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Impact of celiac disease on reproductive performance of women

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Abstract--Celiac disease is an incurable disease caused by a failure of the human body in digesting ingested gluten causing immunological mediated provocative impairment of small- intestinal mucosa. As against classical presentation for diarrhea and abnormal absorption of nutrients from digestive tract, which were earlier more evident, now a spike is noticed in the atypical and silent presentations. The disease prevails to the account of 0.5% to 1% in the western Indian population and Arabic population. The bona fide learnedness about different signs and exposures is essential to give rise to prognosis. Only treatment of Celiac disease is lifelong avoidance of gluten from the diet. The disease is reported to affect women during their productive period and often malabsorption interferes with embryogenesis and foetal nutritional status, growth and development. The celiac disorder has also been associated with various gynaecological and obstetric disorders like late menarche, early age menopause, infertility, intrauterine growth retardation, repetitive miscarriage as well as stillbirth in the recent past. In this narrative review, factors leading to the reproductive function of women with celiac disease can be vividly identified. This review gives valuable insight into the association between celiac disease, nutritional deficiency and reproductive performance of women.

Keywords--Celiac disease, reproductive performance, malabsorption, embryogenesis, menarche, gynecological, obstetric disorder, infertility, stillbirth, early menopause.

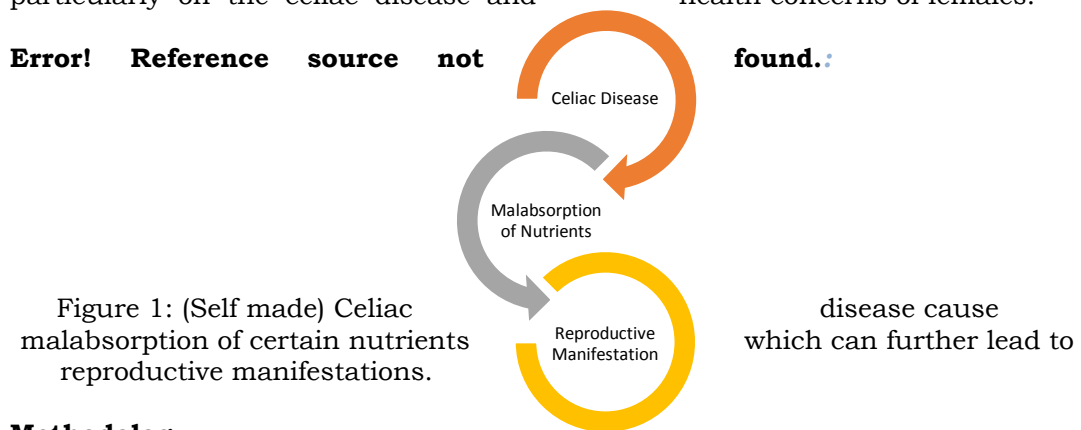
Introduction

Celiac disease is an autoimmune enteropathy caused by an unusual insusceptible response of dietary gluten. Cereals like wheat, rye and barley contain gluten which is a type of protein. The disease is inherited and confirmed by HLA class II molecules DQ2 and DQ8 molecules, which is responsible for introducing disease related peptides to T lymphocytes. Introduction of the immunogenic and anti-inflammatory peptide framework of gliadin, the soluble gluten, may further trigger an inflammatory response. Indigested particles of gliadin with increased intestinal infiltration enter the epithelial border of the digestive system and interact with cells presenting antigen to lamina propria¹. The mutant immune response is directed by celiac disease 4+T lymphocytes in the lamina propria receiving gliadin peptide bound to HLA-DQ2 and -DQ8 molecules within the APCs, leading to the release of cytokine interferon- γ ² and to a B lymphocytes reaction that brings about the creation of autoantibodies like endomysia, hostile to transglutaminase and against gliadin antibodies³. Celiac disorder has become a common disease worldwide Globally ⁴ 0.5% to 1 % of the western Indians and the Arabian population is exposed to this disorder ^{4,5}. In recent years, a great increase in the number of people with the disease is witnessed. Northern India ^{6,7} is supposed to be dominated at the pace of 0.3% ⁸. In India Evaluation has revealed that the disease persists more commonly in the population than earlier estimated with the advent of an increase in technology. The disease is perceived to be more prominent in grown-ups. The disease is more prevalent in females as compared to males. Presently female comprises of 60 ~70% of the populace with the celiac disorder⁹. The same can be attributable to more usage of healthcare facilities by males over females¹⁰. The celiac disease has some common symptoms ranging from minor to serious like malabsorption, persistent, diarrhoea, steatorrhea, pain in abdominal, weakness, nausea, vomiting, anaemia, and growth impediment in youngsters. On the other hand, non-gastrointestinal symptoms and may require timely diagnosis ^{11,12,13}. Atypical forms of celiac disease can have serious health problems if not properly diagnosed. Atypical celiac disease can cause problems such as reproductive disorder infertility, delayed menarche, early menopause, and other pregnancy-related complications which include spontaneous abortion, intrauterine growth retardation, Preterm deliveries, stillbirth¹¹.

