World Journal of Obstetrics and Gynecology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5317/wjog.v4.i4.72

World J Obstet Gynecol 2015 November 10; 4(4): 72-76
ISSN 2218-6220 (online)

EDITORIAL

Infertility and ovarian failure in celiac disease

Hugh James Freeman

Hugh James Freeman, Department of Medicine (Gastroenterology), University of British Columbia, Vancouver V6T 1W5, Canada

Author contributions: Freeman HJ contributed all to this paper.

Conflict-of-interest statement: Freeman HJ declares no conflict of interest or potential conflict of interest related to this manuscript.

Correspondence to: Hugh James Freeman, MD, CM, FRCPC, FACP, Department of Medicine (Gastroenterology), University of British Columbia, 2211 Wesbrook, Mall, Vancouver V6T 1W5, Canada. hugfree@shaw.ca
Telephone: +1-604-8227216
Fax: +1-604-822236

Received: April 7, 2015
Peer-review started: April 9, 2015
First decision: June 3, 2015
Revised: June 10, 2015
Accepted: July 29, 2015
Article in press: August 3, 2015
Published online: November 10, 2015

Abstract

Unexplained infertility in females may be a devastating event for the reproductive-aged female. However, infertility may be due to ovarian failure associated with celiac disease, an immune-mediated disorder that may have few or no symptoms and can be successfully treated. In some prospective serologically-based studies, over 4% of infertile females may prove to have celiac disease. Serological screening for celiac disease is relatively inexpensive and involves testing for antibodies to tissue transglutaminase. If positive, a small intestinal biopsy should be done to confirm the diagnosis. The initial treatment for this disorder is a gluten-free diet. To date, a number of reports have indicated that this treatment for celiac disease may result in successful pregnancy, in spite of prolonged periods of infertility. Celiac disease, when untreated, may also lead to several adverse events following pregnancy including increased risk of recurrent abortions, low birthweight and impaired fetal growth. Recent molecular and pathological studies from different laboratories suggest that altered placental function may be due to binding to cells in the trophoblast by tissue transglutaminase antibodies impairing embryo implantation and leading to failure of early pregnancy or retarded intrauterine growth.

Key words: Celiac disease; Infertility; Ovarian failure; Autoimmune disease; Polyglandular syndrome

Core tip: Females with unexplained infertility should be screened for celiac disease. This involves use of a simple and inexpensive serological quantitative method for detection of tissue transglutaminase antibodies, a marker for celiac disease. If positive, biopsy evaluation should be done to determine if pathological features of untreated celiac disease are present in the small intestinal mucosa. A gluten-free diet may lead to effective management of celiac disease and may promote a favorable pregnancy outcome.

Freeman HJ. Infertility and ovarian failure in celiac disease. *World J Obstet Gynecol* 2015; 4(4): 72-76 Available from: URL: http://www.wjgnet.com/2218-6220/full/v4/i4/72.htm DOI: http://dx.doi.org/10.5317/wjog.v4.i4.72

INTRODUCTION

Infertility is a significant, even devastating clinical issue for some reproductive-aged women. Although infertility

may result from a number of factors, premature ovarian failure may be responsible. Ovarian failure normally occurs with the process of aging, premature failure of ovarian function may be defined as the failure of estrogen production by the human ovaries, usually before the age of 35 to 40 years. There may also be other significant long-term health consequences associated with premature ovarian failure including osteoporosis, heart disease, autoimmune disorders and increased risk of mortality[1]. There are many causes of premature ovarian failure in adults that need to be considered, including celiac disease.

