile women are CD**(Freeman,2015)**.

CD and Menstrual Cycle Alterations:

There is a common menstrual problems which include amenorrhea and oligomenorrhea and dysmenorrhea in an untreated CD women .Astudy confirm that untreated celiac women have 1.5 year first menstrual later**(Kotze, 2004)**. Another study by Molteni et al., on 54 untreaded CD and 54 healthy women found that 38.8 % of cd women have suffer from amenorrhea when compared with9.2% in healthy women**(Molteni et al.,1990)** and also a study confirms that there is an association between CD and amenorrhea**(Martinelli et al.,2010)**.Other research on Slovenia women by Mičetić-Turk et al., documented that , the menarche age about (12-14) in 72.9%CD individuals with 77.3% healthy females and deduced that delayed menarche does not caused by treated or untreated CD(**Mičetić-Turk et al.,2019)**.

Endometriosis in patients with CD:

Endometriosis is gynaecologic defect recognized by the existence of endometrial tissue in the pelvic cavity. Approximately of 5-10% of women complaining from this disorder ,fourty to eighty percent of these women suffer from pelvic ache, and about thirty to fifty percent are infertile**(Bulun 2009)** and it leads to abnormal uterine bleeding **(Al-Saleem et al.,2019)**.The pathogenesis of endometriosis may be multifactor, that the primum movens appears to be symbolized by retreat endometrial wrack reflux into the peritoneal cavity and this induces the oxidative stress increasing and decreases inflammation **(Szczepańska et al.,2003)**. The macrophages in peritoneal produce growth and angiogenic factors , pro-inflammatory cytokines that in charge of conserve the reducing and disturbance reproductive function and the and the causing of endometriosis**(Sakamoto et al.,2003)**.About 20-50% of endometriosis women are infertility**(Barnhart et al.,2002)** CD is an autoimmunologic disease with auto-antibodies production and accompanied with a many of autoimmune disorders include decreasing IgA , autoimmune thyroiditis and diabetes mellitus **(Green & Jabri 2006)**. Endometriosis and CD, when accompanied becomes tricky to diagnosis because they have the same symptoms (bowel changes ,abdominal pain ,infertility and menstrual disturbance **(Caserta et al.,2014)** .A study by Aguiar et al., found that 9 of the 120 endomeriosis women were positive to transglutaminase antibody (anti-tTGA) and 5 of them were positive to anti-endomysium (anti-EMA), 3 of these patients were diagnosed CD by intestinal biopsy (2.5% prevalence **(Aguiar et al.,2009)**.

The two disorders have the same inflammation pathways. Indeed, major increases in interleukin-6 and interferon-g increasing are recognized in both CD**(Schuppan et al.,2009)** and endometriosis **(Othman et al.,2008)**. More ever , HLA-DQ7 has been appeared twice as popular in endometriosis patients **(Ishii et al.,2003)**, and there is a risk of CD in patients with endometriosis **(Monsuur et al.,2008)**.

CD and PCOS:

PCOS is a popular endocrine disturbance impacts 5-18 female during reproductive age. It is caused because of ovarian and hypothalamic dysfunction, insulin resistance, and epigenetic and genetic susceptibility **(Joham et al.,2022)**.Only one study done by Kuscu et al. about this association , found that from 52 women with PCOS and 50 with same age control women,8 women from the PCOS and 1 women from the health group were positive for IgG gliadin antibody. There is a negative for IgA endomysium and IgA gliadin antibodies. There is no CD from 6 women who have seropositive and submit to endoscopic analysis and the study concluded that there is no association between CD and PCOS**(Kuscu et al.,2002)**.

Gonadotropin secretion disturbance with increased luteinizing hormone(LH)level , associated with decreased or normal follicle stimulating hormone (FSH) level. In several, a moderate increasing of serum testosterone is visible. The cause of the (PCOS) still demands elucidation. A previous research confirm that the PCOS appear in CD **(Freeman,2015).**

Celiac disease and Miscarriage:

Miscarriage is the unprompted pregnancy loss and it is early miscarriage if happened before twelve weeks or late miscarriage if happened from twelve to twenty four weeks of gestation. **(Giakoumelou et al.,2016)**. In a larger study done by Martinelli et al on the Italian reproductive life cycle CD women and found a significant association between celiac disease and risk of abortion ($p < 0.001$). In this study it is found that placental abruption occurred in more than 18% of the Italian CD women but only 1% of controls**(Martinelli et al.,2010)**,and a study done by Ciacci et al. found a marked elevation of miscarriages incidence in pregnant CD patients with a nearly 9-fold elevated risk in contrast with non-CD patients**(Ciacci et al.,1996)**.

Also a study on 13 CD patients with recurrent miscarriages and who began to use the gluten-free diet. Six of the thirteen patients became gravid**(Tursi et al.,2008)**.

