Objective: To investigate the prevalence of positive serologic findings for celiac disease in Indian women with poor reproductive performance.

Design: Cross-sectional except that the women with intrauterine growth restriction were followed prospectively until delivery.

Setting: Department of Obstetrics and Gynecology of a tertiary teaching hospital, New Delhi.

Patient(s): Eight hundred ninety-three women (104 women with idiopathic recurrent abortion, 104 women with unexplained stillbirth, 230 cases of unexplained infertility, 150 pregnant women with idiopathic intrauterine growth restriction, 305 control cases).

Intervention(s): None.

Main Outcome Measure(s): The presence of antigliadin IgA and IgG, anti-tissue transglutaminase IgA by ELISA, and IgA antiendomysium antibody by indirect immunofluorescence microscopy.

Result(s): The seroprevalence of transglutaminase IgA was 6.7% in the group with recurrent abortion, 5.7% in the group with stillbirth, 5.6% in the group with infertility, 9.3% in the group with intrauterine growth restriction, and 1.3% in the control group. Rates of previous preterm births, low-birth-weight infants, and cesarean section were higher in seropositive women compared with seronegative subjects.

Conclusion(s): Women having poor reproductive performance had subclinical celiac disease. The serology for celiac disease can be considered in idiopathic cases.

Key Words: Infertility, latent celiac disease, poor reproductive performance, pregnancy, serologic marker
women in the third trimester of pregnancy with IUGR registered in an antenatal clinic, and 250 women with infertility attending the infertility clinic were enrolled for the study. The control group comprised 305 women with normal obstetric history who attended the family planning clinic of the hospital. None of these women had any classic gastrointestinal symptoms of celiac disease. The study was approved by the institutional ethics committee.

A written informed consent was taken from all patients. All subjects were evaluated regarding surety of dates, history of prolonged cycles, history of fever, skin rashes, congenital malformation in the previous infant, sign and symptoms of preeclampsia, renal disease, diabetes, and dietary and socioeconomical history. Examination included recording of height, weight, nutritional status, blood pressure, and anemia. The women with IUGR underwent obstetric examination also and were followed until delivery.

The inclusion criteria for unexplained infertility were normal semen analysis from the husband (World Health Organization criteria, 1993); normal ovulation assessed by premenstrual endometrial biopsy; normal postcoital test results (for cervical factor of infertility); normal serum LH, FSH, and ovulation assessed by premenstrual endometrial biopsy; normal postcoital

Table 1:

<table>
<thead>
<tr>
<th>Serologic marker</th>
<th>Recurrent abortion group</th>
<th>Stillbirth group</th>
<th>IUGR group</th>
<th>Infertility group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1, no. (%)</td>
<td>2, no. (%)</td>
<td>3, no. (%)</td>
<td>4, no. (%)</td>
<td>5, no. (%)</td>
</tr>
<tr>
<td>IgA tTG</td>
<td>7 (6.70)</td>
<td>97 (93.26)</td>
<td>6 (5.70)</td>
<td>98 (94.23)</td>
<td>13 (6.69)</td>
</tr>
<tr>
<td>IgG AGA</td>
<td>7 (6.70)</td>
<td>97 (93.26)</td>
<td>6 (5.70)</td>
<td>98 (94.23)</td>
<td>13 (6.69)</td>
</tr>
<tr>
<td>IgA EMA</td>
<td>5 (4.81)</td>
<td>98 (95.19)</td>
<td>5 (4.81)</td>
<td>98 (95.19)</td>
<td>11 (4.79)</td>
</tr>
</tbody>
</table>

Note: EMA = antiendomysium antibody.

*P value.

Statistical analysis was performed with use of the Statistical Package for the Social Sciences software for Windows (version 15.0; SPSS Inc., Chicago, United Kingdom). To decrease the false positivity, the initially reactive samples were retested in duplicate and considered ELISA positive if at least two of three results were reactive. An antiendomysium IgA level showing $\geq 20$ RU/mL, antigliadin IgG level showing $\geq 30$ RU/mL, and anti-tissue transglutaminase IgA level showing $\geq 5$ U/mL were taken as positive.
The qualitative data such as results of the serologic test, preterm delivery, and cesarean rate between the two groups were compared by use of the χ²-Fisher exact test. Multivariate analysis could not be done because of the very small number of seropositive cases. The data of each study group were compared with those of the control group. A P value < .05 was considered the cutoff point for level of significance.

RESULTS

Data of 104 consecutive women with a history of idiopathic recurrent spontaneous abortion, 104 women with a history of unexplained stillbirth, 150 women with unexplained IUGR, 230 women with unexplained infertility, and 305 control women with a normal obstetric history were analyzed. The mean age and body mass index of women with a history of recurrent spontaneous abortion were 26.47 ± 3.80 years and 22.36 ± 3.24 kg/m², of women with a history of stillbirth 26.87 ± 3.54 years and 23.86 ± 3.55 kg/m², of women with IUGR 28.31 ± 4.00 years and 22.68 ± 4.03 kg/m², of women with infertility 29.71 ± 4.64 years and 23.44 ± 4.00 kg/m², and of control women 27.75 ± 4.48 years and 21.08 ± 3.54 kg/m², respectively.

