Muralidhar Jatla, M.D., Ritu Verma, M.D., Series Editors

Celiac Disease and Reproductive Health

by Alice Bast, Tom O'Bryan, Elizabeth Bast

Despite re-classification of celiac disease as a rare disease of childhood to a common disease affecting men, women and children at any age, most of the three million estimated sufferers remain undiagnosed. Proper education concerning the various symptoms and manifestations of the disease is necessary to increase prompt and accurate diagnosis. Celiac disease's potentially negative effect on reproductive health is among the most pressing matters associated with advancing awareness. Men and women with unexplained infertility, women with recurrent abortions, intrauterine growth retardation, low birth weight babies and menstrual disorders are rarely screened for celiac disease despite scientific studies that indicate a correlation. In the following article, we will examine the evidence for these occurrences in a literature review, examine potential theories about their cause, and discuss the need for additional research and the addition of a celiac testing to the differential diagnosis in women with reproductive health problems.

INTRODUCTION

Celiac disease is a common (1% prevalence) chronic immune-mediated, inflammatory disorder of the small intestine induced by a permanent intolerance to dietary wheat, barley, and rye (1,2). The gluten and glutenin proteins of these grains may be contained in various food products, additives, or medicines. Celiac disease is a unique autoimmune disorder in that the environmental precipitant is known. Until 2004, medical schools taught that celiac disease was a rare disease of childhood. However, current estimates state that nearly three million Americans suffer from celiac disease, but 95% of them remain undiagnosed, making celiac disease the most common, and one of the most under diagnosed, hereditary autoimmune diseases in the United States (3,4). Celiac disease (CD) is a permanent intolerance to gluten, for which the only treatment currently available is a lifelong adherence to a Gluten-Free Diet (GFD). Once patients are diagnosed with celiac disease and begin the gluten-free diet 70% report symptom relief within two weeks (5).

When a patient with celiac disease consumes gluten an inflammatory cascade occurs primarily in the proximal part of small intestinal mucosa. Specifically, this means that the adaptive immune pathway is thought to provide the major immune response, but recent evidence also indicates the involvement of the innate immune system (6). Besides increased T lymphocytes, other cell types are also increased, including B lymphocytes, NK cells, neutrophils, eosinophils, macrophages and mast cells. In particular, a chronic recruitment of activated neutrophils is present even in complete remission of celiac disease (7,8).

When celiac disease patients consume gluten, the inflammatory cascade is initiated within hours resulting in a compromise of barrier integrity, followed by tissue degradation and eventual inhibition of nutrient absorption. Celiac disease (CD) has a multifactorial pathogenesis (9).

Alice Bast, President and Founder, National Foundation for Celiac Awareness, Ambler, PA. Dr. Tom O'Bryan, Adjunct Faculty, Institute for Functional Medicine, National University of Health Sciences, Chicago, IL. Elizabeth Bast, Student, Harvard University, NFCA Intern, Boston, MA.

Common symptoms may include bulky stool, constipation, anemia, delayed growth, failure to thrive and infertility (10,11). Celiac disease used to be perceived as presenting with gastrointestinal symptoms suggestive of malabsorbtion, such as edema secondary to hypoalbuminemia, hypocalcemia, vitamin deficiency states and osteomalacia (12). This manner of presentation is now described as the "classic" or "typical" form. Patients with celiac disease may have the "silent" or "atypical" form with no gastrointestinal symptoms and the condition may present outside the intestines and can affect any organ system (13). The ratio of extra-intestinal to classical symptomatology is 8:1 and, thus, the vast majority of patients have silent celiac disease and the condition does not present with overt GI symptoms (14). Patients with this disorder suffer from generalized poor absorption. Celiac patients can be eutrophic or have mild to severe malnutrition depending on several factors such as site and length of the intestine involved in the disease, grade of malabsorption, and interval between the first symptoms and a correct diagnosis. Thus, they may present selective or universal malabsorption of nutrients. Functional hypopituitarism and atrophy of reproductive organs are associated with malnutrition (15).

