The Evaluation of the Effects of Paternal and Maternal Silent Coeliac Disease on Birthweight and Gestational Age in Newborns

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ABSTRACT

Objective: *Coeliac disease is a chronic disease and is common all over the world. It has many other associated systemic side effects. This study investigated the effect of paternal and maternal silent coeliac disease on birthweight and gestational age in newborns.*
Methods: *The study group consisted of 81 newborns who were hospitalized for prematurity or term-intrauterine growth retardation. The parents of premature and/or small for gestational age babies born with coeliac disease-specific antigens were investigated.*
Results: *The differences were not statistically significant in fathers' tissue transglutaminase levels between premature appropriate gestational age, premature small gestational age and term small gestational age infants (*$p > 0.05$*), but statistically significant in mothers (*$p < 0.05$*).*
Conclusions: *Silent coeliac disease may occur in parents, especially in mothers of preterm and small for gestational age infants, even in the absence of apparent clinical indications.*

Keywords: Coeliac disease, gestational age, newborn, premature

La Evaluación de los Efectos de la Enfermedad Celíaca Silenciosa Paterna y Materna en el Peso al Nacer y la Edad Gestacional en los Recién Nacidos H

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RESUMEN

Objetivo: *La enfermedad celíaca es una enfermedad crónica común en todo el mundo. Tiene muchos otros efectos secundarios asociados sistémicos. Este estudio investigó el efecto de la enfermedad celíaca silenciosa paterna y materna sobre el peso al nacer y la edad gestacional en los recién nacidos.*
Métodos: *El grupo de estudio consistió en 81 recién nacidos que fueron hospitalizados por nacimiento prematuro o por retraso del crecimiento intrauterino. Se investigó a los padres de los bebés prematuros y/o pequeños para la edad gestacional, nacidos con antígenos específicos de la enfermedad celíaca.*
Resultados: *Las diferencias no fueron estadísticamente significativas en los niveles de trans-glutaminasa del tejido de los padres entre los infantes de edad gestacional prematura adecuada, pequeños para la edad gestacional prematura, y pequeños para la edad gestacional a término (*$p > 0.05$*), pero fueron estadísticamente significativas en las madres (*$p < 0.05$*).*
Conclusiones: *La enfermedad celíaca silenciosa puede ocurrir en los progenitores, especialmente en las madres de los infantes pretérmino y pequeños para la edad gestacional, incluso en la ausencia de indicaciones clínicas evidentes.*

Palabras claves: Enfermedad celíaca, edad gestacional, recién nacido, prematuro

West Indian Med J 2014; 63 (5): 470

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 DOI: 10.7727/wimj.2013.166

INTRODUCTION

Both gestational age and birthweight have a significant effect on the newborn's health. Fetal growth retardation and prematurity are associated with perinatal morbidity and mortality (1–3). This important public health problem may cause a lot of problems later in life such as increased risks of diabetes, hypertension and cardiovascular diseases (4).

Coeliac disease (CD) is an autoimmune disorder characterized by gluten sensitivity in genetically susceptible individuals. It includes gastrointestinal, neurological, reproductive and systemic disorders (5). Coeliac disease is associated with chromosomal abnormalities and Type 1 diabetes, autoimmune hepatitis and thyroiditis (6–8). Silent coeliac patients have no clinical abnormalities and, while they are most common in the so-called risk groups, can also be found among the general population. Risk groups are composed of silent coeliac patients who have family members with CD or associated clinical problems (9). The clinical spectrum of CD has been compared to an iceberg, in which the symptomatic form is the visible part, while the silent forms are seven times more frequent than the visible part (10). Coeliac disease has been increasing in recent years worldwide [current prevalence around 0.6–1.4%] (9). Today, CD is often identified by improved serological tests in individuals with suspected silent coeliac disease (11).

The effects and mechanism of maternal and paternal CD on newborns is not clear (12). Studies have shown that the babies of mothers with CD have higher risk for low birthweight or preterm delivery and CD in fathers caused low birthweight in their babies (13–15). In this study, we investigated the effect of paternal and maternal silent CD on birthweight and gestational age in infants.

SUBJECTS AND METHODS

This study was performed at the Newborn Intensive Care Unit at the Ministry of Health, Nenehatun Children's and Obstetric-gynaecology Hospital. Permission was obtained from the parents of all newborns studied. The study was approved by the local Ethics Committee.