Seven (6.7%) of 104 subjects in the group with recurrent spontaneous abortion, 6 (5.7%) of 104 women in the group with stillbirth, 13 (5.6%) of 230 women in the group with infertility, 14 (9.3%) of 150 women in the group with IUGR, and 4 (1.3%) of 305 in the control group tested positive for IgA tTG (Table 1). On the basis of IgA tTG, odds ratios (95% confidence interval) were 5.43 (1.34–25.72), 4.61 (1.06–22.56), 4.51 (1.36–19.19), and 7.75 (2.36–32.76) for groups with recurrent spontaneous abortion, stillbirth, unexplained infertility, and IUGR, respectively. The seroprevalence of the IgA tTG and IgA antiendomysium antibody was similar in all the groups, that is, recurrent spontaneous abortion, stillbirth, infertility, and IUGR (P > .05).

The prevalence of anemia in IgA tTG–seropositive women in the group with recurrent spontaneous abortion was 71.4%, in the group with stillbirth 100%, in the group with infertility 30.8%, in the group with IUGR 64.3%, and in the control group 25% (Table 2). The history of preterm labor was found to be significantly higher in IgA tTG–seropositive women in the groups with recurrent spontaneous abortion and IUGR. History of having low-birth-weight infants was found to be significantly higher in IgA tTG–seropositive women in groups with recurrent spontaneous abortion and stillbirth compared with seronegative groups. History of cesarean section in previous pregnancy was found to be significantly higher in IgA tTG–seropositive women in all groups (Table 3). However, the preterm delivery (<37 weeks) rate was higher in seropositive women in the index pregnancy of the group with IUGR, though the difference was not statistically significant. All cesarean sections were performed for obstetric indications. The obstetric outcome was comparable in IgA tTG–seropositive and IgA tTG–seronegative women in the group with IUGR (Table 4).

DISCUSSION

The prevalence of latent or subclinical celiac disease has increased after the availability of improved and more accessible diagnostic tools for screening. Celiac disease has been associated with increased risk of adverse pregnancy-related events (1). It is important to diagnose celiac disease in the population having poor reproductive outcome because a simple therapeutic intervention such as a gluten-free diet may result in conception and a favorable outcome of pregnancy.

The present study for the first time shows that celiac disease is associated with high rates of unexplained infertility, recurrent...
TABLE 3

In the present study a history of preterm delivery, low birth weight of infants, and lower-segment cesarean section (LSCS) were significantly higher in the seropositive women in the group with recurrent spontaneous abortion; a history of low birth weight of infants and LSCS was significantly higher in the seropositive women in the stillbirth group; and a history of preterm delivery and LSCS was significantly higher in the seropositive women in the group with recurrent spontaneous abortion, 4.61 times in the group with stillbirth, 7.75 times in the group with IUGR, and 4.51 times in the group with unexplained infertility in comparison with the controls. A case-control study in 125 pregnant women with celiac disease showed a relative risk of abortion to be 8.9 times higher in untreated celiac disease (14). A study by Meloni et al. (11) also showed the rate of celiac disease to be threefold higher in infertile women than in the general population. This variation might be because of genetic variation in different geographic regions.

According to a National Institutes of Health Consensus Panel Statement (2004) on celiac disease (15), serologic testing is the first step in pursuing a diagnosis of celiac disease, and the best available tests are IgA anti-human tissue transglutaminase (tTG) and antigliadin IgA antibodies. Similar findings also were found in the present study. The measurement of tTG IgA by ELISA was comparable to the findings of antigliadin antibody IgA. The serologic tests for IgA AGA and IgG AGA showed high positivity as compared with IgA tTG and IgA antigliadin antibody, thus showing less specificity. Patients with atopic eczema, pemphigus, pemphigoid, Sjögren’s syndrome, rheumatoid arthritis, and sarcoid have elevated levels of IgG AGA (2, 16, 17). Therefore, the AGA IgA and AGA IgG antibody tests no longer are recommended routinely because of their lower and highly variable sensitivity and specificity. Approximately 5% of the normal population will have positive results for gliadin IgG antibodies. On the basis of evidence and practical considerations, including accuracy, reliability, specificity, and cost, measurement of tTG IgA by ELISA is recommended as the initial test for silent celiac disease (2). The endomysial IgA antibody titers have been shown to parallel the intestinal histopathologic pattern seen on biopsy, with more severe intestinal atrophy correlating with a higher titer. This indirect immunofluorescent assay relies on the use of scarce materials, such as monkey tissues, and is observer dependent, time consuming, and with added cost. Therefore, from the present study it appears that measurement of a single serologic marker tTG IgA by ELISA can be used for initial testing of celiac disease.