FACTORS ASSOCIATED WITH FEMALE INFERTILITY

A number of different factors may lead to investigation of altered female fertility and, traditionally, these may be considered anatomically to include local factors in the cervix (*e.g.*, altered cervical mucus) and uterus (*e.g.*, congenital uterine abnormalities), fallopian tubes (*e.g.*, adhesions) as well as ovarian failure. Ovarian failure *per se* may have several causes, including polycystic ovary syndrome, hyperprolactinemia or hypothalamic amenorrhea, often associated with pituitary disorders, including tumors, or some medications. Ovulatory dysfunction may also occur in association with endocrine disorders, particularly those associated with an altered autoimmune process, including hypothyroidism or adrenal insufficiency (if together, Schmidt's syndrome, and when coupled with diabetes, Carpenter's syndrome). Either of these, but particularly autoimmune thyroiditis, may be frequently observed with celiac disease. Alternatively, an autoimmune polyglandular syndrome affecting several endocrine tissues can lead to ovarian failure. Polyendocrinopathy-candiasis-ectodermal dystrophy syndrome (APECED) is considered a rare autosomal recessive disease caused by mutations in the autoimmune regulator (*AIRE*) gene. Typical clinical findings include candidiasis, Addison's disease, hypoparathyroidism, diabetes, alopecia, vitiligo, ectodermal dystrophy, autoimmune thyroiditis, pernicious anemia, chronic active hepatitis, celiac disease and premature ovarian failure[2].

CELIAC DISEASE

Celiac disease is an immunologically-mediated gluten-sensitive small intestinal mucosal disorder primarily detected in genetically-susceptible persons[3,4]. Gluten peptides found in grains appear to be a triggering environmental factor following dietary exposure. Mechanisms involved in the pathogenesis of celiac disease are beyond the scope of this article, but have been recently detailed[4]. Chronic diarrhea, malabsorption of major and minor nutrients, and weight loss may occur. Development of serum antibodies to tissue transglutaminase also occurs in celiac disease and quantitation of these antibodies is a useful method for serological screening of populations or case finding in clinical practice. Endoscopic biopsies of the proximal small intestinal mucosa in untreated celiac disease show typical inflammatory changes along with moderate to severe alterations in mucosal architecture. Usually, these clinical, serological and pathological changes in untreated celiac disease respond to a gluten-free diet. Recognition of celiac disease is important because of the potential for later development of other co-morbidities, including osteoporosis and malignancy. Extra-intestinal or autoimmune processes may also occur, including dermatological changes, such as dermatitis herpetiformis, and endocrine disorders, including hypothyroidism associated with autoimmune thyroiditis. Often, these extra-intestinal features may be the presenting symptoms to an underlying small intestinal mucosal disorder that may be clinically silent.

CLINICALLY SILENT CELIAC DISEASE

Celiac disease has now become more often appreciated to have few or limited intestinal symptoms. Minimal diarrhea without weight loss may be evident. Often, females with celiac disease and reproductive disorders have no overt symptoms, or perhaps, only decreased energy with iron deficiency or, if more significant, iron deficiency-associated anemia[5]. As a result, impaired female fertility or changes that include delayed onset of menses, amenorrhea and early menopause may conceivably be the initial clinical presentation that eventually leads to recognition of underlying celiac disease. Owing to the increased ability to serologically screen for celiac disease, up to 1% to 2% of individuals in the general population in some countries have been detected with this disorder, especially in women of child-bearing age[4]. Screening biopsies may also be done and these studies have demonstrated that young adult females, in particular, are the most common adult age group first diagnosed with celiac disease[6]. Conceivably, premature ovarian failure leading to infertility could be reflect underlying immune-mediated mechanisms occurring in celiac disease, or alternatively, negative nutritional consequences of impaired absorption in celiac disease *per se*.

