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Original article

Association of increased maternal ferritin levels with gestational diabetes and intra-uterine growth retardation

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Abstract

Aim. – The objectives of the present study were to determine whether or not increased serum ferritin in women with premature labour is associated with gestational diabetes mellitus (GDM) and intra-uterine growth retardation (IUGR) and, if so, whether or not such increased levels reflect excess maternal iron stores, and have an effect on neonatal iron status and outcome.

Methods. – This prospective, single-hospital, observational study involved 63 mothers and their 90 preterm neonates. Full blood counts as well as serum ferritin, soluble transferrin receptor (sTfR) and erythropoietin concentrations were compared across the three study groups based on maternal ferritin levels at the time of delivery. Perinatal history, neonatal morbidity and early outcomes were also assessed.

Results. – High maternal ferritin levels were significantly associated with higher rates of GDM and IUGR. However, there was no correlation between maternal ferritin and sTfR levels or between maternal and neonatal iron status.

Conclusion. – Elevated maternal ferritin is not a reflection of excess iron stores, but is related to an increased risk of GDM or IUGR. Also, maternal ferritin levels are not associated with either neonatal iron status or neonatal outcomes.

Keywords: Pregnancy; Serum ferritin; Preterm delivery; Neonate; Outcome; Gestational diabetes

Résumé

Association d'une augmentation de la ferritinémie maternelle au diabète gestationnel et au retard de croissance intra-utérin.

Objectif. – Déterminer si une augmentation de la ferritinémie chez les femmes présentant un accouchement avant terme, est associée au diabète gestationnel (DG) et au retard de croissance intra-utérin (IUGR), préciser si elle est associée à une augmentation du fer maternel et si elle affecte le statut martial et l'évolution néonatale à court terme.

Méthodes. – Dans cette étude observationnelle, prospective et monocentrique, ont été inclus 63 mères et leurs 90 nouveaux nés prématurés. La numération globulaire, la ferritinémie, le récepteur soluble de la transferrine (sTfR) et les concentrations d'érythropoïétine ont été comparées dans trois groupes constitués selon la ferritinémie maternelle au moment de l'accouchement. L'anamnèse périnatale, la morbidité néonatale et le pronostic précoce ont aussi été aussi évalués.

Résultats. – Une ferritinémie maternelle élevée était significativement associée au diabète gestationnel et au retard de croissance intra-utérin. Il n'y avait pas de corrélation entre la ferritinémie, les concentrations du récepteur soluble de la transferrine maternelle, ni entre les concentrations de fer maternelles et celles des nouveaux-nés.

Conclusion. – L'augmentation de la ferritinémie maternelle ne reflète pas de réserves excessives en fer, mais elle associée étroitement au diabète gestationnel et au retard de croissance intra-utérin. La ferritinémie n'est associée ni au statut martial des nouveaux-nés ni à leur évolution à court terme.

Mots clés : Prématurité ; Ferritine ; Accouchement avant terme ; Retard de croissance intra-utérin ; Nouveau-né ; Diabète gestationnel ; Évolution néonatale

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1. Introduction

Serum ferritin concentration can be used as a proxy for body iron stores as it is highly correlated with bone marrow iron [1,2]. Also, not surprisingly, elevated serum ferritin levels have been documented in many inflammation-related diseases, given that ferritin is an acute-phase reactant that increases in both acute and chronic inflammation [3–6].

Iron is an essential element for both pregnant women and the growing fetus, and the majority of pregnant women routinely receive iron supplementation [7–9], despite the fact that such prophylactic iron supplementation is still a matter of controversy. Indeed, animal studies suggest that the administration of iron daily at the current recommended dosages may be neither desirable nor innocuous [10].