DIAGNOSIS

The diagnosis of early developing celiac disease should be based on a combination of clinical features, histology, serology, and genetics. Conventional histology is no longer a gold standard in the diagnosis of the various stages of this disease (16). Numerous authorities have identified that the majority of celiac patients visit five or more doctors prior to diagnosis, with a median time for diagnosis of five-to-11 years after initial presentation (10,16,17). Historically, diagnosis was suggested by positive serology and confirmed with endoscopy. Serum immunoglobulin IgA-class endomysial (EmA) and transglutaminase 2 (TG2) antibodies are powerful tools in diagnosing celiac disease with overt villous atrophy (18). However, with an overwhelming majority of patients presenting silent celiac disease (ratio of 8:1), knowledge of the limitations of serology is important (19). Recent literature shows that serology (not only EmA, but also TG2) seems to be ineffective in detecting most patients affected by subclinical or silent disease (20). An evaluation of endomysial antibodies showed that the sensitivity of this marker was 100% in patients with total villous atrophy, but the value plummeted to 31% in patients with celiac disease who had partial villous atrophy. Antibodies to tissue transglutaminase likewise correlate with the degree of villous atrophy (21).

The diagnosis of celiac disease requires the presence of small intestinal mucosal villous atrophy and crypt hyperplasia, (Marsh III). However, evidence suggests that small bowel mucosal damage in celiac disease develops gradually from mucosal inflammation to crypt hyperplasia and, finally, to partial and subtotal villous atrophy. Mucosal intraepithelial lymphocytosis evincing normal villous architecture (Marsh I) precedes this lesion. From the pathologist's point of view, an increased number of intraepithelial lymphocytes in an architecturally normal duodenal mucosa always suggests potential celiac disease (18,22,23). The 2004 NIH Consensus Development Conference Statement confirms that genetic markers HLA-DQ2 and HLA-DQ8 are present in those with celiac disease (90% and 10% respectively). Gluten interacts with HLA molecules activating an abnormal mucosal immune response and inducing tissue damage.

AUTOIMMUNITY

While many individual autoimmune diseases are rare, collectively they are thought to affect approximately 8% of the United States population (24). Celiac disease patients contract other autoimmune disorders 10 times more commonly than the general population (12). Impaired hypothalamic-pituitary regulation of gonadal function is a well-recognized complication of celiac disease. These changes occur independently of the general nutritional status and an auto-immune mechanism has been theorized (15,25).

Autoimmune polyendocrine syndromes (APS) were initially defined as multiple endocrine gland insufficiencies associated with an autoimmune disease in a patient. Thyroid autoimmune diseases are the most frequent autoimmune diseases in the population with a prevalence rate of 7%–8% of the general population, (approximately 24 million people) in the U.S.(26). A

classification of APS has identified APS-3 as autoimmune thyroid diseases associated with other autoimmune diseases, including celiac disease. Fifty-two percent of patients with autoimmune thyroid disease can be considered affected by APS-3. During the first trimester, pregnant women with an increase in thyroid autoimmunity (TAI) carry a significantly increased risk for a miscarriage compared to women without TAI, even when euthyroidism was present before pregnancy (27). Autoimmune thyroid disease is the second most prevalent autoimmune disorder associated with celiac disease after Type 1 diabetes (28). Patients with celiac disease are at risk for developing thyroid disease with an overall three-fold higher frequency than in controls. Between 30% and 43% of celiac disease patients will present with thyroid disorders. The prevalence of thyroid antibody positivity in euthyroid subjects was four-fold higher in celiac disease patients than in controls (29,30).

Antiphospholipid syndrome is a syndrome of arterial and venous thrombotic disease, thrombocytopenia, and fetal wastage. Of the three most commonly associated antibodies in antiphospholipid syndrome (lupus anticoagulant, anticardiolipin and anti-b2-glycoprotein-1 antibodies), the anti-b2-glycoprotein-1 antibodies were associated with an unusually high proportion of pregnancy losses after the tenth week of gestation, as high as 38.5% (31,32). Fourteen percent of untreated celiac disease patients will have an elevation of antiphospholipid antibodies, and, as a result, be at a higher risk of pregnancy loss.

In a review of 57 patients diagnosed with antiphospholipid syndrome and 171 healthy controls, celiac disease-suggestive anti-endomysial antibody (EMA) positive serology was found in 62.5%. All of these EMA positive patients also presented with elevations of the primary pregnancy-risk antibody, anti-b2-glycoprotein-1 antibodies, the primary pregnancy risk antibody of antiphospholipid syndrome versus 47% of EMA negative patients (33). A case study gives a stunning example of the positive impact of celiac diagnosis and the implementation of a gluten-free diet. A 34 year old female with APS had suffered two spontaneous abortions at week 16. After six months on a gluten-free diet, all previously elevated antibodies were undetectable, including anti-b2Glycoprotein-1, antiendomysial, transglutaminase, anti-thyroglobulin antibodies and lupus anticoagulant (34).

