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The Relationship between Celiac disease Antibodies and Primary female Infertility

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ABSTRACT

Background - *Celiac disease is a chronic autoimmune disorder whichaffects the small intestine and can presents with gastrointestinal and non gastrointestinal manifestations. In women, it may presents with manifestation of gynecologic or obstetric disorders. Some reports have linked female infertilitywith undiagnosed celiac disease.*

AIM OF THE STUDY:

To explore the possible associationbetween celiac diseaseantibodies and primary female infertility.

PATIENT AND METHODS:

The primary infertility cases group comprised of (50) women (mean age 20-40 years) whom were examined and treated for primary infertility in the Department of infertility and In Vitro Fertilization of our hospital (Al –Sader medical city in Najaf). As a control group, we had taken (50) women,every one of them had (2) and more children, alsoeverywomanhad regular visits for a primary care unit for family control program (in Imam Hassan primary care center in Al-Addala district in Najaf governorate). Venous blood samples were taken from all females enrolled in the study. The Antigliadin Antibodies (AGA), for bothIgA (Immunoglobulin class A) and IgG (Immunoglobulin class G), were tested using a Commercial ELISA (Enzyme

Linked Immunosorbent Assay).All subjects' sera that tested for IgA (Immunoglobulin class A) and IgG (Immunoglobulin class G) antigliadin antibodies were then tested for Anti-endomysial antibody by indirect immunofluorescence. SPSS (Statistical Package for the Social Sciences) Software version (23.0) was used for performing statistical analysis.

RESULTS:

The mean age of primary infertility cases group is (30.20 ± 3.98), while for control group the mean age is (31.86 ± 3.66). (Chi-square) test was conducted to test the relationship between the presence of Antigliadin antibodies and primary female infertility in the cases group comparing to control group. There was no statistically significant relationship between Antigliadin antibodies and primary female infertility;$X2$ (1, N = 100) = 1.89, p = 0.169. Risk was estimated using odds ratio. The odds of having primary infertility are (4.26) times greater for women with positive Antigliadin antibodies. Comparison between primary infertility cases and controls regarding Anti-endomysial antibody was performed using (Chi-square) test, and also there was no statistically significant relationship between Anti-endomysial antibody and primary female infertility, $X2$ (1, N = 100) = 1.89, p = 0.209.Odds ratio for risk estimation shows that women with Anti-endomysial antibody are (4.26) times more likely to have primary infertility.

CONCLUSION:

Females with positive celiac serology have a higher chance to have primary infertility.

INTRODUCTION:

Celiac Disease:

Celiac disease is a chronic autoimmune disease that is induced by the eating of gluten, the protein which isfound in wheat, barley and also rye. Celiac disease is a known cause of malabsorption of nutrients. Although celiac disease was considered largely a disease of white individuals, especially persons of European community, nowobservations have established that it is common with multiple and different manifestations, a wide distribution, and its incidence in the USA (United States of America) is (1) in (113) persons, which is considered high. Its incidence has elevated in the past (50) years. This disease has had different other names, of them are celiac sprue, adult celiac disease, non tropical sprue and gluten sensitive enteropathy. The cause of celiac disease is unknown, but environmental, immunological, and genetic factors may be of importance. Celiac disease is regarded an "iceberg" disease. A small percentage of individuals have classical symptoms related to malabsorption along with a different history; the beginning of symptoms can occur at all points from year (1) of life to the eighth decade. Larger

