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

V. Soubasi, S. Petridou, K. Sarafidis, Ch. Tsantali, E. Diamanti, G. Buonocore, V. Drossou-Agakidou

1st Department of Neonatology, Aristotle University of Thessaloniki, 54642 Thessaloniki, Greece
1st Department of Pediatrics, Aristotle University of Thessaloniki, 54642 Thessaloniki, Greece
Department of Pediatrics, Obstetrics, and Reproductive (G. B.) University of Siena, Siena, Italy

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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.

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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.

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

* Corresponding author. 1st Department of Neonatology, Medical School, Aristotle University of Thessaloniki, and Hippokration General Hospital, Konstantinopoleos 49, 54642, Thessaloniki, Greece. Tel.: +302310892426; fax: +302310992787. E-mail address: soubasi@med.auth.gr (V. Soubasi).

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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 less 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.
2.4. Statistical analysis

Numerical data are expressed as means ± standard deviation (SD). Differences in continuous variables were assessed using t tests and one-way parametric analysis of variance (ANOVA), with post-hoc analysis performed where appropriate. Categorical variables were compared using chi-square or Fisher’s exact tests. Spearman’s rank correlation was performed to correlate the mothers’ and neonates’ laboratory values for iron status. Statistical significance was defined as P < 0.05. Statistical analysis was performed using the SPSS 15.0 for Windows (SPSS Inc, Chicago, IL, USA).

3. Results

Characteristics of both the mothers and neonates were tested according to the mothers’ ferritin levels. Consequently, by study design, the mothers were divided into three groups (group A [n = 7], group B [n = 32] and group C [n = 24]), as were the neonates (group A [n = 12], group B [n = 47] and group C [n = 31]).

3.1. Perinatal characteristics and maternal laboratory indices

The three groups of mothers were comparable in terms of age, conditions during pregnancy (smoking, hypertension, preeclampsia; Table 1) and mode of delivery (Table 2). Duration of pregnancy was lesser than 34 weeks with no difference among the groups. Maternal body-weight gain was within the normal range for the duration of pregnancy. A positive family history for diabetes was found in 8% of the mothers; 54 of the 63 mothers were primigravida; and none of the remaining mothers had a history of GDM or a previous large-for-gestational-age baby.

As expected, ferritin values differed significantly among the three groups (P < 0.0001, ANOVA), whereas sTfR levels were similar. Although haematocrit (Ht) and haemoglobin (Hb) levels were lower in group A, the differences were not significant compared with the two other groups. Mean corpuscular volume (MCV) was significantly lower in group A (P < 0.01 ANOVA), while serum EPO values were significantly higher in group A compared with the other two groups (Table 1). The group of mothers with high ferritin levels was associated with a significantly higher rate of GDM (5/24) compared with the other two groups taken together (1/39) (P = 0.026, Fisher’s exact test). Also, there was a 2.5-fold greater risk of GMD in mothers with elevated serum ferritin (95% CI: 1.4–4.1), but no correlation between ferritin and sTfR levels (correlation coefficient [r] = –0.1271, P = 0.267).

3.2. Neonatal clinical characteristics and laboratory indices

The three groups of neonates were similar at birth in terms of birth weight, gestational age, APGAR score, haematological values and iron metabolism (Table 2). The rate of IUGR was