INFERTILITY

Twelve percent of the reproductive age population in the United States, about 7.3 million American couples, suffers from infertility (35). Infertility is commonly diagnosed when people are unable to conceive after six-to-12 months without using birth control, depending on several factors, such as age. Women with recurrent spontaneous abortions are also considered infertile (36). In an effort to have children, couples seek various treatments, such as surgery or artificial insemination. The average couple spends about $10,000 per attempt on Assisted Reproductive Technology (ART). However, nearly one third of all pregnancy losses are the result of undiagnosed, treatable diseases (37).

While infertility in 27 % of infertile couples is the result of ovulation disorders and 25 % the result of identified male disorders, 17% of couples remain infertile for unexplained reasons (38). Researchers have found the rate of celiac disease to be 2.5 to 3.5 times greater in women with unexplained infertility than in women with normal fertility (39).

The suggested relationship between proper nutrition in females and the ability to conceive is an additional worthy note. It has been suggested that positive energy balance, as well as increased fat storage in females as a result of proper nutrition, creates an environment within the reproductive system that enhances a female's potential to conceive. A continuum of ovarian function has been proposed, indicating that ovarian function and associated fecundity may be subject to minor changes in energetic environment, creating changes below the "clinical horizon" of menstruation. For example, studies have shown that rates of ovarian steroidogenesis in women with positive energy balances are significantly higher than in those in negative energy balance who are subject to follicular suppression (40).

Malnutrition and its derived symptoms most commonly present in undiagnosed females with celiac disease. This symptom can directly compromise the potential and ability to conceive due to a negative

(continued on page 15)

(continued from page 12)

energy balance and the decreased ability to maintain fat storage in afflicted females. Those with undiagnosed celiac disease and who do not follow a gluten-free diet may intensify unfavorable conditions for conception within the body and, more specifically, within the reproductive system. Men also suffer from infertility stemming from undiagnosed celiac disease (25). Affected males show a picture of tissue resistance to androgens. The increases of follicle-stimulating hormone and prolactin may indicate an imbalance at hypothalamus-pituitary level (41). Hypogonadism is a known factor in male infertility and has been found in 7% of celiac males in one survey. Endocrine dysfunction unaccompanied by other features of hypogonadism was found commonly and 19% of male celiacs were infertile.

Improvement in semen quality and successful pregnancy in previously infertile women is associated with gluten withdrawal by their male partners. The most striking endocrine findings in a study of 41 recently diagnosed men with celiac disease was increased plasma testosterone and free testosterone index, reduced dihydrotestosterone (testosterone's potent peripheral metabolite), and raised serum lutenizing hormone, a pattern of abnormalities indicative of androgen resistance. As jejunal morphology improved, hormone levels returned to normal (42). These higher rates of infertility among sufferers of celiac disease, as well as improvement associated with the gluten-free diet, indicate the value of celiac-related antibody testing in couples, both the male and female partners with unexplained infertility.

EARLY INDICATION: MENARCHE, MENOPAUSE AND AMENORRHEA

Although few reproductive health organizations currently have an official stance on celiac disease's impact on fertility, multiple studies concerning celiac disease sufferers and their ages at menarche and menopause indicate a potential link between celiac disease and fertility. Women with untreated celiac disease who did not maintain a gluten-free diet were found to have their first menstrual periods up to 1.5 years later than women on gluten-free diets. This delay was increased with increased malnutrition (43). Those with untreated celiac disease were also found to enter menopause four or five years before those who were avoiding gluten. Periods of secondary amenorrhea, when menstrual periods cease for at least three months, were found in 39% of those with untreated celiac disease, but only 9% of those on gluten-free diets (44).

In a study examining 59 mother-daughter pairs, 10 of whom had untreated or late onset celiac disease and 49 who were treating their celiac disease with gluten-free diets, researchers found a significant difference between ages of menarche. Daughters with untreated or late onset celiac disease showed a mean age at menarche of 16.16 years and their mothers showed 15.49 years. This contrasted greatly with the treated celiac patients who had significantly earlier onsets, which respectively showed a mean age of 12.33 and 13.82 years in the countryside, 13.08 and 13.49 in a small town and 12.90 and 12.33 in an urban area. Overall, this finding demonstrates a strong correlation between celiac disease, maintaining a gluten-free diet and a beneficial effect on the reproductive system (45). In a British study, in which 68 patient-control pairs were matched to examine celiac disease's impact on reproductive health, researchers found similar results. The mean age at menarche was older in patients with celiac disease than in controls at 13.6 years and 12.7 years, respectively (46). In summary, a delay in menarche could be an early symptom of undiagnosed celiac disease and may warrant testing for celiac disease.