number of individuals have “atypical celiac disease”, with features that are not related to intestinal malabsorption (for example anemia, osteopenia, infertility, and neurologic symptoms). Finally, an even larger number of persons have “silent celiac disease”; they are essentially asymptomatic despite abnormal small intestinal histopathology and serological testes. The hallmark of celiac disease is an abnormal intestinal biopsy and the response of the condition (including symptoms and histological changes) to the stopping of gluten from the food. The histological changes have different localization of severity, which is explained by the exposure of the intestine to different amounts of dietary gluten. Patients symptoms do not necessarily correlate with histological changes, especially as many newly diagnosed patients with celiac disease may be asymptomatic or only minimally symptomatic (often with no gastrointestinal symptoms). The symptoms of this disease begin with the addingof cereals to an infant’s food, although spontaneous remissions often occur in the twentieths of life that may persist or followed by the reemerging of symptoms over few years, or symptoms may firstly started at any age during adulthood. In the majority of cases, frequent on and off symptoms may occur. These symptoms may be revealed as malabsorption of nutrients, with diarrhea, steatorrhea, weight loss, nutrient deficiency (anemia and metabolic bone disease), to no gastrointestinal symptoms in spite of evidence of the deficiency of one nutrient (iron or folat deficiency, osteomalacia, edema from protein loss). Relatives of celiac patients whom are asymptomatic have been diagnosed with celiac disease either by intestinal biopsy or by serology (anti-endomysial antibodies, tissue transglutaminase (tTG), deamidatedgliadin peptide). The availability of these “celiac serology” has led to a substantial increase in the frequency of diagnosis of celiac disease, and the diagnosis is now being made primarily in patients without “classic” symptoms but with atypical and subclinical presentations. The cause of celiac disease is unknown, but environmental, immunologic, and genetic causes maythe etiology. Environmental factor is the obvious relationship of the disease with the gliadin, which is a part of gluten. Additionally, the effect of gluten reduction in management, the instillation of gluten into the normal appearing rectum and the ileum of celiac patients results in morphologic changes within few hours. An immunologic component in the pathogenesis of celiac disease is critical and involves both adaptive and innate immune responses. Serum antibodies: Immunoglobulin class (A) antigliadin, anti-endomysial, and anti-tissue transglutaminase antibodies are identified, even though, it isunknown whether these antibodies are primary or secondary to damaged tissues. The presence of anti-endomysial antibody is (90–95%) sensitive and (90–95%) specific; the antigen recognized by anti-endomysial antibody is transglutaminase, which deaminate gliadin, which is presented to HLA-DQ2 or HLA-DQ8 (HLA=Human Leukocyte Antigen). Antibodies are beneficial to identify patients with celiac disease, but patients with these antibodies have to undergo duodenal biopsy to confirm the diagnosis. This autoantibody has not been linked to a pathogenetic mechanisms responsible for

celiac disease. This antibody is useful in demonstrating the real prevalence of celiac disease in the community. A (4) week course of treatment with prednisolone induces a remission in a celiac patient who continues to eat gluten and converts the “flat” abnormal biopsy to a normal appearing one. In addition, gliadin gives reaction with gliadin-specific T cells (Thymic Cells) that causeinjury to tissues and enhance the release of cytokines (e.g., interferon γ (Gama)) that cause tissue pathology. Genetic factors are also had part in celiac disease. The incidence of symptomatic celiac disease varies in different population (high among whites, low among blacks and Asians) and is (10%) among first-degree relatives of patients with celiac disease. However, serologic studies provide clear evidence that celiac disease is present worldwide. All celiac patients express the HLA-DQ2 or HLA-DQ8 (HLA=Human Leukocyte Antigen) allele, although only a small percentage of people expressing DQ2/DQ8 have celiac disease. Absence of DQ2/DQ8 excludes the diagnosis of celiac disease.(1)

Classically celiac disease symptoms is diarrhea, flatulence and malabsorption, but it is also associated with different manifestations including bone disease, diabetes, thyroid disease and lymphoproliferative malignancies(2). Improvements in screening serology, increasing number of patients are diagnosed due to non gastrointestinal manifestations.

Many studies revealed implications of celiac disease on the reproduction of women. For example, untreated celiac may be associated with recurrent fetal loss(3)(4) intrauterine growth retardation, preterm labor and low birth weight (5)(6)(7)(8). Reports suggested a relationship between gynecologic diseases such as endometriosis(9) or amenorrhea(8)(10)(11) with celiac disease.

Others suggest a higher percentage of undiagnosed celiac disease in patients with infertility(4)(12) (13)(14)(15). These prevalence ranges from (2–6%) comparing with (1%) in the general population(15). Others do not show an increased percentage(16)(17). So revealing the real percentage of celiac disease in infertile populations is an important step.

Celiac disease is believed to occur in about (1%) from population around the world, with minor variations in different populations; higher rates is seen in European, Middle Eastern and in North African regions and lower rates is seen in Southeast Asia(18)(2)(19). Majority of the studies to test celiac disease prevalence in infertile women were done inEurope (only two studies till now have been conducted in the USA(United States of America) (15)(16)). Identifying infertile women with celiac disease is important if a gluten-free diet can improve fertility. Other studies also showed that patients with celiac disease areusually complaining from conceiving problems of infertility and miscarriages(20). All demonstrated that females with untreated celiac disease had increasing percentage of abortions than controls; also(21),

demonstrated an increasing incidence oflow birth weight,spontaneous abortions and decreased duration of breast feeding seen in non treated celiac disease women by gluten free diet.