### Table 1
Maternal characteristics and laboratory data.

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>7</td>
<td>32</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>29.1 ± 4.9</td>
<td>29.9 ± 5.6</td>
<td>31.7 ± 5.1</td>
<td>0.354</td>
</tr>
<tr>
<td>Smoking (n [%])</td>
<td>1 (14.3)</td>
<td>2 (6.25)</td>
<td>1 (4.2)</td>
<td>0.626</td>
</tr>
<tr>
<td>Hypertension (n [%])</td>
<td>0 (0)</td>
<td>6 (12.8)</td>
<td>3 (9.7)</td>
<td>0.416</td>
</tr>
<tr>
<td>Preeclampsia (n [%])</td>
<td>0 (0)</td>
<td>2 (6.25)</td>
<td>3 (12.5)</td>
<td>0.493</td>
</tr>
<tr>
<td>GDM (n [%])</td>
<td>0 (0)</td>
<td>1 (2.1)</td>
<td>5 (16.1)</td>
<td>0.026a</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>10.4 ± 1.9</td>
<td>11.2 ± 1.3</td>
<td>11.4 ± 1.5</td>
<td>0.301</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>31.3 ± 5</td>
<td>33.7 ± 3.9</td>
<td>33.6 ± 4.5</td>
<td>0.384</td>
</tr>
<tr>
<td>MCV (µm³)</td>
<td>82.8 ± 2.3</td>
<td>89.3 ± 7.8</td>
<td>90.6 ± 5.5</td>
<td>0.023</td>
</tr>
<tr>
<td>Ferritin (µg/L)</td>
<td>7.8 ± 1.1</td>
<td>30.3 ± 12.6</td>
<td>117.4 ± 53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>sTfR (nmol/L)</td>
<td>30.2 ± 18</td>
<td>20.4 ± 8.3</td>
<td>20.1 ± 9.5</td>
<td>0.057</td>
</tr>
<tr>
<td>Erythropoietin (mU/mL)</td>
<td>57.6 ± 33</td>
<td>24.4 ± 20.6</td>
<td>28.3 ± 15.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD unless otherwise specified; GDM: gestational diabetes mellitus; MCV: mean corpuscular volume; sTfR: soluble transferrin receptor. a Correlation of group C vs groups A + B (Fisher’s exact test); continuous variables were assessed using one-way parametric analysis of variance (ANOVA).

### Table 2
Initial neonatal characteristics and laboratory data.

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>12</td>
<td>47</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>30.7 ± 2.8</td>
<td>29.9 ± 2.4</td>
<td>30.7 ± 2.2</td>
<td>0.329</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1550 ± 557</td>
<td>1324 ± 354</td>
<td>1316 ± 322</td>
<td>0.150</td>
</tr>
<tr>
<td>IUGR (n [%])</td>
<td>1 (8.3)</td>
<td>8 (17)</td>
<td>11 (35.4)</td>
<td>0.033b</td>
</tr>
<tr>
<td>Singletons (n [%])</td>
<td>4 (33)</td>
<td>19 (40)</td>
<td>16 (51)</td>
<td>0.468</td>
</tr>
<tr>
<td>Caesarean section (n [%])</td>
<td>11 (91.7)</td>
<td>40 (85.1)</td>
<td>29 (93.5)</td>
<td>0.482</td>
</tr>
<tr>
<td>Prenatal steroids (n [%])</td>
<td>11 (91)</td>
<td>37 (79)</td>
<td>23 (74)</td>
<td>0.452</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>15.5 ± 1.3</td>
<td>15.5 ± 1.9</td>
<td>15.3 ± 1.8</td>
<td>0.882</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>46.9 ± 4.3</td>
<td>46.5 ± 5.6</td>
<td>46.2 ± 6.2</td>
<td>0.935</td>
</tr>
<tr>
<td>MCV (µm³)</td>
<td>109.9 ± 6.8</td>
<td>111.9 ± 6.6</td>
<td>110.8 ± 6.3</td>
<td>0.571</td>
</tr>
<tr>
<td>Reticulocytes (%)</td>
<td>7.2 ± 4.5</td>
<td>7.5 ± 4.2</td>
<td>8.2 ± 3.2</td>
<td>0.689</td>
</tr>
<tr>
<td>Ferritin (µg/L)</td>
<td>102 ± 56</td>
<td>154 ± 124</td>
<td>154 ± 106</td>
<td>0.326</td>
</tr>
<tr>
<td>sTfR (nmol/L)</td>
<td>43.7 ± 21.5</td>
<td>39.8 ± 21</td>
<td>41.4 ± 22.8</td>
<td>0.845</td>
</tr>
<tr>
<td>Erythropoietin (mU/mL)</td>
<td>10.7 ± 7</td>
<td>18.4 ± 27</td>
<td>17.9 ± 10.7</td>
<td>0.507</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SD unless otherwise specified; IUGR: intrauterine growth retardation; MCV: mean corpuscular volume; sTfR: soluble transferrin receptor; Groups were allocated according to maternal ferritin levels (group A. Ferritin < 10 µg/L; group B. Ferritin 10–60 µg/L; Group C. Ferritin > 60 µg/L). b Correlation of group C vs groups A + B (Fisher’s exact test).
Table 3
Neonatal complications and clinical course.