MISCARRIAGES AND STILLBIRTHS

Studies have shown an increase in miscarriages and stillbirths in women with celiac disease who are not on a gluten-free diet, illustrating the need for a proper diagnosis and the education of obstetrics, gynecologists and fertility specialists. An Italian study demonstrated in 2000 that testing for celiac disease can prevent unfavorable outcome of pregnancy. Since up to 50% of female celiac pregnancies result in unfavorable outcomes or miscarriages, researchers screened 845 pregnant women for celiac disease and found 12. Of these 12 pregnancies, seven outcomes were unfavorable. There were three deaths, five premature births and three children born with low birth weights. However, after six months on a gluten-free diet, these 12 women with celiac disease had six successful pregnan-

cies (47). In a case-control study, comparison of 94 untreated and 31 treated celiac women indicated that the relative risk of spontaneous abortion was 8.9 times higher, the relative risk of low birth weight baby was 5.84 times higher and duration of breast feeding was 2.54 times shorter in untreated mothers. None of these markers related to the severity of celiac disease in the untreated women. The high incidence of spontaneous abortion, low birth weight babies and shortened duration of breastfeeding was effectively corrected with a gluten-free diet (48).

In a study of female fertility, obstetric and gynecological history in celiac disease patient-control pairs illustrated a higher incidence of miscarriages in patients with untreated celiac disease. Fifteen percent of pregnancies among women with untreated celiac disease ended in miscarriage, in contrast to the 6% in controls. Mothers with untreated celiac disease produced 120 live babies and seven stillbirths, as opposed to 161 live babies and one stillbirth found in controls (49). A study using patients with previously failed pregnancies, those who began gluten-free diets showed a 35.6% drop in pregnancy loss and 39.4% drop in producing babies with low birth weights (44).

Cumulatively, these studies provide evidence that there is a strong correlation between incidences of miscarriage, stillbirth and undiagnosed celiac disease, while also indicating that maintenance of the gluten-free diet is imperative to maintaining reproductive health in celiac disease patients.

INTRAUTERINE GROWTH RETARDATION

An important mechanism of low fertility in untreated celiac patients may be due to intrauterine growth retardation (IUGR). Also called intrauterine growth restriction or fetal growth restriction, IUGR is defined as a poorly growing fetus whose weight is less than the tenth percentile for its gestational age based on a standard curve for the general population (50). In addition to common causes such as smoking and alcohol abuse, numerous studies have linked celiac disease and IUGR. In a retrospective study of 48 patients with known celiac disease and 143,663 controls, rates for IUGR were significantly higher in celiac patients, 6.3% versus 2.1%, respectively. The same study also showed a higher rate of labor induction at 29.2% and 11.9% (51). The authors concluded that perinatal outcomes of celiac disease patients are generally favorable; however, higher rates of IUGR exist in celiac patients. According to the authors, these results indicate the need for careful surveillance for detection of IUGR and the advise that prospective studies should focus on screening for celiac disease among patients presenting with IUGR without a known cause (48). In a 1999 Danish study of 211 infants and 127 mothers with celiac disease and 1,260 control deliveries, Norgard found a 3.4-fold increased risk of IUGR in infants whose mothers had untreated celiac disease. In contrast, mothers on gluten-free diets had no increased risk of bearing children with fetal growth restriction. This study also found that women with celiac disease gave birth to infants with a mean birth weight that was 238 g lower than observed in the control deliveries. However, the women with celiac disease who were on gluten-free diets gave birth to babies 67 g heavier than the controls (52).

Investigating the correlation from a reverse perspective, Gasbarrini showed that patients with both repeated spontaneous abortions (RSA) and IUGR showed a statistically significant higher frequency of celiac disease when tested serologically than did the controls (with no RSA or IUGR). Specifically, 8 % (3/40) RSA patients and 15% (6/39) IUGR patients were positive for celiac antibodies, whereas all controls were negative (53). Similarly, Kumar placed 45 patients in two test groups, one comprised of patients positive for IUGR and one with patients undergoing a normal trimester. Two patients in the IUGR group tested positive for celiac antibodies whereas none of the controls did (54). Greco, et al in Italy demonstrated that one in every 70 pregnant women admitted to a major city hospital suffered from untreated celiac disease; 70% had a poor outcome of pregnancy, and 8/9 women had a second healthy baby after one year on a gluten free diet (55). In a follow up study, Grecco's group demonstrated that the increased risk of spontaneous abortions and IUGR achieved statistical significance in symptomatic celiac disease pregnant women (55). An unfavourable neonatal outcome was not only associated with maternal celiac disease but also with paternal celiac disease. Infants of celiac mothers weighed 222 g less than the population average, and

infants of celiac fathers weighed 266 g less than the population average. The risk of a low birth weight baby to celiac fathers was five times higher than that in the general population (11% versus 2.5%) (56).