Female Infertility:

Infertility defined as the inability to become pregnant after one year of unprotected intercourse of reasonable frequency. It is divided into primary infertility, which means a female with infertility had no previous pregnancies, andsecondary infertility, referring to infertility after at least one previous conception.Successful pregnancy needs a cascade of events which is firstly ovulation, ovum pick up by the fallopians, fertilization, then transport of fertilized ovum to the uterus, and implantation into the uterine cavity. Remembering these event helps to direct the clinician to an appropriate evaluation and treatment strategy. Generally, infertility caused by the female partner by one third, the male partner by one third, and both partners in the remaining. So there is importance of assessing both members of the couple before treatments(24).

Tubal Factors:

Symptoms of chronic pelvic pain or dysmenorrheasuggest tubal obstruction or pelvic adhesions or both. Adhesions prevent normal tubal movement, ovum pickup, and transport of fertilized egg into uterus. A wide rangeof etiologies may contribute to tubal factors, of them, pelvic infection, endometriosis, and previous pelvic surgeries. A history of PID (Pelvic Inflammatory Disease) is suspicious for pelvic adhesions or damage to the fallopians. Tubal infertility is estimated to follow in (12)%, (23)% , and (54)% of women following (1), (2) , or (3) cases of PID (Pelvic Inflammatory Diseases), respectively. Nevertheless, an absent PID (Pelvic Inflammatory Diseases) history is not always reassuring, as nearly (1) half of patients with tubal damage have no history of antecedent disease. Approximately (1) third to (1) fourth of all infertile women in developed countries have diagnosed with tubal disease. In the USA(United States of America), the common causes of tubal disease are infection of Chlamydia trachomatis or Nisseria gonorrhea. In contrast, in developing countries, genital tuberculosis may account for (3) to (5) % of infertility cases. As a result, this diagnosis should be considered in immigrant populations from countries with endemic infection. In those, tubal damage and endometrial adhesions are the underlying causes. Genital tuberculosis typically follows hematogenous seeding of the reproductive tract from an extra-genital primary infection. The probability of return to fertility after anti tubercular medications is low, and IVF(In Vitro Fertilization) with embryo transfer is the most reliable solution. Within implants of endometriosis, inflammation and chronic bleeding can also lead to fallopian tube obstruction or the development of pelvic adhesions. Also, a history of ectopic pregnancy, even is treated with methotrexate, giving a probability of significant tubal damage. Residual adhesion is

common after the most meticulous pelvic surgery. This is true in patients with pelvic inflammation because of blood, infection, or irritation results from mature cystic teratoma (dermoid) contents. (Salpingitis isthmicanodosa) is an inflammatory condition of the fallopian tube, characterized by nodular thickening of its isthmic portion. Histologically, smooth muscle proliferation and diverticula of tubal epithelium contribute to this thickening. This uncommon condition is typically bilateral and progressive and may lead eventually to tubal obstruction and infertility. The risk of ectopic pregnancy is increased with salpingitis isthmicanodosa(24).

Hormonal Factors:

Ovulation may be affected by abnormalities in the hypothalamus, anterior pituitary, or in the ovaries. Hypothalamic disorders is acquired or inherited. Acquired disorders include those due to lifestyle, as in excessive exercise, eating disorders and stress. Also dysfunction or incorrect migration ofthe hypothalamic gonadotropin releasing hormone neurons sometimes is inherited, as what occurs in IHH (idiopathic hypothalamic hypogonadism) or in Kallmann's syndrome. Thyroid dysfunction and hyperprolactinemia may contribute to menstrual irregularities which may lead to infertility(24).

Unexplained:

Unexplained female infertility is infertility that is without cause in the sense that its etiology remains not known even after infertility workup, usually includes assessment of ovulation and fallopian tubes in the woman.