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 12)</th>
<th>Group B (n = 47)</th>
<th>Group C (n = 31)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchopulmonary dysplasia (n [%])</td>
<td>1 (8.3)</td>
<td>7 (14.9)</td>
<td>5 (16.1)</td>
<td>0.801</td>
</tr>
<tr>
<td>Necrotizing enterocolitis (n [%])</td>
<td>1 (8.3)</td>
<td>5 (10.6)</td>
<td>2 (6.4)</td>
<td>0.814</td>
</tr>
<tr>
<td>IVH $\geq$ grade 3 and/or PVL (n [%])</td>
<td>0 (0)</td>
<td>2 (4.2)</td>
<td>3 (9.7)</td>
<td>0.394</td>
</tr>
<tr>
<td>Retinopathy of prematurity (n [%])</td>
<td>1 (8.3)</td>
<td>3 (6.4)</td>
<td>3 (9.7)</td>
<td>0.865</td>
</tr>
<tr>
<td>Transfused neonates (n [%])</td>
<td>6 (50)</td>
<td>23 (48.9)</td>
<td>13 (41.9)</td>
<td>0.806</td>
</tr>
</tbody>
</table>

Groups were allocated according to maternal ferritin levels (group A. Ferritin < 10 $\mu$g/L; group B. Ferritin 10–60 $\mu$g/L; Group C. Ferritin >60 $\mu$g/L); IVH: intraventricular haemorrhage; PVL: periventricular leukomalacia.

significantly higher in group C (11/31) (neonates whose mothers had high ferritin levels) compared with the two other groups combined (9/59; P = 0.033). The majority of IUGR neonates were singletons (17/20). The number of transfused neonates was similar in the three groups (Table 3). Evaluation of serum ferritin, sTfR, EPO levels and Ht, Hb, MCV and reticulocytes at one and two months of age revealed no differences among the three infant groups (Fig. 1). Also, the clinical course (BPD, NEC, ROP), growth and early neurological outcomes (data not shown) were similar in all three groups of studied neonates.

3.3. Correlation of maternal to neonatal iron status

No correlation was found between the iron status of the mothers and neonates in terms of ferritin ($r = -0.01$, $P = 0.92$), sTfR ($r = -0.008$, $P = 0.94$) and Hb ($r = 0.08$, $P = 0.49$). In addition, there was no association between iron status at birth and neonatal clinical course (Table 3).

4. Discussion

In the present study, we demonstrated an association between elevated ferritin levels in the serum of pregnant women with premature labour and an increased risk for GDM or IUGR in their offspring. However, the sTfR was not related to either high ferritin levels or excess iron stores, and maternal serum ferritin did not correlate with sTfR, Hb or MCV. In addition, maternal iron stores had no effect on either neonatal iron status or early outcomes.

To our knowledge, the present study is the first to explore both serum ferritin and sTfR levels in relation to the risk of GDM and/or IUGR. An extensive body of data suggests that higher iron stores are associated with type 2 diabetes risk in non-pregnant subjects [22–25]. Consistent with our findings, the recently published data from the Camden study found that serum ferritin levels were significantly increased in patients with GDM compared with those without GDM [15]. Furthermore, Lao et al. [26–28] reported significantly increased ferritin levels at 28–30 weeks of gestation in pregnant Chinese women with impaired glucose tolerance and in patients with GDM compared with control subjects. In pregnant women, higher Hb levels (> 13 g/dL) are an independent risk factor for GDM [28], whereas women with iron-deficiency anaemia are reported to have a reduced risk of GDM [29]. Results from the Camden study do not support the hypothesis that higher ferritin levels reflect excess iron stores in patients with GDM, given that high Hb values (> 13 g/L) in pregnant women were not associated with an increased risk for GDM. Interestingly, however, neither of the above studies referred to neonatal iron status and outcome.