(anti-tTG) and immunoglobulin G (IgG) antibodies bind to trophoblastic cells**(**outer layer blastocyst, that important in implantation and forming placenta**)**, these lead to decreased the placental cells invasiveness through a layer of extracellular matrix, and decreased the cellular matrix metalloprotease (MMP) activity and apoptosis of cells. **(Freeman,2015; Di Simoneet al.,2010; Peshevska-Sekulovska et al.,2023)**.Also the anti-tissue transglutaminase-2 (anti-TG2) antibodies bind to human endometrial endothelial cells (HEECs) and leads to inhibit matrix metalloprotease-2 MMP-2 activation and reduced newly created vessels both in vivo and vitro, this happened by inhibiting the activation of matrix metalloprotease-2 MMP-2, alteration the mechanical and physical properties of cell membranes, disarranging the fibers of cytoskeleton, and inhibiting the intracellular phosphorylation of focal adhesion kinase FAK and extracellular signal-regulated kinases (ERK). can lead to a reduction in cell motility, proliferation, survival, and invasion, causing defects in cell spreading and adhesion structure turnover **(Di Simone et al.,2013)**.

Adverse Outcomes in CD patients:

In a research by Martinelli et al., on Italian CD patients, a significant correlation has found of CD and placenta abruption, gestational hypertension ,intrauterine growth restriction , serious anemia and uterine hyperkinesia ($p < 0.001$) **(Martinelli et al.,2010)**.

Also another document confirm that untreated CD females have a risk to deliver babies with a preterm birth and small gestational age in contrast with women without CD**(Khashan et al.,2010)**. Saccone et al., found that CD patients had a significantly higher risk of evolution an obstetric complexities that involved intrauterine growth restriction, preterm birth, stillbirth, small gestational age and low birthweight, gluten-free diet treatment leads to preterm delivery **.(Saccone et al.,2016).**

The pathogenesis of CD regarding disturbance of reproductive need to clarification. CD can cause malabsorption and lacks of folic acid , vitamin K and iron which are important for organogenesis**(Stazi & Trinti,2005 ; Kotze,2004)**.

Immunological Profile of Breast Milk in Celiac Mothers:

Existence of food antigens is important for development of immune system in child, preventing disease and induce baby health. Several popular food antigen proteins are existence in milk of breast. A study found that gluten immunogenic peptide (GIP) was recognized in about seventy five percent of breast milk in non CD patients , and eighty two percent of CD mother was negative to these proteins **(Ruiz-Carnicer et al.,2024)**.

The breast milk in CD mother is characterized by decreased immune-protective proteins transforming growth factor (TGF-β1 and_secretory immunoglobulin sIg A). The diminish ion in these proteins could reduce the immunologic compounds of breast-feeding to the child's and leads to develop CD**(Olivares et al.,2015)**.

The immunoglobulin (IgM and IgA) was significantly reduced in CD milk mothers through the late lactation (from six to twelve months) after delivery. The tumor necrosis factor-α , interleukin-6 and monocyte chemoattractant protein-1 were most existence in milk CD mothers, the prevalence of soluble Toll-like receptor-2 in CD milk mother was lower **(Villamil et al.,2021)**.

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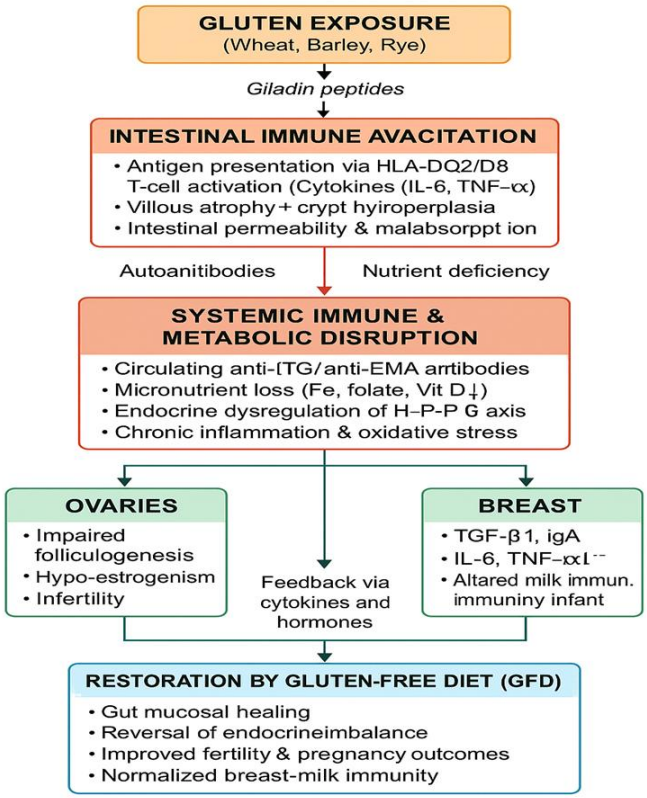

Figure 1. Conceptual diagram illustrating the immunopathogenic and reproductive interactions in celiac disease (Designed by author).

The illustration shows the progression from gluten contact to intestinal immune system activation and systemic inflammation which leads to reproductive and lactational problems until the body recovers after adopting a gluten-free diet.

CONCLUSION:

Our studies documented that female reproductive life cycle may be disturbance in an CD which is an autoimmune disorder , lead to inflammation, villous atrophy, and malabsorption , deficiencies of micronutrients that are important for female reproductive organs and child organogenesis. The existance of anti-tTG and anti-tTG**2** reduced an endometrial angiogenesis and caused some of these disturbances .Milk breast composition may be affected in CD women by decreasing immune-protective proteins and other compounds changing the level of other compounds. Treatment of CD by administration of gluten-free diet may be reduced these disturbance .

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