CELIAC DISEASE AND POLYCYSTIC OVARY SYNDROME

An important consideration in the broad differential diagnosis of premature ovarian failure is the polycystic ovary syndrome, initially described by Stein and Leventhal in 1935. Since then, this syndrome has been extensively investigated, and appears to be very heterogeneous with clinical features that include menstrual changes, chronic anovulation and excessive androgen levels, often with hirsutism. Anatomically, large cystic ovaries are often detected, but in up to

Table 1 Celiac screening studies in females with infertility

Number[1]	Country	Celiac disease[2]	Ref.
150 (98)	Finland	2.7% (4.1%)	[12]
99	Italy	3.03%	[14]
192	Israel	2.65%	[15]
47	Finland	2.1%	[16]
200[3]	Italy	2.5%	[18]
51	United States	5.9%	[20]
29	Brazil	10%	[21]

[1]Number with infertility (number in parentheses, unexplained infertility subgroup); [2]Celiac disease suspected with serological screening, usually with tissue transglutaminase or endomysial antibodies, and confirmation with small intestinal biopsy; [3]Infertility group for assisted reproduction technology.

a third of women with the same clinical features, the ovaries appear to be normal. Gonadotropin secretion appears to be abnormal with elevated levels of luteinizing hormone, or LH, combined with normal or low levels of follicle stimulating hormone, or FSH. In some, a mild elevation of serum testosterone is evident. The cause of the polycystic ovary syndrome still requires clarification. An earlier study suggested that the polycystic ovary syndrome may also occur in celiac disease[7]. Unfortunately, the data needed to fully examine this relationship (even with development of easy-to-perform serological screening measures) are currently not available. Some patients labeled with the polycystic ovary syndrome, especially with normal-appearing ovaries, could also conceivably have occult celiac disease, potentially amenable to a gluten-free diet.

ALTERED FEMALE FERTILITY IN CELIAC DISEASE

First cases noted a possible relationship between celiac disease and female infertility[8,9]. In one, subsequent treatment with a gluten-free diet resulted in pregnancy, confirming observations in 2 other reports[10,11]. Later, more extensive population-based studies were done to explore this potential relationship (Table 1). A detailed serological evaluation of 150 women with infertility due to all causes from Tampere, Finland demonstrated an apparent overall rate of celiac disease (*i.e.*, 2.7%)[12], (although subsequent serological screening studies from Finland in otherwise healthy subjects have revealed a relatively high rate of celiac disease in Finland compared to other countries[13]). For women with unexplained fertility, however, this study also reported rates of detection of celiac disease of over 4%[14]. Similar results were later reported in 99 couples from Northern Sardinia[15], estimated to be a rate of approximately 3%. Using more modern serological assays, a study from Israel employed assays for both tissue transglutaminase and endomysial antibodies in 192 Arab females with unexplained infertility. Among these, positive serological tests were noted in 2.65%[15]. In all, small intestinal biopsies were positive for changes of celiac disease, if serological studies were positive. Like most serological screening studies of populations, however, biopsies in serologically negative patients were not defined. Other studies have provided different results. Interestingly, a different center in Finland[16] could not confirm earlier study results from the same country[12]. A Czech investigation reported increased serum antibody positivity for celiac disease in women with infertility, but biopsies were not reported[17]. In a study from Italy that evaluated a group of infertile women specifically referred for assisted reproduction, a significant association with serology could not be defined[18] while a Swedish population-based cohort study of biopsy-defined celiac disease suggested that fertility was not decreased until the final 2 years preceding diagnosis[19]. Data from the United States demonstrated a prevalence of celiac disease in 5.9% of patients with unexplained infertility[20], while a Brazilian study evaluated 170 infertile women screened for tissue transglutaminase antibodies followed by small bowel biopsies in serologically-positive patients[21]. In this aforementioned Brazilian study, the prevalence of celiac disease was 10.3% in women with unexplained fertility. This contrasted with a prospective primary care study of over 2 million women from the United Kingdom where no overall impairment in fertility was recorded in celiac disease compared to non-celiac disease women[22]. However, in the same study[22], infertility rates were over 40% higher in celiac disease patients between ages 25 to 29 years compared to a similar age-matched population without celiac disease. Finally, a recent report[23] describing a meta-analysis in 105 relevant studies reported that "all-cause" infertility was 3.5 times higher in women with celiac disease compared to controls while "unexplained infertility" in women with celiac disease was 6 times higher than controls. Thus, recent population-based studies of women with unexplained infertility suggest a significant occurrence of occult celiac disease. Moreover, some of these celiac patients were reported to have a successful pregnancy following treatment with a gluten-free diet.