The study of the early development of celiac disorder must be depend on the different clinical manifestations, endoscopy, serology, histology and hereditary. However, Histology cannot be counted amongst the best indicators of different phrase of celiac disease¹⁴. The research on the celiac disease was recommended by positive examination of serology and affirmed with endoscopy. There are two main antibodies like Serum Immunoglobulin IgA-class endomysial (EmA) and transglutaminase 2 (TG2) both are considered best in screening for celiac disorder with unconcealed villous atrophy¹⁵. Studies reveal that greater numbers of patients are being diagnosed with silent celiac disease in a proportion of 8:1¹⁶. Some recent studies have also demonstrated the failure of serology in distinguishing most patients influenced by silent disease¹⁷. The endometrial antibody tests show the discovery of this label was observed to be 100% in patients with severe atrophy, whereas, the costing at least 31% in patients

suffered from celiac with incomplete atrophy. Antibody to tissue transglutaminase is also associated with a higher rate of atrophy¹⁸.

The treatment comprises of exclusion of gluten from the diet which interferes with the immune system¹⁹. The main challenge in treatment is the dietary adherence and strict vigilance of this disease. The treatment should be done under complete supervision of qualified dieticians or nutritionists accompanied with follow-up by a multidisciplinary group which is a prerequisite for identifying the early diagnosis of nutritional deficiency²⁰. In this article, the main focus is on the effect of celiac disorder on the conceptive and reproductive capacity of females and particularly on the celiac disease and health concerns of females.



Methodology

Various literature research methods were used to study the reproductive performance of women suffering from celiac disease. Various research platforms such as pub med and Google search engines were used with full futility to prepare an overview of the understanding of the impact of celiac disease on the reproductive performance of women. Multiple search terms or keywords like "Celiac Disease", "Reproductive Performance" and "Nutritional Deficiencies" in women were used. Relevant cross-references are also mentioned vividly to refer to previous studies about the relationship of other nutritional deficiencies with celiac disease in women.

Effect of celiac disease on the reproductive health of females

Over the past few decades, researchers have found a direct relationship between reproductive disorder, degenerative issues, and celiac disease which is detrimental to female's well-being^{21,22}.

The study conducted in past has revealed that celiac disease with other persistent inflammatory diseases may increase infertility and can cause pregnancy-related problems²³. Whereas as per some research studies, the low rate of fertility is one of the main complications of CD. The effect of celiac disorder leads to the increased rate of abortions, miscarriages, underweight babies, or growth retardations which is being minutely evaluated & is also a serious matter of concern. However, the conducted research has been minutely focused on the small sample size due to capacity constraints, and also the actual fertility rates

cannot be evaluated ^{24,25,26}. CD is postulated to be taken into consideration within the pre-conception examination of sufferers with reproductive issues, however for non-celiac gluten sensitivity, impact on fertility is not always but validated ²⁷.

Infertility

Celiac ailment has been linked with infertility by many researchers but the same is still rarely advisable as assessment in infertility owing to a lot of ambiguities in the subject matter. Conducted researches have also revealed that 7.4% to 14% of females in North America have suffered from infertility with rate of 15% of this infertility is owing to unknown causes of post hormonal and anatomical reasons ^{28,29}.

