Celiac serology in women with severe pre-eclampsia or delivery of a small for gestational age neonate

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delivery. This has been attributed to the direction of the expulsive force toward the perineal body and delivery of a larger diameter caused by a deflexed head [2].

With occipitoanterior deliveries the mechanism is different, but in both types of delivery the tear is caused when the fetal head is directed posteriorly. With occipitoanterior deliveries this may be caused by an anatomical variation of the pelvis or a large fetal head. In the present case the neonate was larger than average, but we also noted that the perineal body was longer than usual. The combination of these factors may have directed the expulsive forces posterior to the introitus. The fetal head subsequently split the posterior vaginal wall and rectovaginal septum from the perineal body and came into direct contact with the muscles of the perineal body, tearing them with subsequent pushing. Of note, this did not happen when the woman was pushing in the hands and knees position; this is because gravitational forces cause the fetal head to fall away from the posterior pelvis. In the present case a combination of these factors may have caused this unusual tear.

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Celiac serology in women with severe pre-eclampsia or delivery of a small for gestational age neonate

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Celiac disease is a genetically-determined permanent intolerance to gluten. Untreated disease can result in a varying degree of intestinal villous atrophy and malabsorption. The prevalence is between 0.3% and 1.2%, with a high percentage (about 60%) of subclinical cases [1]. Some studies suggest that even in subclinical cases, malnutrition and vitamin deficiency during pregnancy could result in fetal growth restriction or pre-eclampsia.

To test this hypothesis we performed a case-control study of women who delivered at the Academic Medical Center, Amsterdam, between 1993 and 2004. The study was approved by the medical ethical committee of our hospital. Inclusion criteria were white nulliparous women with a singleton pregnancy who delivered a small for gestational age (SGA) neonate after 34 weeks of pregnancy and who had a frozen serum sample (stored at −18 °C) taken during the first half of pregnancy. A total of 103 women were included. SGA was defined as a birth weight below the 10th percentile. The women in the study group were electronically matched by year of delivery in a ratio of 1:2 with 206 white nulliparous women (control group) with a singleton pregnancy who delivered a normal birth weight neonate after 34 weeks of gestation and who also had a frozen serum sample taken during the first half of pregnancy. Relevant congenital abnormalities were excluded.

A third group consisted of 131 white women who had been admitted due to severe pre-eclampsia and had delivered before 34 weeks of pregnancy between 1993 and 2005. All of

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Table 1 Demographic, perinatal, and celiac serology test outcome data (anti TgA and anti EmA positive) for the three study groups [a]

	SGA group	Pre-eclampsia / HELLP group	Control group
No.	103	131	206
Age, years	30.4±5.9	30.3±4.7	30.2±6.4
BMI	22.9±5.1 [b]	25.8±4.7 [c]	23.0±4.2
Smoking ≥1 cigarette/day	41 (40) [b,c]	26 (20)	51 (25)
Max. diastolic blood pressure, mm Hg	83±14 [b]	107±20 [c]	79±12
Gestational age, weeks	39.1±1.9 [b, c]	30.0±2.4 [c]	40.0±1.6
Birth weight, g	2461±413 [b, c]	1015±352 [c]	3322±257
Birth weight ratio	0.76±0.08 [b, c]	0.68±0.14 [c]	1.01±0.05
Positive serology, no.	1	1	0
Percentage with 95% confidence limits	1.0 (0.0–5.1)	0.8 (0.0–3.2)	0.0 (0.0–0.9)

Abbreviations: SGA, small for gestational age neonate; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Values are given as number (percentage) or mean±SD unless otherwise indicated.

[b] $P<0.05$ compared with the severe pre-eclampsia/HELLP group.

[c] $P<0.05$ compared with the control group.

the women included in group 3 had a laboratory examination for thrombophilia between 3 and 6 months after delivery. In this group, tests were assayed from frozen samples (before 2001) or directly after sampling (after 2001). Severe pre-eclampsia was defined as a diastolic blood pressure of more than 110 mm Hg and proteinuria of more than 0.3 g/24 hours or the development of HELLP syndrome indicated by hemolysis (haptoglobin <0.2% or lactate dehydrogenase ≥600 U/L), elevated liver enzymes (aspartate aminotransferase ≥70 U/L), and low platelets ($<100\times10^9$/L).

All women were screened for tissue transglutaminase antibodies (TgA) by an in-house enzyme-linked immunosorbent assay with guinea pig tissue transglutaminase as substrate. Sera with borderline or positive TgA were subsequently tested for IgA antiendomysium (EmA) and IgA antihuman recombinant tissue transglutaminase (Celikey; Pharmacia diagnostics, Freiburg, Germany). Patients were considered to have positive celiac serology if both TgA and EmA were positive [2].

Sample size calculation was based on a prevalence of asymptomatic celiac disease of 1% in the general population [1]. A total of 100 cases and 200 controls would enable detection of an odds ratio of 7 or larger for celiac disease in women with pre-eclampsia or who delivered a small for gestational age neonate with $\alpha=0.05$ and $\beta=0.2$.