In the present study a history of preterm delivery, low birth weight of infants, and lower-segment cesarean section (LSCS) were significantly higher in the seropositive women in the group with recurrent spontaneous abortion; a history of low birth weight of infants and LSCS was significantly higher in the seropositive women in the stillbirth group; and a history of preterm delivery and LSCS was significantly higher in the seropositive women in the group with IUGR (P<.05). Similar findings have been reported stating that undiagnosed maternal celiac disease is a risk for unfavorable fetal outcomes (low birth weight, small for gestational age, and preterm birth) (18, 19). However, the risk is reduced when the disease is diagnosed and treated (20). In contrast, a population-based study reports that the actual prevalence of unfavorable events of pregnancy in patients with celiac disease was not statistically different from that observed in the population without celiac disease (21). During the follow-up of the patients with IUGR, it was found that a higher percent of serologically positive women delivered before 37
Table 4

Obstetric outcome of subjects of group with IUGR.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Seropositive (n = 14)</th>
<th>Seronegative (n = 136)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of labor, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>10 (71.4)</td>
<td>110 (80.9)</td>
<td>.29</td>
</tr>
<tr>
<td>Induced</td>
<td>3 (21.4)</td>
<td>14 (10.3)</td>
<td>.20</td>
</tr>
<tr>
<td>Augmented</td>
<td>1 (7.1)</td>
<td>12 (8.8)</td>
<td>.65</td>
</tr>
<tr>
<td>POG at delivery (wk), mean ± SD</td>
<td>37.90 ± 1.86</td>
<td>37.68 ± 2.59</td>
<td>.78</td>
</tr>
<tr>
<td>Mode of delivery, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>14 (100)</td>
<td>117 (86.0)</td>
<td>.13</td>
</tr>
<tr>
<td>LSCS</td>
<td>0 (0)</td>
<td>19 (13.9)</td>
<td></td>
</tr>
<tr>
<td>Fetal bradycardia, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13 (92.9)</td>
<td>126 (92.6)</td>
<td>.97</td>
</tr>
<tr>
<td>Yes</td>
<td>1 (7.1)</td>
<td>10 (7.3)</td>
<td></td>
</tr>
<tr>
<td>Meconium-stained fluid, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>14 (100)</td>
<td>127 (93.4)</td>
<td>.40</td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0)</td>
<td>9 (6.6)</td>
<td></td>
</tr>
<tr>
<td>Infant weight (g), mean ± SD</td>
<td>1,850 ± 300.22</td>
<td>1,814.36 ± 350.89</td>
<td>.74</td>
</tr>
</tbody>
</table>

Note: Seropositive for IgA tTG. POG = period of gestation.


weeks of gestation than of seronegative women. However, risk of cesarean section was found to be similar between the two groups. Tata et al. (22) reported that risk of cesarean section is higher in pregnancy with celiac disease and the risks of other adverse pregnancy outcomes such as assisted birth, breech birth, preeclampsia, postpartum hemorrhage, ectopic pregnancy, stillbirth, and termination were similar in women with or without celiac disease. Further studies with a large celiac disease–seropositive cohort are required to establish a cause-effect relationship.

None of the 44 IgA tTG–seropositive women had overt signs of malnutrition, showed stunting of growth, or were underweight. Therefore, nutritional factors were probably not of major importance in unfavorable pregnancy outcomes. A greater prevalence of positive serology for celiac disease was seen in patients with hemoglobin <11 gm/dL (23). Iron and folate deficiency anemia are seen more often in patients with celiac disease because these nutrients are absorbed in the upper two parts of the intestine where damage can occur in earlier stages. As celiac disease progresses, the lower part of the small intestine can be damaged and causes vitamin B12 deficiency. Anemia without other clinical clues of intestinal malabsorption is one of the most common extraintestinal manifestations of celiac disease (23, 24). Iron deficiency anemia was reported in up to 46% of patients with subclinical celiac disease with a higher prevalence in adults than children (25). In the present study, there was association of anemia with IgA tTG seropositivity in the group with stillbirth only. The baseline prevalence of anemia in the control group was 47.21% (144/305). Therefore, it is possible that the latent celiac disease may not be manifested overtly as anemia in this background. However, the number of seropositive subjects with anemia is too small to draw any significant conclusion.

In conclusion, the increased proportion of nondiarrheal celiac disease has been attributed to the introduction of serologic testing and increased awareness among practicing clinicians. Women having unexplained infertility, recurrent abortions, stillbirths, or IUGR could have subclinical celiac disease, which can be detected by serologic screening tests. Therefore, consideration should be given to serologic screening for celiac disease in patients with poor reproductive performance.

References