The pervasiveness of reproductive issues were not identical in womens and men with celiac disease. Altogether, two celiac men were noticeable had fertility complications but difference among male patients and controls were not statistically massive ³⁰.

Women with fertility problem had three times higher rate of having CD in contrast with the controlled populace. Further, females with “unexplained infertility” had 6 times higher rate of getting CD than control group with infertility³¹. ‘CD is greater generic in females with all cause infertility and unexplained infertility that in common populace’³¹.

Researchers are also apprehensive of the increase in the rate of celiac disease from 4% to 8% in females with unexplained fertility^{32,33}. A Finnish research conducted on 98 females with unexplained infertility found that 4% amongst them also suffered from celiac disease³². A comparative research study conducted in Sardinia found approximately 3 of 98 females with infertility had celiac disease³³of the approximately 25 females with unexplained infertility, two were recently investigated to have symptoms of celiac disease in contrast with the common populace.

A study conducted by Shamaly et al. demonstrated that in around 192 Arabic females had unexplained infertility, utilizing EMA all out IgA and tTG antibody for testing and analytic biopsy for any positive serology or IgA inadequacy. An aggregate of around five out of 192 females was determined to have celiac disease, as opposed to one analysed in prolific controls³⁴.The author however pointed out that the expansion pervasiveness of celiac disease in the infertile cohort did not arrive at importance due to the small sample size.

Increased incidences of Celiac ailment in unexplained infertility was once more revealed in Italian research, which examined in detail the prevalence of celiac disease in females’ whoopt for assisted reproductive strategies³⁵. In contrast to research conducted by Shamaly, the significant findings could not be identified. Tiboni et al observed that the 200 females experiencing assisted reproductive techniques that were tested for a Celiac ailment using EMA and tTG, 5 females were determined to have developed the disease on biopsy contrasted with 2 in the control group. The results indicated that female patients who had another cause for searching assisted reproductive methods were the most effective one and were

successful in In vitro fertilization (IVF), which finally led to miscarriages. However, researchers have argued on the inadequacy of sample collection for the conducted study.

In order to probe on the pervasiveness of celiac disorder in the case of infertility, more focus should be on individual investigations for effective results. However, studies revealed that the disease is more prone to multi-occurrence in the patient's life span. Studies revealed that every 17 out of 641 females with infertility have been identified with the celiac disorder as in contrast with 20 out of 2167 controls, which showed notable significant differences to understand better the implications of the disease.

Studies suggest that a direct relationship exists between the fertility rate amongst women and the period at which the disease was treated. The women who were treated after contracting the disease were less fertile in comparison to those who were given timely treatment with a gluten-free diet.

Sher and berry found that the average number of children born to celiac patients were significantly less compared to pre-diagnostic results while after diagnosis and treatment, patients had more children similar to controls. Author has shown that the complete reproductive difference between celiac females and control is due to infertility before diagnosis and correction by gluten restricted diet³⁶. These studies indicated that reduced rate of fertility is more frequent in patients with active CD when a gluten restricted diet is unlikely to be started.

Early Indication: Menarche, Menopause use & Amenorrhea

Studies conducted in the recent past have proved the existence relationship between celiac disease and fertility during the life stages of menarche and menopause.

Females who did not adhere to gluten-restricted dietary habits were observed to undergo on their first period of menstruation approximately 1 to 1.5 years later than those who excluded gluten from their dietary routine. The rate of increase in delay increases with malnutrition³⁷. To conclude, it is imperative for women with untreated celiac disease to avoid gluten as they are more prone to enter menopause four to five earlier than others. Females with untreated celiac disorder were found to be 39% prone to secondary amenorrhea (causes when women have at least one menstrual period and stop menstruating for three months or longer), but only 9% were on a gluten-free diet³⁸.