![Fig. 1](image-url) Ferritin, soluble transferrin receptor (sTfR), erythropoietin and haemoglobin (Hb) levels in the three groups of neonates at birth, and at age one and two months. The infants were grouped according to their maternal ferritin levels (group A. Ferritin < 10 $\mu$g/L; group B. Ferritin 10–60 $\mu$g/L; Group C. Ferritin >60 $\mu$g/L). There was no difference among neonatal groups in any of the above parameters, suggesting that maternal ferritin levels had no effect on neonatal iron status early after birth.
Ferritin, the major iron storage protein, provides an indirect estimate of body iron stores, and is also a positive acute-phase reactant. Low ferritin is an accurate index of iron deficiency in pregnant women. Indeed, in the present study, mothers with low serum ferritin levels (<10 μg/L) had significantly higher EPO and lower MCV, indicative of iron-deficient erythropoiesis. This fact is supported by the higher sTfR levels observed in this maternal group, although it did not reach statistical significance, probably because of the small number of mothers in this group. In cases of high ferritin values, however, increased maternal ferritin did not correspond with Hb levels. Indeed, we were better able to evaluate ferritin values using sTfR levels, which are sensitive indicators of iron status even in inflammatory states [30,31].

Accordingly, the inflammation hypothesis may be more consistent with increased maternal serum ferritin. Pregnancy in itself is an inflammatory state; serum C-reactive protein (CRP) levels are raised as early as week 4 of gestation [32], and it is increasingly being recognized that there is systemic inflammation in GDM, as indicated by higher levels of CRP and/or interleukin-6 [33,34]. Inflammatory cytokines have been shown to induce ferritin synthesis in experimental models [9], and sTfR is assumed to reliably reflect the degree of tissue iron supply. The lack of association, therefore, between ferritin and sTfR in our present study supports the presence of inflammation. The association of IUGR with inflammation has been ascertained elsewhere [9].

Differentiating between excess iron stores and inflammation is crucial, as it offers precise implications for the clinician. In addition, there is the potential concern that some women who are not truly anaemic may be taking large doses of supplemental iron during pregnancy. Such a strategy has been suggested as a way to build up the mother’s iron stores and to increase blood viscosity to impair uteroplacental blood flow [35–37]. However, increased maternal iron stores appear to have a negative impact on birth weight although, as also shown in our study, they are not associated with Hb [28]. It is possible that increased levels of plasma “free iron” as a result of daily iron supplementation at recommended doses also increases oxidative damage to DNA in the maternal–fetal unit [7]. It may also play an important role in the development of IUGR even in the presence of maternal GDM, where macrosomia is usually expected. Nevertheless, low-dose iron supplementation has recently been associated with a reduced risk of low-birth-weight infants in pregnant women with no anaemia without increasing the risk of preeclampsia or GDM [38].

Our small study population, which was limited to “healthy” pregnant women with premature labour, was one weakness of the present study. Also, the clinical usefulness of maternal ferritin levels in predicting neonatal outcome is limited [39]. Accumulation of ferritin is not harmful to tissues per se, as it is the increased non-protein-bound iron that promotes the generation of the reactive oxygen species responsible for organ dysfunction in iron overload conditions [7]. Preterm infants are, therefore, particularly vulnerable due to their poorly developed antioxidative systems. Iron-mediated oxidative stress has been shown to play a significant role in common perinatal conditions such as BPD and ROP [9]. In the present study, the clinical course and complications of prematurity (ROP, BPD, NEC, severe IVH and/or PVL) as well as early neurological outcomes were not affected by either maternal or neonatal iron status at birth.

In conclusion, elevated maternal serum ferritin is associated with an increased risk of GDM or IUGR, and suggests the involvement of systemic inflammation in the pathophysiology of GDM rather than an excess of iron stores. Further studies combining serum ferritin, CRP and sTfR or other iron status indices are clearly required to shed more light on this important issue.

Conflicts of interest

None.

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