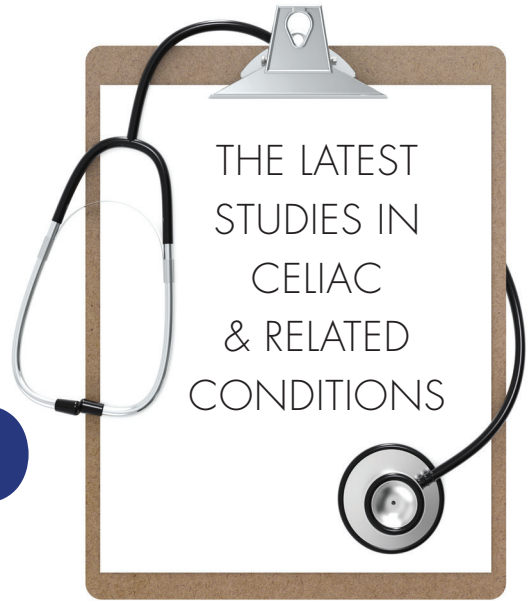
Research Roundup



Is there a connection between celiac disease or non-celiac gluten sensitivity and fertility? This question frequently comes up in our clinic. Therefore, I have decided to review what clinical science thinks about this problem. Although the published data are not consistent, most of the publications show a negative effect of celiac disease on female fertility and even pregnancy outcomes. While the topic is still quite controversial, for those with celiac disease, a lifelong gluten-free diet is expected to prevent complications in pregnancy.

The assessment of ovarian reserve in women of reproductive age with celiac disease.

Ovarian reserve is defined as the capacity of the ovary to provide egg cells that are capable of fertilization, resulting in a healthy and successful pregnancy.

The study aimed to investigate ovarian reserve in patients of reproductive age with celiac disease using anti-Müllerian hormone (AMH) levels, antral follicle counts (AFCs), and ovarian volume.

The study included 46 women with celiac and 40 healthy women of reproductive age, ages 18 to 45. Venous blood samples were taken from both groups on days two to four of the menstrual cycle, and follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), prolactin (PRL), and AMH levels were measured. Data on body mass index (BMI), gravidity/parity/abortions/alive counts, disease duration, and Marsh histological classification were recorded.

There were no statistically significant differences between celiac and control groups in terms of mean age, BMI, or median gravidity/parity/abortions/alive counts ($p>0.05$).

There were no statistically significant differences between the two groups in terms of mean FSH, LH, E2, PRL levels, right and left ovarian volumes, and median right and left ovarian AFCs ($p>0.05$).

However, AMH level was significantly lower in the celiac disease group ($p=0.032$).

There were no statistically significant correlations between AMH levels and age, BMI, FSH, LH, E2, PRL levels, right and left ovarian volumes, right and left ovarian AFCs, or Marsh histological classification using the Spearman correlation test ($p>0.05$).

However, an inverse correlation was detected, showing that AMH levels decrease with increasing celiac disease duration ($r=-0.054$, $p=0.001$).

In conclusion, the authors demonstrated that AMH level and ovarian reserve was decreased in celiac patients of reproductive age compared to healthy controls, and that AMH level and ovarian reserve decreased with increasing disease duration in celiac patients.

Reference:
Ovarian Reserve Assessment in Celiac Patients of Reproductive Age. *Medical Science Monitor.* 2018 Feb 24;24:1152-1157. Cakmak, E., Karakus, S., et al.

Meta-analysis data on prevalence of celiac disease in women with infertility.

The first connection between infertility and celiac disease was described by Morris et al. in 1970, who also explained the reversion of infertility after a gluten-free diet in three celiac disease women. In recent years, the interest in gynecologic and obstetric manifestations of celiac disease has increased.

A systematic review of 23 published articles showing numerical data of anti-transglutaminase type 2 or anti-endomysium antibodies, or intestinal biopsy information were included. The study group comprised of women with overall infertility, unexplained infertility, or recurrent spontaneous abortions.

After meta-analysis, the pooled seroprevalence was very similar for overall and unexplained infertility, with a pooled proportion of around 1.3 to 1.6 percent. This implies three times higher odds of having celiac in infertility when compared to controls.

A common feature of the great majority of studies evaluating celiac prevalence in women with infertility is the low sample size studied. Seroprevalence based on anti-TG2 and EMA data shows a three times higher risk in women with overall and unexplained infertility than in healthy women. Furthermore, there could be some cases of seronegative celiac.