A survey was conducted on a pair of 59 mother-daughters, 10 of whom were not treated for illness and two of 49 who adhered to the gluten-restricted diet and a significant difference were observed in the first menstrual period between the two. Where the daughters with untreated condition experience menstruation approximately at 16 years of age and their respective mothers experience at 5 years of age. This was incomplete contrast of the patients suffering from celiac disease having average age of 12 to 13 years in the rural areas, 13 years of age in the village and 12 years of age in the metro cities. Thus, these results have shown a strong association between diet, disruption and a positive impact on the

reproductive system³⁹. During a survey, conducted on 68 control couples and they were compared for assessing the impact of disruption on women's reproductive health and outcome exhibited similarity to some extent.

The average age at onset of menstruation was late in women suffering from CD than in control women at 13 years of age and 12 years of age respectively³⁶. Hence it is concluded that the delay within monarch is the main sign of an undiagnosed celiac disorder and requires proper testing for diagnosis.

In the study of 162 healthy females between the age group of (18 to 55 years) and 145 females with celiac disease between the age group of (15 to 51 years) were assessed the age at menarche and characteristics features of menstrual period with the help of questionnaires. It was observed that in Slovenia, the females suffered from celiac disease, the menarche occurred at the age of 12 years that was similar to that in healthy females. Its miles concluded that CD either treated or untreated might not be connected with late menarche⁴⁰.

Pregnancy Complications

Till now many research studies have emphasized the relationship between CD and adverse pregnancy complications, reproductive disorders too. Women suffering from celiac disease are at higher risk of complications during pregnancy. Several research studies also noted a considerable point that celiac disorder is observable at a higher rate in many patients in the categories of high_risk having a case of genital issue. The complications like unexplained infertility, miscarriages, IUGR, and stillbirths can be experienced by women suffering from CD.

Miscarriages and Still Birth

So far research studies have revealed the repercussions of celiac disease on critical pregnancy complications like miscarriages or stillbirth. It is also observed that women with celiac disease are more prone to complications during their reproductive life cycle. One more point to be considered is that celiac disease can be easily detected at a higher frequency in women with a medical past history of reproductive problems. Most cases are prone to unexplained infertility, recurrent abortion, stillbirth and premature babies.

Recent research has shown a significant rise in stillbirths and miscarriages in females suffering from celiac disorder and was not following gluten restricted dietary regiment and recommended proper diagnosis, knowledge, information by obstetrics, gynaecologists, doctors and dietician. An Italian research study stated in the year 2000 that testing for celiac disease at the right time can prevent unfavourable complications of pregnancy. About 50%of unintended pregnancies in women cause side effects or miscarriage. The study targeted 845 pregnant women with the celiac disease and 12 pregnancies in adverse state. Seven pregnancies were not good, three deaths were identified, five births of premature babies and three babies were delivered having low birth weight. Moreover, after following gluten restricted diet for 6 months, these 12 women with the disorder had 6 successful pregnancies²⁶. During a study, comparison of 94 uncured

women with CD and 31 celiac cured women showed 8.9-fold increases in the higher risk of miscarriage, 5.84-fold chance of having low birth weight infants and shorter time of breast-feeding in uncured women. None of the statistics have shown the criticality of this disorder in uncured women. The highest incidences of miscarriage, stillbirth, and short-term breastfeeding was successfully treated with a gluten-restricted diet⁴¹.

In a maternity analysis study, the history of obstetrics and gynaecology of controlled pregnancy patients show higher chances of miscarriage in women with uncured complications with respect to 6% of controlled. The mother with untreated problem produced 102 live birth and seven unborn babies, in contrast to 161 live births and one single birth found stillbirth³⁶. A cases-specific study of patients who started a gluten- restricted diet demonstrated approximately 36% reduction in gestational loss and 39% reduction within the association of low birth weight infants³⁸.

Before the analysis of CD, a higher rate of unfavourable effect of pregnancy was observed, while after the analysis, no effect on reproductive outcome turned into discovered. A cohort comparison study was done on 6319 females suffered from CD with non-celiac females and identified reproductive activities between the ages of 15 to 50 years. The risk during pregnancy, molar or ectopic being pregnant, miscarriages, still birth due to foetal disease become equal. The result proposes that undiagnosed CD can have an effect on reproductive life of females so it is important to focus on prior detection of CD among females to prevent reproductive problems⁴². This analysis shows, there is a strong link among cases of miscarriage and stillbirth. This also shows adherence to gluten restricted dietary regiment which is essential for maintenance of a healthy reproductive life cycle in women with CD.