In humans, elevated iron stores during pregnancy have been associated with maternal and neonatal morbidity. Women with raised ferritin levels in the third trimester of pregnancy have a greatly increased risk of preeclampsia, intrauterine growth retardation (IUGR) and preterm delivery [7,11]. Furthermore, high serum ferritin levels have been linked with type 2 diabetes and the development of gestational diabetes mellitus (GDM) in pregnant women [12–14]. There is a twofold increase in GDM risk in women in the highest quartile of serum ferritin [15]. However, data on whether or not elevated serum ferritin is an independent risk factor for diabetes, and whether or not higher levels reflect inflammation or increased iron stores, are conflicting [14]. Serum transferrin receptor (sTfR) levels are a sensitive indicator of iron deficiency in inflammatory states as well as anaemia in chronic diseases, as its concentration is not influenced by the acute-phase response and is, therefore, considered a useful marker for monitoring erythropoiesis in various clinical situations [16–18].

Based on these considerations, the aims of the present study were:

- to assess whether or not maternal serum ferritin levels are associated with an increased risk of GDM and IUGR in cases of premature labour, and their relationship to sTfR;
- to correlate maternal and neonatal iron status to evaluate whether or not maternal iron stores can affect the growing fetus and neonate.

2. Material and methods

2.1. Subjects and study design

The subjects were participants in a longitudinal study of cognitive development in premature infants in relation to their perinatal iron status. This prospective, observational study involved 63 mothers and their 90 preterm neonates at delivery. The study was approved by the ethics committee of our hospital, and written informed consent was obtained from all participating mothers.

Infants were eligible for the study if they were lesser than 34 gestational weeks, aged 0–48 h at the time of study entry, and likely to survive beyond the first 72 h of life. Infants with major congenital anomalies born to mothers with clinical chorioamnionitis, rupture of membranes more than 24 h and possible (clinical and laboratory evidence) or confirmed (positive blood culture) early-onset sepsis were excluded. Lack of parental consent was also an exclusion criterion.

The mothers and, subsequently, their neonates were divided into three groups according to maternal ferritin levels. More specifically, the mothers were defined as having low iron stores when their serum ferritin was lesser than 10 μg/L (group A), normal iron status when their serum ferritin was 10–60 μg/L (group B) and increased iron stores if their serum ferritin was greater than 60 μg/L (group C) [7].

Detailed records of the perinatal histories of both mothers and neonates were obtained. Maternal data included an oral glucose tolerance test (OGTT) – at our hospital, a tertiary perinatal centre, a 75-mg OGTT test is performed in all pregnant women between 24–28 weeks, according to the guidelines of the American Diabetes Association [19] – family history of diabetes, history of previous GDM, previous heavy babies and weight gain during pregnancy.

Discharge data were collected for all surviving neonates. As fetal growth is not affected before 33 weeks in twin gestations [20,21], the evaluation of growth in twins enrolled in the present study was based on charts used for singleton pregnancies. Data on neonatal morbidity included IUGR (defined as a birth weight lesser than –2 SD on a standardized birth-weight curve), incidence of bronchopulmonary dysplasia (BPD; oxygen administered at 36 postmenstrual weeks), retinopathy of prematurity (ROP; stage 3 or higher), severe intraventricular haemorrhage (IVH; grade 3 or higher) and/or periventricular leukomalacia (PVL), and necrotizing enterocolitis (NEC; Bell's stage II or higher). Transfusion information was recorded from birth to study completion. At hospital discharge, evaluations included a standardized neurological examination, anthropometric measurements and cranial ultrasonography.

2.2. Laboratory investigation

Venous blood was obtained from both neonates (around 1.5 mL) and their mothers at the time of delivery as well as during the first and second months of life in neonates. Full blood cell counts and red cell indices were determined using an automated haematology analyzer, whereas reticulocytes were calculated manually. Commercially available enzyme-linked immunosorbent assay (ELISA) kits were used to measure serum ferritin, sTfR and erythropoietin (EPO).

2.3. Iron supplementation

Studied infants received enteral iron at dosages of 3–4 mg/kg per day when they achieved an enteral intake of 120 mL/kg per day. Iron was also prescribed after discharge throughout the first year of life in addition to enteral folate supplements (25–50 μg/day). Mothers were receiving routine iron supplementation at dosages of 40–80 mg/day during pregnancy.