FERTILITY, NUTRITION AND CELIAC DISEASE

In 2007, Chavarro showed that many cases of infertility due to ovulatory disorder could be prevented through changes in diet and lifestyle (57). These results indicate a niche for celiac disease. Protein from food is efficiently and almost completely absorbed by the proximal part of the small intestine. As celiac disease mainly affects precisely this area of the small intestine, absorption of proteins can be compromised and decreased quantities are detected in the plasma.

Fat malabsorption is a common consequence of celiac disease due to the inflammatory cascade, impaired meal-induced release of gut hormones (i.e. cholecystokinin) secondary to the loss of enterocyte mass (villous atrophy) and increased somatostatin levels (58). Within the discussion of reproductive system imbalances, the fat-soluble nutrients Vitamins A, D, E and K merit special attention. Vitamin A is fundamental for the maintenance of spermatogenesis (59) and testosterone secretion (60). Retinols appear to act on three main types of testicular cells (Sertoli cells, germ cells and Leydig cells) of both adult and fetus (60). A decrease in testosterone production leads to atrophy of the accessory sex organs (61). Vitamin D controls Th1-driven autoimmunity by down-regulating nuclear factor-kB (NF-kB) activity, increasing IL-10 production and decreasing IL-6, IL-12, IFN-c, and TNF-a production, leading to a cytokine profile which favors less inflammation (62,63). Vitamin E supports the correct differentiation and function of epididymal epithelium, spermatid maturation, and secretion of proteins by the prostate (62). Vitamin K deficits in pregnant women can harm the fetus, leading to chondrodysplasia punctata with nasal hypoplasia and spinal cord abnormalities (64). Hypoprothrombinemia caused by malabsorption of vitamin K is a well-known complication of celiac disease. Prolonged prothrombin time is reported in 18.5% of adults and 25.6% of children with celiac (65). Given the preponderance of studies showing a correlation between undiagnosed celiac disease and IUGR discussed previously, Rostami investigated the correlation between celiac disease and reproductive disorders proposing possible causal relationships. He noted that 25% of celiac patients have hyperprolactinaemia, which may be one of the causes of impotence. Furthermore, the most likely causes of reproductive disorders resulting from malnutrition are zinc deficiency, selenium deficiency and anemia (66).

Selenium deficiencies have been linked to fertility problems (65,67), iron deficiency to fetal-maternal morbidity (49,62,68), and folate deficiency to congenital malformations, recurrent spontaneous miscarriage, abruption placentae, and pre-eclapisa (11,35,50). Zinc is an essential trace element key in numerous functions including DNA synthesis, cell division, protein synthesis and immune response (66,35,69). Zinc has also been linked to fertility and zinc deficiency has been associated with impaired synthesis/secretion of FSH and LH, as well as abnormal ovarian development and obstetrical disorders, including IUGR (32,33). Zinc also has been proposed as a factor in male fertility issues (34), specifically in spermatozoal function. Zinc deficiency is associated with fertility problems, spontaneous abortions, congenital malformation, still birth pre-eclampsia, and intrauterine growth retardation (25,26,32,34). Intestinal biopsy correlated inversely with plasma zinc concentration. Decreased concentrations of zinc and other micronutrients may be attributable to an acute phase response and reverses with treatment with a gluten-free diet (70).

Women with celiac disease are often deficient in iron, as well as other micronutrients, and have altered reproductive function, including infertility. Chavarro investigated the effect of iron intake on risk of ovulatory infertility among apparently healthy women. The results showed an inverse relationship between iron intake and risk. Chavarro concludes overall that iron is important in ovulatory function, but may also be important in other aspects of fertility as many celiacs are shown to have low-iron and also show idiopathic infertility (71).

FUTURE IMPLICATIONS

It is surprising that although clear reports were given the pilot work (67,72) about 20 years ago, celiac dis-

ease has not yet gained adequate attention among obstetricians. In the subsequent two decades, many epidemiological studies clearly showed that it is a very common disease, one of the most common life-long disorders in both the U.S. and Europe (13), that it affects women more than men, and that it has to be considered in relation to reproductive function.