Intrauterine Growth Restriction

Intrauterine Growth delays can be a condition in which a newly developed foetus may be less than 10th percentile for its gestation period depending on a normal human curve⁴³. At the time of study among celiac patients and controls, the rates of IUGR were increased among patients with celiac disease, approximately 6% compared to 2% respectively. It shows the highest percentage of labour induction was approximately at 29% and 12%⁴⁴. Author concluded, the birth outcomes of women with CD were favourable. However, high levels of Intrauterine Growth restriction were present in celiac women. As per author, the results of IUGR diagnosis should be considered and advised that it requires attention in celiac examination among patients presenting with IUGR for no visible reason⁴¹. Danish research was conducted during 1999 on 211 children and 127 women suffering from celiac disease and around 1,200 to 1,260 control deliveries. Norgard identified an additional approx. 3.5 higher chance of IUGR in babies whose mothers followed gluten restricted diets had no higher risk of birth defect. The conducted research indicated that females diagnosed from celiac disorder delivered low birth weight babies, 2.3 grams lower than those women in observation in control deliveries. On the other hand, women suffering from celiac disorder and adhered to gluten restricted dietary routine gave birth to heavier weight babies over control⁴⁵. Gasbarrini proved that patients with recurrent

abortions and IUGR have a higher degree of celiac disorder when tested neurologically than did the controls. Specifically, approximately 8 % patient of RSA and 15% patients of IUGR were diagnosed with celiac antibody, while each one controls were negative ⁴⁶. Another study conducted by Kumar on 45 patients, the patients were comprised of two groups. One comprised of IUGR positive patients and the other having a pregnancy with usual trimester. Around 2 patients from IUGR category were screened for presence of celiac antibodies but none of these came from controls ⁴⁷.

A study in Italy by Greco et al suggested that 1 in 70 pregnant mothers were hospitalized with an outsized incurable disorder; 70% of them suffered from the after-effect of pregnancy and 8 out of 9 women can give birth to their second child in a year with the help by following a gluten-free regime ⁴⁸. Grecco's group showed during a follow-up study that in pregnant women increased the danger of miscarriage and IUGR gained achieved statistical significance in symptomatic disorder.

It was observed that in a study conducted by Pogacar et al, a high number of celiac women had problems in conception of the primary baby in contrast to healthy controls. Further, celiac patients experienced greater risk of complication than healthy controls during being pregnant like recurrent abortion or intrauterine growth retardation ³⁰.

The impact of celiac disease on short term breastfeeding period has also been revealed. In a study on the scenario of before and after control, Ciacci et al established that as compared to healthy mothers the time of breastfeeding was shorter in mothers suffering from celiac disease. The doctors and nutritionists suggest an information and knowledge of increased gluten restricted diet in the time of breastfeeding by approximately 2.5 times to reinstitute the level similar to a healthy woman ⁴¹.

Relationship between nutritional deficiencies, Celiac disease & reproductive function

The actual cause of the onset of celiac disorder in women is yet to be deeply researched in order to comprehend better ways to get rid of severe complications during the reproductive life cycle. So far research studies have indicated the possibility of a direct relationship between nutritional deficiencies in females with patients suffering high frequency of celiac disease which is due to a malabsorption a common limitation of GFD which has certainly a direct impact on the reproductive life cycle.

The comprehensive medical signs and manifestations of celiac disorder is due to the malnourished state as a result of the abnormal absorption of many micro and macronutrients. It has been cautioned that infertility as well as pregnancy related complication may be an effect of the endocrine issues as a result of some macro and micro nutrient deficiencies. Equal selective nutrient deficiencies as in CD may be the cause of infertility in patients with non-celiac gluten sensitivity ²⁷.

One major characteristic of Celiac disease is an unusual villous structure of the small intestine that results to malabsorption and produce minor haematologic abnormalities, anaemia and other nutrient deficiencies, like zinc, selenium, folic acid, Iron, Vitamin B12 as well as Vitamin D ^{27,49,50,51,52,53}, which plays a significant role during pregnancy and in foetal development.