In unexplained infertility, the pathology is virtually present but not visualized by our current diagnostic methods. The problems can be that the ovum is not released at the accurate time for fertilization, not enter the fallopians, or sperm not able to reach the ova, fertilization may not occur, movement of the zygote may be affected, or implantation not occur. It is becoming noticed that the ovum quality is of importance and females of advanced age may have ova of decreasing capacity for successful fertilization. Polymorphisms in folat pathway genes may be a cause for complications in conception in some females having unexplained infertility. Defects in reproductive immunology as in decreased maternal immune tolerance to the embryo may be an explanation. Increasing evidencesuggests that epigenetic changes in sperm may be responsible in part(30).

Aim of the Study:

To explore the possibleassociationbetween celiac disease antibodies and primary female infertility.

PATIENTSAND METHODS:

Our study is a Case – control study. In our study, the primary infertile group comprised of (50) women (mean age 20—40 years) whomwere examined and treated for primary infertility in the Department of infertility and In Vitro Fertilization of Al –Sader medical city in Najaf. All subjects were taken between August (2016) and December (2016). The etiology of infertility was typified according to the following : (1) Hormonal factor by evaluation of the endocrine causes, which are pituitary gonadotrophins, prolactin ,thyroid hormones, androstenedione and testosterone,. (2) Tubal factor as a patency was investigated by hysterosalpingography. As a control group, we had taken (50) women, everyone one of them had (2) and more children (exclusion criteria are infertility and celiac disease), also, each of them had regular visits for a primary care unit for family control program (in Imam Hassan primary care centre in Al-Addala district in Najaf governorate).Venous blood samples were taken from females enrolled in the study. After separation of blood samples by centrifugation, females sera were stored at (-20°) centigrade. The AGA (antigliadin antibodies) tests, for both IgA (Immunoglobulin class A) and IgG (Immunoglobulin class G) , were tested using commercial (ELISA) (Enzyme Linked Immunosorbent Assay), company name is (AESKU.DIAGNOSTICS GmbH&Co.KG, Germany). The cut off values of (7) IU for antigliadin antibody IgA (Immunoglobulin class A) and of (15) IU for antigliadin antibody IgG (Immunoglobulin class G) respectively, were provided by the manufacturer. The diagnostic sensitivity and specificity of this method of antigliadin antibody assay have been provided as (78%) [±14 confidence interval (CI)] and (98%) (±4 confidence intervalCI) for IgA (Immunoglobulin class A) , and (94%) (± 8 confidence intervalCI) and (79%) (±12confidence interval CI) for IgG (Immunoglobulin class G) respectively (22). Sera that tested for IgA (Immunoglobulin class A) and IgG (Immunoglobulin class G) class antigliadin antibody were then tested for anti-endomysial antibodies by indirect immunofluorescence, employing sections of human umbilical cord, which were then counterstained with fluorescein-labelled goat antihuman IgA (Immunoglobulin class A), company name is (NOVA Lite). Anti-endomysial antibodies, which is detected on human umbilical cord, have a sensitivity of (93%) and a specificity of (100%)(22).

STATISTICAL ANALYSIS:

SPSS(Statistical Package for the Social Sciences) Software version (23.0) was used for performing statistical analysis. Continuous data are presented as mean ± standard deviation and qualitative data are presented as number and percentage. Comparison of study groups was carried out using (chi-square) test and odds ratio. P value of (< 0.05) was considered statistically significant.

RESULTS:

The research included a total of (100) participants: (50) women with primary infertility and (50) age-matched subjects as controls. All participants had underwent laboratory investigations for IgA (Immunoglobulin class A) antigliadin antibody, IgG (Immunoglobulin class G) antigliadin antibody, and anti-endomysial antibody. The mean age of cases group is(30.20 ± 3.98), while for control group the mean age is (31.86 ± 3.66). Age groups of study participants are summarized in figure(3.1). Comparison of age groups between cases and controls is presented in table (3.1). Cause of infertility in the cases group are represented in figure (3.2).

The number of children for the women in control group ranged from (2) to (7) children, with a median number of (4) children.