After meta-analysis, the pooled seroprevalence was very similar for overall and unexplained infertility, with a pooled proportion of around 1.3 to 1.6 percent. This implies three times higher odds of having celiac in infertility when compared to controls.

An accurate value for prevalence could not be achieved, but considering the values of seroprevalence, higher risk of celiac should be expected in infertile women. Thus, these meta-analyses open again the debate about supporting routine screening for celiac among infertile patients. It is of utmost importance to make celiac women aware of the potential positive impact in the adoption of a strict gluten-free diet on fertility.

Reference:
Systematic Review and Meta-Analysis of Prevalence of Coeliac Disease in Women with Infertility. *Nutrients.* 2019 Aug 20;11(8):1950. Mercedes Castaño, M., Gómez-Gordo, R., et al.

The connection between celiac disease and early recurrent pregnancy loss.

Historically, celiac has been associated with pregnancy loss and infertility. The purpose of the study was to screen unselected women with recurrent pregnancy loss (RPL) for markers of celiac to determine whether a correlation exists between RPL and celiac serum markers.

Frequencies of three serum markers of celiac were determined by enzyme-linked immunoassay (ELISA):

- Tissue transglutaminase (TTG) IgA
- Endomysial (EMA) IgA
- Deaminated gliadin peptide (DGP) IgA

Included in the study were 708 women who had two or more failed clinical pregnancies (cases) and 100 women with at least one live birth and no miscarriages (controls).

All cases had a full workup for RPL based on the American Society for Reproductive Medicine's 2013 guidelines. Antiphospholipid antibodies (aPL) were correlated with celiac markers based on their potential prothrombotic (blood clotting) role.

The results show no significant difference in the prevalence of celiac autoantibodies when comparing the RPL patients with the controls. Over half of the patients who tested positive for serum markers for celiac also had positive aPL.

In conclusion, screening of unselected women with RPL who are asymptomatic for celiac is not supported based on these data. Women who test positive for celiac may be candidates for aPL testing based on the association of adverse pregnancy outcomes.

Reference:
Comparison of celiac disease markers in women with early recurrent pregnancy loss and normal controls. *American Journal of Reproductive Immunology.* 2019 Jul;82(1):e13127. Kutteh, M., Abiad, M., et al.

In conclusion, screening of unselected women with RPL who are asymptomatic for celiac is not supported based on these data. Women who test positive for celiac may be candidates for aPL testing based on the association of adverse pregnancy outcomes.

Long-term gastrointestinal outcomes and prevalence of celiac disease among offspring of mothers with celiac disease.

Perinatal outcomes, as well as long-term gastrointestinal morbidity of offspring of mothers with and without celiac disease were assessed. The study groups were followed until 18 years of age for gastrointestinal-related morbidity.

During the study period, 243,682 deliveries met the inclusion criteria, of which 212 (0.08%) were to mothers with celiac disease.

Maternal celiac disease was noted as an independent risk factor for low birth weight and cesarean delivery. Offspring born to mothers with celiac disease had higher rates of gastrointestinal related morbidity (Kaplan-Meier log rank test $P < 0.001$).

In conclusion, this study was the first to investigate the long-term gastrointestinal morbidity in offspring of mothers with celiac disease. The authors showed a significant increase in gastro-duodenal disease, celiac disease, and total gastrointestinal morbidity. In addition, the study demonstrated higher rates of adverse perinatal outcomes such as cesarean delivery and low birth weight in mothers with celiac disease.

Reference:
Perinatal Outcome and Long-Term Gastrointestinal Morbidity of Offspring of Women with Celiac Disease. *Journal of Clinical Medicine.* 2019 Nov 8;8(11):1924. Abecassis, A., Wainstock, T., et al. SGF

Maternal celiac disease was noted as an independent risk factor for low birth weight and cesarean delivery. Offspring born to mothers with celiac disease had higher rates of gastrointestinal related morbidity (Kaplan-Meier log rank test $P < 0.001$).

As always, consult a medical professional before beginning any new protocol.

ABOUT THE AUTHOR:
***Dr. Alexander Shikhman**, founder of the Institute for Specialized Medicine, is board certified in internal medicine and rheumatology. Dr. Shikhman also launched Gluten-Free Remedies™, a line of all natural supplements which help treat the complications that can arise from celiac disease. Find Dr. Shikhman at **ifsmed.com** and **glutenfreeremedies.com**.*