One woman in the SGA group and 1 woman in the severe pre-eclampsia group tested positive for both TgA and EmA (Table 1). Neither woman had gastrointestinal symptoms and their hemoglobin levels were normal. None of the women in the control group tested positive for TgA or EMA.

The present strategy of using TgA as a screening test and EmA for confirmation of a positive serological test has a sensitivity of 90.4% and a specificity of 99.7% when using intestinal biopsy as gold standard for the diagnosis of celiac disease [2]. Based on these test characteristics, we may have underestimated the prevalence in our population by 9.6% of the observed prevalence. With an observed prevalence of 1% at most, such underestimation is negligible. The high specificity makes false positive results unlikely.

Three studies have assessed the incidence of low birth weight in women diagnosed with celiac disease registered in a national or regional health register and compared with the remaining women. The incidence of SGA neonates was 6%–8% in the cases and 2%–3% in the controls (OR, 1.6–3.4) [3–5]. The first two studies observed the higher incidence of SGA only in untreated women; the third study did not observe a difference between treated or untreated women.

Two studies have described the prevalence of women with positive serological markers (TgA and EmA) in a cohort of women who had SGA neonates, similar to our study [6,7]. These studies confirmed positive screening results by small intestinal biopsy. The first study (39 SGA neonates) observed a prevalence of 15% in women with an SGA neonate; the second study (n=448) had a prevalence of 1.6%, which was assumed to be 2 times higher than in the general population.

Two cohort studies, based on regional disease classification registers, observed a similar incidence of pre-eclampsia in women with celiac disease as in a control group, although power was insufficient to exclude small differences [5,8].

Combining our study and the study of Salvatore et al. [7], the relative risk for celiac disease in women with an SGA neonate may be approximately 2. This low relative risk and the conflicting data regarding the effect of dietary treatment on perinatal outcome suggest that serological screening for subclinical celiac disease before or at the beginning of pregnancy is not indicated. Similarly, testing for asymptomatic celiac disease is not indicated routinely in women after delivery of an SGA neonate or after pre-eclampsia.

Acknowledgments

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Cryoglobulinemic vasculitis in pregnancy

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A rash occurring during pregnancy is a diagnostic challenge. Rashes peculiar to pregnancy are pruritic urticarial papules and plaques of pregnancy (PUPPP), prurigo of pregnancy, pruritic folliculitis of pregnancy, and pemphigoid gestationis [1,2]. Cryoglobulinemic vasculitis presents clinically with a palpable pruritic rash and occasionally involves the internal organs. Its early detection has diagnostic and therapeutic significance [3].

A 21-year-old primigravida was hospitalized at 26 weeks of pregnancy with a pruritic rash involving the lower extremities. It was not associated with fever or malaise. There was no history of cold sensitivity or cold-induced urticaria, allergy to food or drugs, recent infection, autoimmune disorder, or malignancy. Physical examination revealed a palpable macular rash involving both legs (Fig. 1). Initial laboratory investigations suggested mild leukocytosis and thrombocytosis, but examination of peripheral blood smear revealed pseudoleukocytosis and pseudothrombocytosis. Small irregular grayish-blue extracellular precipitates were seen in the background. Renal and liver profiles were normal. There were no antinuclear, anti-double-stranded DNA (anti-dsDNA), antineutrophil, or anti-beta 2-glycoprotein I antibodies. Rheumatoid factor was mildly elevated (titers 1:80). Perinuclear-staining antineutrophil cytoplasmic antibodies (pANCA) and cytoplasmic-staining antineutrophil cytoplasmic antibodies (cANCA) were absent. Complement component 3 (C3) was normal; however, C4 was reduced (0.19 g/L). Serologic tests for syphilis and hepatitis B antibodies were negative. Third-generation anti-HCV (hepatitis C virus) enzyme-linked immunosorbent assay test containing synthetic peptide HCV antigens was also negative.

Serum protein electrophoresis revealed M-spike; and further analysis by immunofixation detected polyclonal immunoglobulin G (IgG) and monoclonal immunoglobulin M (IgM) kappa. Screening for cryoglobulins was positive. Skin biopsy from the leg showed leukocytoclastic vasculitis (Fig. 2). An ultrasound examination for fetal well-being was unremarkable.

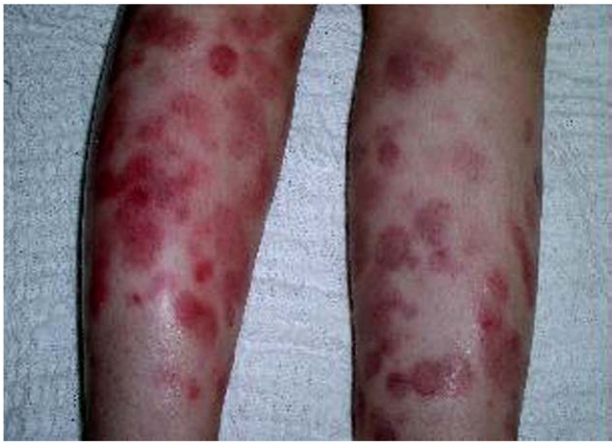

Figure 1 Essential mixed cryoglobulinemia: Macular rash on legs.

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