The bottom-line drawn from countless studies on celiac disease and infertility over 25 years is the importance of diagnosis, yet celiac disease is not commonly tested as part of preconception health requirements in those suffering from reproductive issues. Despite the strong recommendation of many studies prompting a strict dietary treatment to prevent neoplastic and systemic complications, decrease mortality and reverse the risk to many complications of pregnancy, neither the American College of Obstetricians and Gynecologists (ACOG) nor the March of Dimes officially recommend testing for celiac disease. Both groups are waiting for more studies in the United States as their knowledge of celiac disease's causal effects on fertility is continually evolving. Despite this argument, the cost-to-benefit ratio of testing for celiac disease is clear. The only negative repercussion to testing for celiac in unexplained infertility is the comparatively nominal cost of the test, whereas testing positive may give potential parents the answer to the problem without the use of costly and invasive procedures. Above all, it is imperative that those with celiac disease are diagnosed and begin their gluten free diet as soon as possible in order to maintain their health in all respects. ■

Acknowledgment

A special thanks to Sydney Lupkin, undergraduate at Boston University and NFCA Intern.

References

1. Recovery from Celiac Disease. *NEJM*, 2002; Vol. 336.
2. Murray J. The widening spectrum of Celiac Disease. *Am J Clin Nutr,* 1999;69:354–365.
3. http://consensus.nih.gov/2004/2004CeliacDisease118html.htm
4. Green P, Jones R. Celiac Disease; A Hidden Pandemic.
5. Taranta A, Fortunati D, Longo M, Rucci N, Iacomino E, Aliberti F, Facciuto E, Migliaccio S, Bardella MT, Dubini A, Borghi MO, Saraifoger S, Teti A, Bianchi ML. Imbalance of osteoclastogenesis-regulating factors in patients with celiac disease. *J Bone Miner Res*, 2004; 19: 1112-1121.
6. Torres MI, Lopez Casado MA, Rios A. New aspects in celiac disease. *WJ Gastroenterol*, 2007; 13: 1156-1161.
7. Stazi AV, Trecca A, Trinti B, Osteoporosis in celiac disease and in endocrine and reproductive disorders. *WJ Gastroenterol,* 2008;14(4):498-505.
8. Diosdado B, van Bakel H, Strengman E, Franke L, van Oort E, Mulder CJ, Wijmenga C, Wapenaar MC. Neutrophil recruitment and barrier impairment in celiac disease: a genomic study. *Clin Gastroenterol Hepatol,* 2007; 5: 574-581.
9. Alaedini A, Green PH. Narrative review: celiac disease: understanding a complex autoimmune disorder. *Ann Intern Med*, 2005; 142: 289-298.
10. Fasano A. *Arch Intern Med,* 2003; Vol 163.
11. Stazi A, Montovani A, A risk factor for female fertility and pregnancy: celiac disease. *Gynocol Endocrinol,* 2000;14:454-463.
12. Green P. Mechanisms underlying Celiac Disease and its Neurologic Manifestations. *Cell Molecul Life Sci,* 2005;62:791–799.
13. Fasano A. Celiac Disease - How to Handle a Clinical Chameleon. *NEJM*, 2003; 348: 2568-2570.
14. Fasano A, Catassi C. Current Approaches to Diagnosis and Treatment of Celiac Disease: An Evolving Spectrum. *Gastroenterology*, 2001;120:636-651.
15. Kotze L. 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; Vol 38, Number 7.
16. Kaukinen K, Maki M, Collin P. Immunohistochemical features in antiendomysium positive patients with normal villous architecture. *Am J Gastroenterol*, 2006;101(3):675-676.
17. Kumar V. American Celiac Society, Nov.9,1996
18. Salmi TT, Collin P, Järvinen O, Haimila K, Partanen J, Laurila K, Korponay-Szabo IR, Huhtala H, Reunala T, Mäki M, Kaukinen K. Immunoglobulin A autoantibodies against transglutaminase 2 in the small intestinal mucosa predict forthcoming coeliac disease. *Aliment Pharmacol Ther,* 2006;24(3):541-552.
19. Abrams J., Diamond B., Rotterdam H., Seronegative Celiac Disease: Increased Prevalence with Lesser Degrees of Villous Atrophy. *Dig Dis Sci,* 2004;49(4):546-550.
20. Tursi A. Can histological damage influence the severity of coeliac disease? An unanswered question. *Digist Liver Dis,* 2007;39:30–32.
21. Lebwohl B, Green P. Screening for Celiac Disease. *NEJM*, 2003;1673-1674.
22. Valentino R, Savastano S, Maglio M, Paparo F, Ferrara F, Dorato M, Lombardi G, Troncone R. Markers of potential coeliac disease in patients with Hashimoto's Thyroiditis. *Eur J Endocrinol,* 2002;146: 479–483.
23. Biagi F, Luinetti O, Campanella J, Klersy C, Zambelli C, Villanacci V, Lanzini A, Corazza GR. Intraepithelial lymphocytes in the villous tip: do they indicate potential coeliac disease? *J Clin Pathol,* 2004;57:835–839.
24. NIH. Autoimmune Diseases Coordinating Comm. Autoimmune Diseases Research Plan, 2006 http://www3.niaid.nih.gov/topics/autoimmune/researchActivities.htm
25. Farthing M, Rees L, Edwards C, Dawson A. Male gonadal function in coeliac disease: 2. Sex hormones. *Gut*, 1983; 24, 127-135.
26. Betterle C, Zanchetta R. Update on autoimmune polyendocrine syndromes (APS). *Acta Bio Medica,* 2003; 74; 9-33.
27. Poppe K, Glinoer D, Tournaye H, Devroey P, Schiettecatte J, Haentjens P, Velkeniers B. Thyroid autoimmunity and female infertility. *Verh K Acad Geneeskd Belg,* 2006; 68:357-377.
28. Nelson DA, Jr. Gluten-sensitive enteropathy (celiac disease): more common than you think. *Am Fam Physician,* 2002;66(12):2259-2266. Review