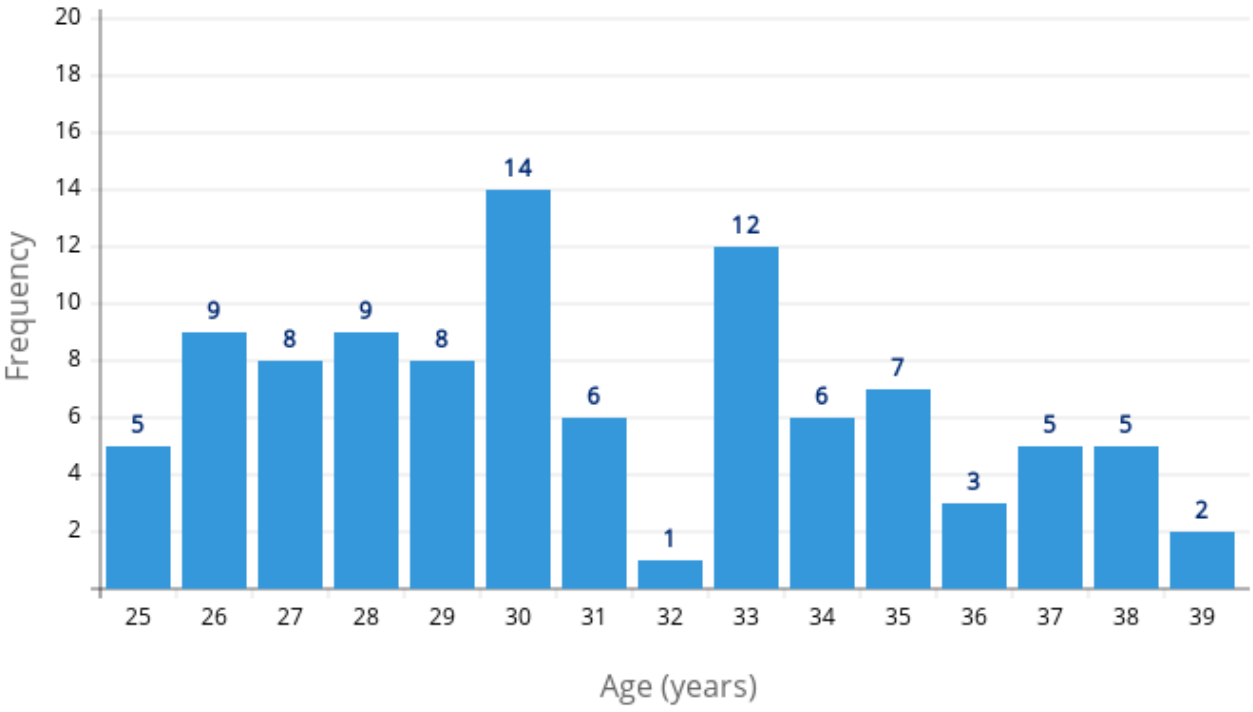

Figure 3.1

Age distribution in study subjects

Table 3.1
Comparison of study groups according to age group

Age group	Infertility cases(n=50)	Controls(n=50)	Total
21-25	4 (8%)	1 (2%)	5 (5%)
26-30	27 (54%)	21 (42%)	48 (48%)
31-35	13 (26%)	19 (38%)	32 (32%)
36-40	6 (12%)	9 (18%)	15 (15%)
Total	50 (100%)	50 (100%)	100 (100%)
p-value		0.233	