Study design and participants

The study group consisted of eighty-one ambulatory children who were hospitalized for prematurity or term-intrauterine growth retardation. The parents of premature and/or small for gestational age (SGA) babies born with coeliac disease-specific antigens were investigated.

The exclusion criteria were use of alcohol or tobacco during pregnancy, prothrombotic risk factors such as protein C deficiency, multi-gravidity, early membrane rupture, pre-eclampsia, eclampsia, chorioamnionitis and uterine abnormality in mothers.

The study was performed in three groups. Preterm birth was defined as a gestational age at delivery < 37 weeks. Small for gestational age was defined according to national growth curves with intrauterine growth retardation corresponding to a weight for age below two standard deviations from the mean.

The socio-economic status and demographic data of the parents were recorded. Blood samples were obtained from parents after birth, between 8:00 and 10:00 am, after a 12-hour fasting to avoid diurnal variations. All blood samples were stored at -80 °C until analysis. Haemogram, ferritin and tissue transglutaminase A were performed according to the manufacturer's instructions.

Biochemical analysis

For Celicheck immunoglobulin A (IgA), the antibodies against neo-epitopes of tissue transglutaminase (tTG) in serum were detected with commercially available solid phase enzyme immunoassay (EIA) kit (AIDA GmbH, D-55543 Bad Kreuznach, Germany) according to the manufacturer's instructions. The assay, employing human recombinant transglutaminase cross-linked with gliadin-specific peptides, displays neo-epitopes of tTG which ensures a significantly increased sensitivity and specificity of the test. The manufacturer recommended cut-offs < 15 U/mL for negative results and >15 U/mL for positive results. The intra- and interassay coefficients of variation (CVs) were 1.9–6.8% and 1.8–6.3%, respectively.

Ferritin levels were determined by conventional laboratory methods. The concentration of IgA was measured by nephelometry (BNII, Siemens, Deerfield, IL, USA), using Dade B ehring calibrators and reagents, and ferritin levels were determined by a Modular Analytics E170 immunoassay analyser (Roche/Hitachi E170, Japan).

Data were subjected to one-way analysis of variance and Pearson Chi-squared using Statistical Package for Social Sciences 18.0 (Armonk, NY, USA) software. Differences among groups were obtained using the least significant difference option and significance was declared at $p \leq 0.05$. The results are expressed as mean ± SEM.

RESULTS

The study group included 42 (51.8%) males and 39 (48.2%) females. Blood samples were collected from all the mothers and fathers. Of the babies included in the study, 60 (74%) were premature (PM) and 21 (25.9%) were full-term SGA. The premature group (n = 60) consisted of 12 (14.8%) SGA infants and 48 (59.3%) appropriate for gestational age (AGA) infants.

One mother of a PM baby (1.20%) had a history of levothyroxine for the treatment of hypothyroidism, one (1.20%) was on epdantoin for the treatment of epilepsy, and five (6.17%) were taking antibiotics for urinary tract infections. Two mothers (2.40%) had been pregnant because of infertility after ovulation induction.

Parents' tTG results are given in Tables 1 and 2. The differences were not statistically significant in fathers' tTG levels between groups ($p > 0.05$), but statistically significant in mothers ($p < 0.05$).

Table 1: Comparison of mothers' tTG value between groups

Groups	Mothers' tTG positivity	Mothers' tTG negativity	*p*-value
Premature AGA	1 (2.1 %)	46 (97.9 %)	
Premature SGA	1 (8.3 %)	11 (91.7 %)	0.014*
Term SGA	5 (23.8 %)	16 (76.2 %)	

According to Pearson Chi-squared test; *$p < 0.05$ is significant
PM – prematurity; SGA – small for gestational age; AGA – appropriate gestational age; tTG – tissue transglutaminase

Table 2: Comparison of fathers' tTG value between groups

Groups	Fathers' tTG positivity	Fathers' tTG negativity	*p*-value
Premature AGA	1 (4.8 %)	20 (95.2 %)	
Premature SGA	0 (0 %)	6 (100 %)	0.471*
Term SGA	2 (13.3 %)	13 (86.7 %)	

According to Pearson Chi-squared test; *$p > 0.05$
PM – prematurity; SGA – small for gestational age; AGA – appropriate gestational age; tTG – tissue transglutaminase