OTHER FERTILITY-RELATED CHANGES IN CELIAC DISEASE

Delayed onset of menses, amenorrhea, early menopause, repeated abortions and diminished pregnancy rates in celiac disease could indicate a possible impairment in fertility. In 74 patients from the United Kingdom[10], the reproductive period appeared to be more prolonged for celiacs on a gluten-free diet compared to celiacs not on a gluten-free diet. Otherwise, maternal health did not appear to be significantly altered. Nonetheless, a lower incidence of spontaneous abortions was noted in celiacs treated with a gluten-free diet. These findings were supported by a subsequent study from Italy[24]. A delay in the onset of menarche

(13.5 years *vs* 12.1 years) was also noted compared to age- and "sexual behavior-matched" controls. Amenorrhea and repeated abortions were more frequent in the celiac group, but menopause onset was not affected. A Polish study[25] suggested that the age of menarche in celiacs could be regulated by a gluten-free diet, while an Italian study[26] suggested that menarche was mainly impacted by the female's maternal history of menses onset. A United Kingdom study showed that celiacs may have limited fertility with a higher incidence of stillbirths and perinatal death[27]. However, the rate of miscarriage appeared to be improved after diagnosis of celiac disease and treatment with a gluten-free diet[27]. Finally, in a report from Brazil[28], gluten-free diet therapy appeared to be instrumental in promoting a positive nutritional state, relevant to reproductive health in patients with celiac disease.

Some earlier studies have evaluated pregnancy outcomes in celiac disease[29,30]. If untreated, celiac disease is associated with an increased risk of recurrent miscarriage and premature deliveries, along with reduced fetal growth and term birthweight[29]. In an Italian study[30] of 94 untreated and 31 treated celiac patients, relative risks of either abortion or delivery of a low birthweight infant were increased while breast feeding duration was reduced. The investigators noted improvement with a gluten-free diet. Similar observations have been recorded by others[31]. Lower birthweight and retarded intrauterine growth have been recorded from European centers[32-35]. For example, in a further Italian study[33], celiac disease was more common than most diseases normally screened for during pregnancy in their health care facility. In another European evaluation[34], undiagnosed maternal celiac disease appeared to be a far greater risk factor than diagnosed celiac disease. However, a later report was not able to confirm an unfavorable pregnancy result[36]. Later studies also suggested that celiac disease in the father was not a risk factor for an adverse outcome of the pregnancy[37,38].

PLACENTAL STUDIES

The precise mechanism for adverse pregnancy outcomes are not clear but have been evaluated to a limited extent. Placentas of some mothers affected with celiac disease, in particular, may be abnormal. Using immunohistochemical methods and *in situ* hybridization, tissue transglutaminase expression and apoptosis were increased in trophoblast cells[39]. This suggested a possible injury mechanism in both fetal and placental portions of the placenta[39]. Maternal celiac disease autoantibodies may bind directly to the syncytiotrophoblast and inhibit placental tissue transglutaminase activity leading to an impaired placenta[40]. Other studies in female celiacs have raised the issue of early pregnancy loss due to altered coagulation affecting placental or fetal microvascular function[41]. Finally, binding of antibodies to tissue transglutaminase by the trophoblast might represent a crucial mechanism causing impaired embryo implantation and pregnancy outcome in pregnant celiacs[42]. Additional studies are needed to explore these intriguing early findings in celiac disease.

CONCLUSION

A preponderance of evidence from multiple studies indicates that infertility or ovarian failure in females may be increased in immune-mediated disorders, including celiac disease. In celiac disease, an immune-mediated small intestinal mucosal disorder is triggered by gluten-containing peptides found in food grains. The primary treatment of celiac disease involves administration of a strict gluten-free diet. In females with untreated celiac disease and infertility, successful pregnancy may occur solely after treatment of the celiac disease with a gluten-free diet. Widespread use of serological screening in different populations suggests that celiac disease may occur in 4% to 10% of females with unexplained infertility. Serological screening using tissue transglutaminase antibodies represents a very inexpensive method for evaluation, and if positive, should be followed by small intestinal biopsies to define the presence of celiac disease and lead to treatment.