The deficiency of zinc has its own adverse implications in terms of decrease secretion to luteinizing hormones (LH) and follicle stimulating hormone (FSH), which may subsequently result in irregular ovarian axis, secondary amenorrhea, recurrent abortions and pre-eclampsia ⁵⁴.

The deficiency of Selenium also affects the secretion of FSH as well as LH ⁵⁴. Therefore, it is often concluded that vitamin B9 (folic acid) is a crucial vitamin in macromolecule metabolism; its deficiency can affect rapidly growing tissues, like embryos and its fetal development. However, Dickey et al, Observing the likelihood that maternal CD could be a risk factor for fetal ectoderm (NTD) risk associated with vitamin B9 (folic acid) deficiency, identified that the majority of NTD was not related to maternal CD ⁵⁵, which suggested that the increasing incidences of CD during this number of deficiency-related defects could not be assessed.

Iron deficiency in women with celiac disorder is more pronounced and changes in reproductive performance, including infertility. Chavarro emphasizes on the importance of Iron ovulatory function and reproductive factors as celiac patients with Iron deficiency have shown signs of idiopathic infertility ⁵⁶. Vitamin K deficiency also damages fetus, causing to chondrodysplasia with nasal hypoplasia and abnormalities in spinal cord ⁵⁷. Hypo-prothrombinemia is caused by a deficiency of Vitamin K leading to malabsorption. Around 18 % of adults and 25% of kids with disorder were found to be prone with prolonged prothrombin. ⁵⁸.

Unfortunately, studies conducted for Celiac Disease on women during pregnancy are limited. The conducted ones are done to examine malabsorption and nutritional deficiency in celiac disease amongst children. The available information however does not prove the nutritional deficiency as the conditions responsible for reproductive failure in patients with celiac disease.

More research studies are required still there is a scope to unravel precisely on the altered absorption of nutrients and nutritional changes in females with untreated CD, the importance of GFD mainly in case of re-establishment of good nutritional status among patients.