(continued on page 21)

(continued from page 18)

29. da Silva K, Kotze L, Nishihara R, daRosa U, Piovezan G, Kotze L. Thyroid disorders in Brazilian patients with celiac disease. *J Clin Gastroenterol,* 2006; 40(1):33-36.
30. Sategna-Guidetti C,Volta U, Ciacci C, Usai P, Carlino A, De Franceschi L, Camera A, Pelli A, Brossa C. Prevalence of Thyroid Disorders in Untreated Adult Celiac Disease Patients and Effect of Gluten Withdrawal: An Italian Multicenter Study. *AJG*, 2001;Vol. 96, No. 3: 751-757.
31. Levine JS, Branch DW, Rauch J. The antiphospholipid sindrome. *NEJM*, 2002; 346: 752-763.
32. Stone S, Khamashta MA, Poston L. Placentation, antiphospholipid syndrome and pregnancy outcome. *Lupus*, 2001;10:67-74.
33. Shamir R, Shoenfeld Y, Blank M, Eliakim R, Lahat N, Sobel E, Shinar E, Lerner A. The prevalence of coeliac disease antibodies in patients with the antiphospholipid syndrome. *Lupus*, 2003;12;394.
34. La Villa G, Pantaleo P, Tarquini R, Cirami L, Perfetto F, Mancuso F, Laffi G. Multiple immune disorders in unrecognized celiac disease: a case report. *World J Gastroenterol,* 2003;9(6): 1377-1380.
35. National Survey of Family Growth, CDC 2002. www.asrm.org/patients/faqs.html
36. American College of Obstetricians and Gynecologists. Infertility page. Available at http://www.acog.org/publications/patient_education/bp136.cfm. Accessed June 5, 2008
37. Collins. Infertility Evaluation and treatment, 1995
38. Pechman RR. Solving the Miscarriage Mystery. Parenting.com, May 2008.
39. Pellicano R., Astegiano M., Bruno M., Fagoonee S., Rizzetto M.. Women and celiac disease: association with unexplained infertility. *Minerva Med,* 2007;98:217-219.
40. Ellison, 2008, Gibson and Mace, 2006 Ellison 2001, Jasienska 2003
41. Stazi A, Trinti A. Reproductive aspects of celiac disease. *Ann Ital Med Int,* 2005 Jul-Sep;20(3):143-157.
42. Farthing M, Rees L, Edwards C, Dawson A. Male gonadal function in coeliac disease: 2 sex hormones. *Gut*, 1983, 24, 127-135.
43. Kotze L. 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;Vol. 38, Number 7.
44. Melin-Rogovin M. Fertility and Pregnancy in Women with Celiac Disease. Celiac.com's Scott-Free newsletter. Autumn 2002. Available at http://www.celiac.com/articles/643/1/Fertility-and-Pregnancy-in-Women-with-Celiac-Disease-by-Michele-Melin-Rogovin/Page1.html. Accessed June 3, 2008.
45. Rujner J. Age at menarche in girls with celiac disease. *Ginekol Pol,* 1999;70:359-362.
46. Sher KS, Mayberry JF. Female fertility, obstetric and gynaecological history in coeliac disease: a case control study. *Acta Paediatr Suppl,* 1996;412:76-77.
47. Martinelli P, Troncone R, Paparo F, Torre P, Trapanese E, Fasano C, et al. Coeliac disease and unfavourable outcome of pregnancy. *Gut*, 2000;46(3):332-335.
48. Ciacci C, Cirillo M, Auriemma G, Di Dato G, Sabbatini F, Mazzacca G. Celiac disease and pregnancy outcome. *Am J Gastroenterol*, 1996;91(4):718-722.
49. Sher KS, Mayberry JF. Female fertility, obstetric and gynaecological history in coeliac disease: a case control study. *Acta Paediatr Suppl,* 1996;412:76-77.
50. Botero D, Lifshitz F. Intrauterine growth retardation and long-term effects on growth. *Curr Opin Pediatr,* 1999;11:340–347.