$X2$ (3, N = 100) = 4.27, p = 0.233

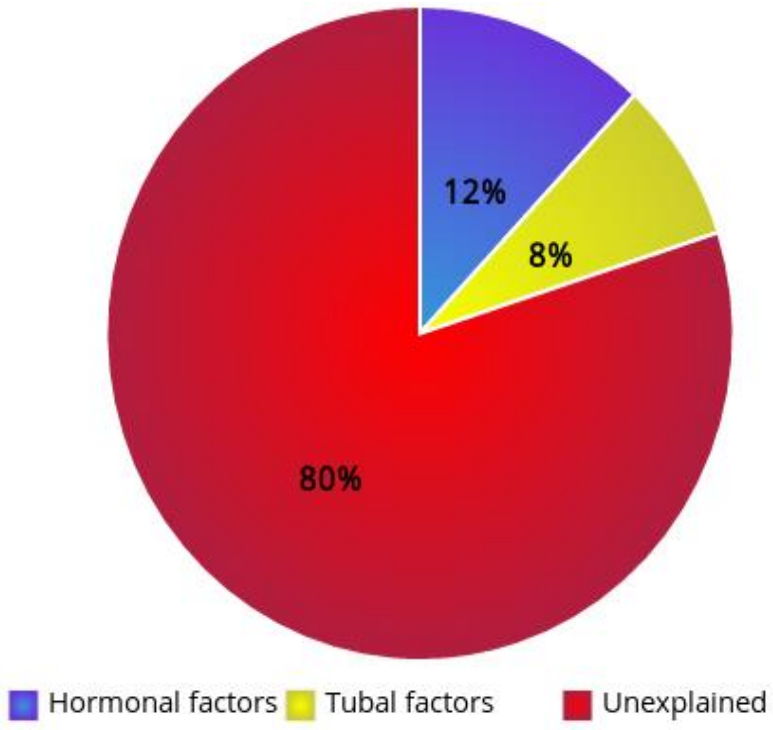

Figure 3.2

CAUSE OF INFERTILITY IN CASES GROUP

All study subjects (cases and controls) were negative of IgA (Immunoglobulin class A) antigliadin antibody, however, some cases and controls were positive for IgG (Immunoglobulin class G) antigliadin antibody and anti-endomysial antibody.

(Chi-square) test was conducted to test the relationship between the presence of IgG (Immunoglobulin class G) antigliadin antibody and infertility. There was no statistically significant relationship between IgG(Immunoglobulin class G) antigliadin antibody and infertility, $X2$ (1, N = 100) = 1.89, p = 0.169.

Risk was estimated using odds ratio. The odds of developing infertility are (4.26) times greater for women with IgG (Immunoglobulin class G) antigliadin antibody present (table 3.2). The 95% confidence interval for odds ratio was 0.46 to 39.55.

Table 3.2

Comparison of IgG (Immunoglobulin class G) antigliadin antibody in cases and controls

IgG (Immunoglobulin class G) antigliadin antibody	Infertility cases(n=50)	Controls(n=50)	Total
Positive	4 (8%)	1 (2%)	5 (5%)
Negative	46 (92%)	49 (98%)	95 (95%)
Total	50 (100%)	50 (100%)	100 (100%)
p-value		0.169	

$X2$ (1, N = 100) = 1.89, p = 0.169

Comparison between infertility cases and controls regarding anti-endomysial antibody was performed using (chi-square) test, and there was no statistically significant relationship between anti-endomysial antibody and infertility, $X2$ (1, N = 100) = 1.89, p = 0.209.

Odds ratio for risk estimation shows that women with anti-endomysial antibody are (4.26) times more likely to develop primary infertility (table 3.3).The 95% confidence interval for odds ratio was calculated to be 0.46 to 39.55.

Table 3.3

Comparison of anti-endomysial antibody in cases and controls

anti-endomysial antibody	Infertility cases(n=50)	Controls(n=50)	Total
Positive	4 (8%)	1 (2%)	5 (5%)
Negative	46 (92%)	49 (98%)	95 (95%)
Total	50 (100%)	50 (100%)	100 (100%)
p-value		0.169	

$$X2\ (1, N = 100) = 1.89, p = 0.169$$

The relationship between the cause of primary infertility and presence of positive serology of celiac disease (IgG(Immunoglobulin class G) antigliadin antibody or anti-endomysial antibody) is assessed using (chi-square), and there was no statistical significance between cause of primary infertility and positive serology of celiac disease, $X2\ (2, N=50) = 2.67, p = 0.263$, (table 3.4).

Table 3.4

Comparison between infertility cause and positive serology of celiac disease

Infertility cause	Celiac disease serology		Total
	Positive	Negative	
Hormonal	1 (25%)	5 (10.87%)	6 (12%)
Tubal	1 (25%)	3 (6.52%)	4 (8%)
Unexplained	2 (50%)	38 (82.61%)	40 (80%)
Total	4 (100%)	46 (100%)	50 (100%)
p-value		0.263	

$$X2\ (2, N=50) = 2.67,\ p = 0.263$$

Cause of infertility relationship with age was tested using (chi-square) test of significance, and there was no statistical significance between cause of infertility and age, $X2\ (6, N=50) = 6.52$, $p = 0.367$, (table 3.5).