The ferritin value of parents are shown in the Figure. Mean ferritin level in the fathers of PM AGA, PM SGA and term SGA was 66.04 ± 7.09 (95% confidence interval (CI): 51, 81.08), 94.46 ± 14.5 (95% CI: 54.1, 134.7) and 76.32 ± 9.38 (95% CI: 55.6, 96.9) ng/mL, respectively. Mean ferritin level in the mothers of PM AGA, PM SGA and term SGA was 32.4 ± 4.2 (95% CI: 23.8, 40.9), 34.13 ± 4.23 (95%, CI: 12.49, 55.77) and 36.1 ± 4.86 (95% CI: 25.88, 46.32) ng/mL, respectively. The differences in mothers' and fathers' ferritin levels were not statistically significant between groups ($p > 0.05$).

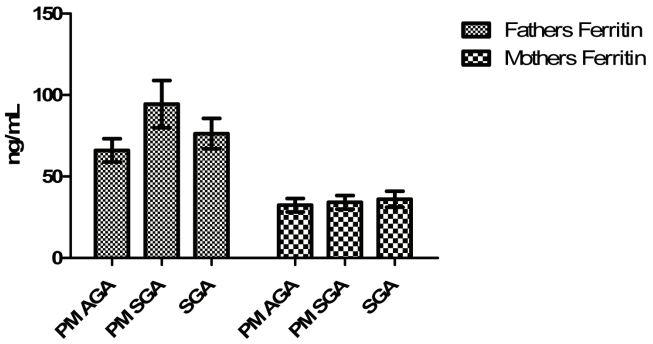

Figure: Comparison of ferritin levels of parents. Bars are means ± SEM. Ferritin levels are defined in ng/mL. PM – prematurity; SGA – small for gestational age; AGA – appropriate gestational age

DISCUSSION

This study estimated the prevalence of silent CD in the parents of preterm and/or SGA infants. Early detection of individuals with CD might be important both for clinical and social implications, especially during the reproductive period (16). In the present study, silent CD in women was associated with an increased risk of SGA birth. This finding is in agreement with recent results found by Ludvigsson *et al* in mothers of low or very low birthweight infants (13). We found no association between untreated paternal CD and birthweight adjusted for gestational age, SGA or preterm birth. Silent CD had increased rates of ferritin levels (17). In this study, correlations between parents' serum ferritin levels and gestational age – birthweight were not detected.

Fetal growth retadation is associated with perinatal mortality and morbidity (18). Coeliac disease is becoming more noticeable in clinical practice. There is a rise in the number of persons affected by CD. The mechanism of adverse effects of CD on pregnancy is still unclear. But in current hypothesis, CD effects may begin in the early intrauterine period at fertilization and continue throughout the embryogenesis and fetal growth periods. Tissue transglutaminase is related to a role in the increase of apoptosis in trophoblasts, which may lead to low birthweight delivery (13, 19); this supports our hypothesis. An interaction between nutritional abnormalities and systemic disorders has been hypothesized to explain the influence of parental CD on pregnancy outcome (9, 15). On the other hand, it may be hypothesized that the lower birthweight for gestational age in infants born to women with silent CD is associated with CD-mediated inflammation or deregulation of the immune system, and nutritional background. In fact, the inflammation in the intestinal system may cause low absorption of nutrients, leading to poor fetal nutrition and weight gain in the neonatal period (20, 21).

An increased risk of adverse pregnancy outcome such as preterm and low birthweight in women with silent CD has been reported (22). Other reports reveal that a diagnosis of CD in pregnancy was not linked with adverse fetal outcome, and introduction of a gluten-free diet may result in a gynecological and obstetric history comparable with healthy controls and a reduction of the risk of abortion or low birthweight (23, 24). More studies are needed to purposely evaluate whether silent CD in women may increase the risk of SGA. It should be noted that studies with stronger power might reveal other effects of silent CD on birth outcome (13, 16).

In conclusion, these findings suggest that silent CD may occur in parents, especially in mothers of preterm and SGA infants, even in the absence of apparent clinical indications. The prevalence of undiagnosed CD in mothers of SGA infants is higher than in the general female population. Undiagnosed CD in women may increase the risk of SGA birth.

AUTHORS' NOTE

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. All authors declare that they have no conflicts of interest.

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