51. Sheiner E, Peleg R, Levy A. Pregnancy outcome of patients with known celiac disease. *Eur J Obstet Gynecol Reprod Biol,* 2006;129(1):41-45.
52. Norgard S, Fonager K, Sorensen HT, Olsen J. Birth outcomes of women with celiac disease: A nationwide historical cohort study. *Am J Gastroenterol,* 1999;94:2435–2440.
53. Gasbarrini A, Torre ES, Trivellini C, Carolis SD, Caruso A, Gasbarrini G. Recurrent spontaneous abortion and intrauterine growth restriction as symptoms of celiac disease. *Lancet*, 2000;356:399.
54. Sharma KA, Kumar A, Kumar N, Aggarwal S, Prasad S. Celiac disease in intrauterine growth restriction. *Int J Gynaecol Obstet,* 2007;98(1):57-59.
55. 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.
56. Greco L. The Father Figure in Celiac Disease. *Gut*, 2001; 49:163–166.
57. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Diet and Lifestyle in the Prevention of Ovulatory Disorder Infertility. *Obstetrics Gynecol,* 2007;110:1050-1058.
58. Rubio-Tapia A, Murray JA. The liver in celiac disease. *Hepatology*, 2007;46(5):1650-1658. Review.
59. Ong DE, Takase S, Chytil F. Cellular vitamin A-binding proteins in the testis. *Ann NY Acad Sci,* 1987; 513: 172-178.
60. Livera G, Rouiller-Fabre V, Pairault C, Levacher C, Habert R. Regulation and perturbation of testicular functions by vitamin A. *Reproduction*, 2002;124:173-180.
61. Sadovsky R, Dhindsa S, Margo K. Testosterone deficiency: which patients should you screen and treat? *J Fam Pract,* 2007;56: S1-S20; quiz S21-S23.
62. Stazi AV, Trinti B. Reproductive aspects of celiac disease. *Ann Ital Med Int,* 2005; 20: 143-157.
63. Cantorna M, Mahon B. D-hormone and the immune system. *J Rheumatol Suppl,* 2005;76:11-20.
64. Menger H, Lin AE, Toriello HV, Bernert G, Spranger JW. Vitamin K deficiency embryopathy: a phenocopy of the warfarin embryopathy due to a disorder of embryonic vitamin K metabolism. *Am J Med Genet,* 1997;72:129-134.
65. Djuric Z, Zivic S, Katic V. Coeliac disease with diffuse cutaneous Vitamin K deficiency bleeding. *Adv Ther,* 2007;24(6):1286-1289.
66. Rostami K, Steegers EA, Wong WY, Braat DD, Steegers-Theunissen RP. Coeliac disease and reproductive disorders: a neglected association. *Eur J Obstet Gynecol Reprod Biol,* 2001;96(2):146-149. Review.
67. Ferguson R, Holmes GK, Cooke WT. Coeliac disease, fertility, and pregnancy. *Scand J Gastroenterol,* 1982;17:65–68.
68. Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States; a large multicenter study. *Arch Intern Med,* 2003;163: 286-292.
69. NIH. Autoimmune Diseases Coordinating Comm. Autoimmune Diseases Research Plan, 2006 http://www3.niaid.nih.gov/topics/autoimmune/researchActivities.htm
70. Eisenbarth GS, Haas JE, Sokol RJ, Taki I, Norris JM, Hoffenberg EJ, Emery LM, Barriga KJ, Bao F, Taylor J. Clinical Features of Children With Screening-Identified Evidence of Celiac Disease. *Pediatrics*, 2004; Vol. 113, No. 5.
71. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Iron Intake and Risk of Ovulatory Infertility. *Obstetrics Gynecol*, 2006;108:1145-1152.
72. Farthing MJ, Edwards CR, Rees LH, Dawson AM. Male gonadal function in coeliac disease: 1. Sexual dysfunction, infertility, and semen quality. *Gut*,1982; 23: 608-614.