REFERENCES

1 **Kovanci E**, Schutt AK. Premature ovarian failure: clinical presentation and treatment. *Obstet Gynecol Clin North Am* 2015; **42**: 153-161 [PMID: 25681846 DOI: 10.1016/j.ogc.2014.10.004]

2 **Fierabracci A**, Bizzarri C, Palma A, Milillo A, Bellacchio E, Cappa M. A novel heterozygous mutation of the AIRE gene in a patient with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED). *Gene* 2012; **511**: 113-117 [PMID: 23000069 DOI: 10.1016/j.gene.2012.09.029]

3 **Freeman HJ**. Celiac disease: a disorder emerging from antiquity, its evolving classification and risk, and potential new treatment paradigms. *Gut Liver* 2015; **9**: 28-37 [PMID: 25547088 DOI: 10.5009/gnl14288]

4 **Gujral N**, Freeman HJ, Thomson AB. Celiac disease: prevalence, diagnosis, pathogenesis and treatment. *World J Gastroenterol* 2012; **18**: 6036-6059 [PMID: 23155333 DOI: 10.3748/wjg.v18.i42.6036]

5 **Freeman HJ**. Iron deficiency anemia in celiac disease. *World J Gastroenterol* 2015; In press

6 **Freeman HJ**. Detection of adult celiac disease with duodenal screening biopsies over a 30-year period. *Can J Gastroenterol* 2013; **27**: 405-408 [PMID: 23862172]

7 **Kuscu NK**, Akcali S, Kucukmetin NT. Celiac disease and polycystic ovary syndrome. *Int J Gynaecol Obstet* 2002; **79**: 149-150 [PMID: 12427401]

8 **Morris JS**, Adjukiewicz AB, Read AE. Coeliac infertility: an indication for dietary gluten restriction? *Lancet* 1970; **1**: 213-214 [PMID: 4189008]

9 **Wilson C**, Eade OE, Elstein M, Wright R. Subclinical coeliac disease and infertility. *Br Med J* 1976; **2**: 215-216 [PMID: 974499]

10 **McCann JP**, Nicholls DP, Verzin JA. Adult coeliac disease presenting with infertility. *Ulster Med J* 1988; **57**: 88-89 [PMID: 3420728]

11 **Ferguson R**, Holmes GK, Cooke WT. Coeliac disease, fertility, and pregnancy. *Scand J Gastroenterol* 1982; **17**: 65-68 [PMID: 7134839]

12 **Collin P**, Vilska S, Heinonen PK, Hällström O, Pikkarainen P. Infertility and coeliac disease. *Gut* 1996; **39**: 382-384 [PMID:

8949641]
13 **Mustalahti K**, Catassi C, Reunanen A, Fabiani E, Heier M, McMillan S, Murray L, Metzger MH, Gasparin M, Bravi E, Mäki M. The prevalence of celiac disease in Europe: results of a centralized, international mass screening project. *Ann Med* 2010; **42**: 587-595 [PMID: 21070098 DOI: 10.3109/07853890.2010.505931]
14 **Meloni GF**, Dessole S, Vargiu N, Tomasi PA, Musumeci S. The prevalence of coeliac disease in infertility. *Hum Reprod* 1999; **14**: 2759-2761 [PMID: 10548618]
15 **Shamaly H**, Mahameed A, Sharony A, Shamir R. Infertility and celiac disease: do we need more than one serological marker? *Acta Obstet Gynecol Scand* 2004; **83**: 1184-1188 [PMID: 15548153]
16 **Kolho KL**, Tiitinen A, Tulppala M, Unkila-Kallio L, Savilahti E. Screening for coeliac disease in women with a history of recurrent miscarriage or infertility. *Br J Obstet Gynaecol* 1999; **106**: 171-173 [PMID: 10426684]
17 **Vanciková Z**, Chlumecký V, Sokol D, Horáková D, Hamsíková E, Fucíková T, Janatková I, Ulcová-Gallová Z, Stěpán J, Límanová Z, Dvorák M, Kocna P, Sánchez D, Tucková L, Tlaskalová-Hogenová H. The serologic screening for celiac disease in the general population (blood donors) and in some high-risk groups of adults (patients with autoimmune diseases, osteoporosis and infertility) in the Czech republic. *Folia Microbiol* (Praha) 2002; **47**: 753-758 [PMID: 12630332]
18 **Tiboni GM**, de Vita MG, Faricelli R, Giampietro F, Liberati M. Serological testing for celiac disease in women undergoing assisted reproduction techniques. *Hum Reprod* 2006; **21**: 376-379 [PMID: 16172142]
19 **Zugna D**, Richiardi L, Akre O, Stephansson O, Ludvigsson JF. A nationwide population-based study to determine whether coeliac disease is associated with infertility. *Gut* 2010; **59**: 1471-1475 [PMID: 20947882 DOI: 10.1136/gut.2010.219030]
20 **Choi JM**, Lebwohl B, Wang J, Lee SK, Murray JA, Sauer MV, Green PH. Increased prevalence of celiac disease in patients with unexplained infertility in the United States. *J Reprod Med* 2011; **56**: 199-203 [PMID: 21682114]
21 **Machado AP**, Silva LR, Zausner B, Oliveira Jde A, Diniz DR, de Oliveira J. Undiagnosed celiac disease in women with infertility. *J Reprod Med* 2013; **58**: 61-66 [PMID: 23447921]
22 **Dhalwani NN**, West J, Sultan AA, Ban L, Tata LJ. Women with celiac disease present with fertility problems no more often than women in the general population. *Gastroenterology* 2014; **147**: 1267-1274.e1; quiz e13-14 [PMID: 25157666 DOI: 10.1053/j.gastro.2014.08.0325]
23 **Singh P**, Arora S, Lal S, Strand TA, Makharia GK. Celiac Disease in Women With Infertility: A Meta-Analysis. *J Clin Gastroenterol* 2015 Jan 1; Epub ahead of print [PMID: 25564410]
24 **Molteni N**, Bardella MT, Bianchi PA. Obstetric and gynecological problems in women with untreated celiac sprue. *J Clin Gastroenterol* 1990; **12**: 37-39 [PMID: 2303686]
25 **Rujner J**. Age at menarche in girls with celiac disease. *Ginekol Pol* 1999; **70**: 359-362 [PMID: 10462981]
26 **Sferlazzas C**, Arrigo T, Salzano G, Pellegrino S, La Fauci G, Rulli I, Magazzù G, De Luca F. Menarcheal age in celiac disease may not be delayed and may be irrespective of age at diagnosis and dietary management. *J Endocrinol Invest* 2008; **31**: 432-435 [PMID: 18560261]
27 **Sher KS**, Mayberry JF. Female fertility, obstetric and gynaecological history in coeliac disease. A case control study. *Digestion* 1994; **55**: 243-246 [PMID: 8063029]