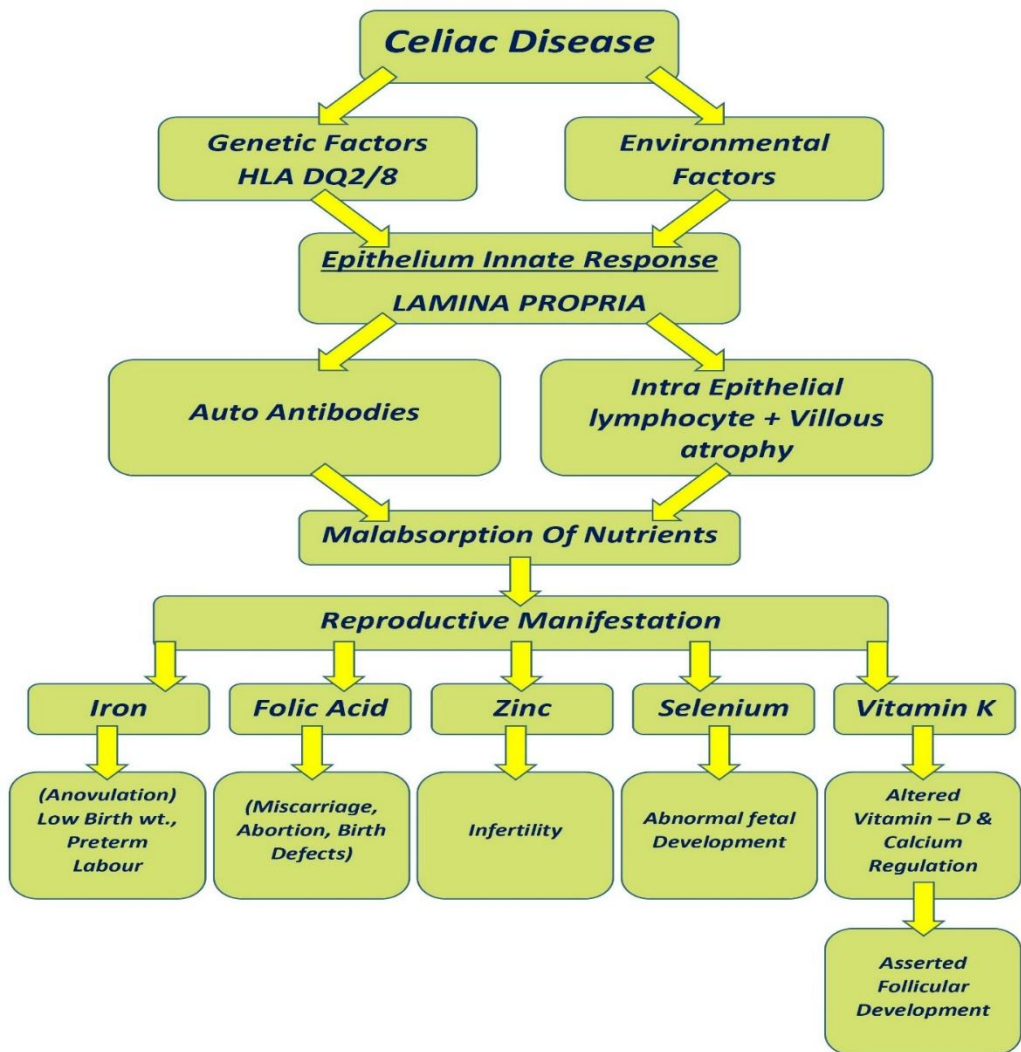


Figure 2: Celiac disease is caused by genetic and environmental factors leading to malabsorption of nutrients which can lead to reproductive manifestations like miscarriage, infertility, preterm labour, low birth weight, abortion and birth defects.

Conclusion

Celiac disease is a serious digestive ailment caused by an abnormal immune reaction to gluten. It is a long-term immunological condition that primarily effects the small intestine. It is also called gluten-sensitivity enteropathy. The cereal and grains including wheat, rye, and barley contain gluten, which is type of protein. The predominance rate of celiac disorder is 1% in the common populace worldwide. There are two types of symptoms of CD, classical symptoms which include abdominal distention, weight loss, malabsorption, deficiency of certain nutrients like protein, calcium, iron, zinc, selenium, vitamin K, vitamin D which are less common now-a-days. Atypical or silent is most common in patients. The

present review studies show the effect of regenerative life on females who suffered from celiac disease. Most of the previous investigations showed that females with idiopathic infertility, spontaneous abortion or intrauterine growth restriction have almost 5 to 6 or 8-fold independently high chances to get affected from celiac disease in contrast with the common populace. The females with the regenerative disease did not show any signs of celiac disease but mostly showed signs of tiredness and weakness related with iron deficiency anaemia. Amenorrhoea, infertility and unfavorable results during the gestational period may be commencing clinical mark that eventually consequences in a diagnosis of CD. Therefore, for the diagnosis of celiac disease serologic screening is carried out by examination of the patients cures for endomysia and anti-TG antibodies particularly recommended for the occurrence of unexplained infertility, spontaneous abortion as well as Intrauterine growth restriction. Although, sufficient data is not obtained for the examination of celiac disease in females with past history of SGA, premature deliveries or pregnancy-induced hypertension or pre-eclampsia. Some studies revealed that females with celiac disease significantly have higher chances of spontaneous abortion, IUGR, low birth weight babies or premature babies in contrast to healthy females whereas no significantly higher chance of repeated pregnancy loss, still, birth and pregnancy induce hypertension which occurs only in females with celiac disease. So, to conclude the celiac disease influences the regenerative life of females both before and after the diagnoses of CD but many investigations described that the chance of IUGR, low birth weight, and premature birth in females with celiac disease was significantly low in females adhering to a strict gluten-free diet. If celiac disease is timely diagnosed and treated properly, then malnutrition and reproductive disease can be prevented in females. The doctors and dieticians must enhance the awareness and educate in detail regarding the disease, complications or reactions to the reproductive life cycle along with the cure of the disease particularly regenerative performance and guide the patients to strictly adhere to a gluten-free diet in order to retain the nutritional values of the body.

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