Table 3.5

Comparison of cause of infertility with age group

Age group	Cause of infertility			Total
	Hormonal	Tubal	Unexplained	
21-25	0 (0%)	1 (25%)	3 (7.50%)	4 (8%)
26-30	5 (83.33%)	3 (75%)	19 (47.50%)	27 (54%)
31-35	1 (16.67%)	0 (0%)	12 (30%)	13 (26%)
36-40	0 (0%)	0 (0%)	6 (15%)	6 (12%)
Total	6 (100%)	4 (100%)	40 (100%)	50 (100%)
p-value		0.367		

$X2$ (6, N=50) = 6.52, p = 0.367

Positive serology for celiac disease was also compared to age group, and (chi-square) test showed no statistically significant relationship between the two variables. $X2$ (3, N=100) = 2.41, p = 0.491. (Table 3.6).

Table 3.6

Celiac disease serology according to age group

Age group	Celiac disease serology		Total
	Positive	Negative	
21-25	0 (0%)	5 (5.26%)	5 (5%)
26-30	4 (80%)	44 (46.32%)	48 (48%)
31-35	1 (20%)	31 (32.63%)	32 (32%)
36-40	0 (0%)	15 (15.79%)	15 (15%)
Total	5 (100%)	95 (100%)	100 (100%)
p-value		0.491	

$X2$ (3, N=100) = 2.41, p = 0.491

DISCUSSION:

Our study is showing that the presence of celiac disease serology is higher in females suffering from primary infertility than in the aged matched general population with observed frequency of celiac disease in the female primary infertility group is about four-fold higher than in the control group.

With the introduction of serology for celiac disease, it has become obvious that the disease remains clinically silent or symptoms appear outside the alimentarytract. Evidence supporting infertility more associated with celiac disease was stated by Meloni et al. (1999) who found that (4) out of (99) infertile women had positive serology for celiac disease(13). This result is lower than our result of our study which was (4) with positive celiac serology out of (50) primary infertile women.

Also in comparison with other researches, results from a meta analysis done in (2014) in the USA (United States of America) revealed that women who have infertility had (3.5) times

higher odds of having celiac disease in comparison with generalpopulation(31).This result is lower than our result which reveals the presence of celiac disease of four times higher in primary infertile women than in aged and sex matched general population.

Other study in Italy (2009) had found an association between infertility and celiac disease which is four times higher than the general population(32).This result is similar to our result. The presence of this relationship between celiac disease and reproductive abnormality can consider celiac disease serological screening in females affected by these gynecological disorders.

In other study in Brazil in (2003), results were (5) positive celiac serology out of (170) infertile women(33).This result is less than the result of our study which is (4) have positive serology for celiac out of (50) primary infertile women.

So celiac disease should be considered and excluded in females with primary infertility. Gluten free diet have to be not be ignored, although the mechanism for the infertility in females with celiac disease is still not known.

Data support that silent celiac disease may be a risk factor for female infertility, but the offending mechanism is still not known. Different hypotheses had been tried to show the etiology of infertility in these females with celiac disease. Celiac females whom eating normal diet have delayed menarche and early menopause and reduced reproductive period (23). Infertility may be represents another feature of the different spectrum of the etiology ofceliac disease.

If it is hypothesized that a causal connection between celiac disease and infertility is present, then an important question to ask is whether gluten free diet can reduce infertility. Olderresearches goes with this possibility(25). The possibility of a gluten free diet to have a positive effect on infertility is supported by the possibility that nutritional defects especially malabsorption of some nutrients including zinc, selenium, iron and folat may under lie reproductive disorders(26).

Even though, gynecological problems cannot be totally explained by malabsorption of some nutrients(27). Infertility is regarded now as a situation in which celiac disease have to be borne in mind(26)(27)(28)(29).

Females with primary infertility and serologically confirmed celiac disease should be put on a diet without gluten to improve fertility, asdeclared previously by others. The results from our

study have to be more confirmed in a much larger group of cases from our area and from different areas, until now they indicated that celiac disease perhaps deserves more attention from gynecologists.

Given the finding of a difference in the presence of celiac disease between the study and control groups, this study can offer a conclusion and suggests the need for more studies to include celiac disease in screening programs.

CONCLUSIONS AND RECOMMENDATIONS:

Females with positive celiac serology have a higher chance to have primary infertility.So recommendation for gynecologist to send patients with primary infertility for celiac screen (antigliadin and anti-endomysial antibodies).

Recommendation for further studies with larger sample are highly suggested.

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