28 **Kotze LM**. Gynecologic and obstetric findings related to nutritional status and adherence to a gluten-free diet in Brazilian patients with celiac disease. *J Clin Gastroenterol* 2004; **38**: 567-574 [PMID: 15232359]
29 **Ogborn AD**. Pregnancy in patients with coeliac disease. *Br J Obstet Gynaecol* 1975; **82**: 293-296 [PMID: 1125150]
30 **Ciacci C**, Cirillo M, Auriemma G, Di Dato G, Sabbatini F, Mazzacca G. Celiac disease and pregnancy outcome. *Am J Gastroenterol* 1996; **91**: 718-722 [PMID: 8677936]
31 **Smecuol E**, Mauriño E, Vazquez H, Pedreira S, Niveloni S, Mazure R, Boerr L, Bai JC. Gynaecological and obstetric disorders in coeliac disease: frequent clinical onset during pregnancy or the puerperium. *Eur J Gastroenterol Hepatol* 1996; **8**: 63-89 [PMID: 8900911]
32 **Nørgård B**, Fonager K, Sørensen HT, Olsen J. Birth outcomes of women with celiac disease: a nationwide historical cohort study. *Am J Gastroenterol* 1999; **94**: 2435-2440 [PMID: 10484005]
33 **Martinelli P**, Troncone R, Paparo F, Torre P, Trapanese E, Fasano C, Lamberti A, Budillon G, Nardone G, Greco L. Coeliac disease and unfavourable outcome of pregnancy. *Gut* 2000; **46**: 332-335 [PMID: 10673293]
34 **Ludvigsson JF**, Montgomery SM, Ekbom A. Celiac disease and risk of adverse fetal outcome: a population-based cohort study. *Gastroenterology* 2005; **129**: 454-463 [PMID: 16083702]
35 **Khashan AS**, Henriksen TB, Mortensen PB, McNamee R, McCarthy FP, Pedersen MG, Kenny LC. The impact of maternal celiac disease on birthweight and preterm birth: a Danish population-based cohort study. *Hum Reprod* 2010; **25**: 528-534 [PMID: 19939833]
36 **Greco L**, Veneziano A, Di Donato L, Zampella C, Pecoraro M, Paladini D, Paparo F, Vollaro A, Martinelli P. Undiagnosed coeliac disease does not appear to be associated with unfavourable outcome of pregnancy. *Gut* 2004; **53**: 149-151 [PMID: 14684590]
37 **Ludvigsson JF**, Montgomery SM, Ekbom A. Coeliac disease in the father and risk of adverse pregnancy outcome: a population-based cohort study. *Scand J Gastroenterol* 2006; **41**: 178-185 [PMID: 16484123]
38 **Khashan AS**, Kenny LC, McNamee R, Mortensen PB, Pedersen MG, McCarthy FP, Henriksen TB. Undiagnosed coeliac disease in a father does not influence birthweight and preterm birth. *Paediatr Perinat Epidemiol* 2010; **24**: 363-369 [PMID: 20618726]
39 **Hadziselimovic F**, Geneto R, Buser M. Celiac disease, pregnancy, small for gestational age: role of extravillous trophoblast. *Fetal Pediatr Pathol* 2007; **26**: 125-134 [PMID: 17886023]
40 **Anjum N**, Baker PN, Robinson NJ, Aplin JD. Maternal celiac disease autoantibodies bind directly to syncytiotrophoblast and inhibit placental tissue transglutaminase activity. *Reprod Biol Endocrinol* 2009; **7**: 16 [PMID: 19228395 DOI: 10.1186/1477-7827-7-16]
41 **Ciacci C**, Tortora R, Scudiero O, Di Fiore R, Salvatore F, Castaldo G. Early pregnancy loss in celiac women: The role of genetic markers of thrombophilia. *Dig Liver Dis* 2009; **41**: 717-720 [PMID: 19395327 DOI: 10.1016/j.dld.2009.02.050]
42 **Di Simone N**, Silano M, Castellani R, Di Nicuolo F, D'Alessio MC, Franceschi F, Tritarelli A, Leone AM, Tersigni C, Gasbarrini G, Silveri NG, Caruso A, Gasbarrini A. Anti-tissue transglutaminase antibodies from celiac patients are responsible for trophoblast damage via apoptosis in vitro. *Am J Gastroenterol* 2010; **105**: 2254-2261 [PMID: 20571491 DOI: 10.1038/ajg.2010.233]

P- Reviewer: Blumenfeld Z, McCarthy RJ, Rodrigo L **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Wu HL

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com