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High maternal serum ferritin in early pregnancy and risk of spontaneous preterm birth

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Abstract

Previous studies have reported inconsistent associations between maternal serum ferritin concentrations and the risk of spontaneous preterm birth (sPTB). The aim of the present study was to examine the association between Fe biomarkers, including serum ferritin concentrations, and the risk of total (<37 weeks), early (<34 weeks) and moderate-to-late (34–36 weeks) sPTB. The study cohort included 2254 women with singleton pregnancies attending first-trimester screening in New South Wales, Australia. sPTB included births following spontaneous labour or preterm premature rupture of the membranes. Serum collected at a mean gestational age of 12·0 (SD 0·9) weeks was analysed for Fe biomarkers, including serum ferritin and soluble transferrin receptor (sTfR), and the inflammatory biomarker C-reactive protein. Multivariate logistic regression analysis evaluated the association between low and high Fe levels and sPTB. Women with elevated serum ferritin concentrations were more likely to be older, nulliparous or have gestational diabetes. The multivariate analysis found increased odds of sPTB for women with elevated ferritin levels defined as >75th percentile (≥43 μg/l) (OR 1·49, 95 % CI 1·06, 2·10) and >90th percentile (≥68 μg/l) (OR 1·92, 95 % CI 1·25, 2·96). Increased odds of early and moderate-to-late sPTB were associated with ferritin levels >90th percentile (OR 2·50, 95 % CI 1·32, 4·73) and >75th percentile (OR 1·56, 95 % CI 1·03, 2·37), respectively. No association was found between the risk of sPTB and elevated sTfR levels or Fe deficiency. In conclusion, elevated maternal serum ferritin levels in early pregnancy are associated with an increased risk of sPTB from 34 weeks of gestation. The usefulness of early pregnancy ferritin levels in identifying women at risk of sPTB warrants further investigation.

Key words: Iron: Ferritin: Preterm: Risk factors: Pregnancy

Preterm births continue to be the main cause of perinatal morbidity and mortality in developed countries, which increases the risk of neurocognitive and pulmonary deficits in surviving infants[1]. Spontaneous preterm birth (sPTB) of unknown aetiology accounts for 40–50 % of all preterm deliveries[1], with the remainder attributable to maternal or fetal indications in which labour is induced or the infant is delivered by pre-labour caesarean section[2].

The aetiology of sPTB remains elusive[2]. There is a body of evidence which suggests that infection in pregnancy may be related to preterm birth[3]; however, the majority of randomised trials have not shown a significant reduction in preterm births following maternal administration of antibiotics[4]. Early pregnancy factors associated with sPTB remain an important area of investigation for identifying at-risk women to study specific interventions and treatments.

The relationship between maternal Fe status and the risk of preterm delivery is uncertain[5]. Both low and elevated maternal Fe levels have been associated with the risk of preterm birth[6]. While some randomised trials of Fe supplementation in pregnancy have reported a reduction in preterm births[7], the most recent Cochrane[8] and systematic reviews[9] of intervention trials have found no significant effect of Fe supplementation in pregnancy on the risk of preterm birth. In contrast, there are several observational studies that have found an association between elevated serum ferritin (a biomarker of Fe stores) in

Abbreviations: APDC, Admitted Patients Data Collection; CHeReL, Centre for Health Record Linkage; CRP, C-reactive protein; GDM, gestational diabetes mellitus; NSW, New South Wales; PPROM, preterm premature rupture of the membranes; sPTB, spontaneous preterm birth; sTfR, soluble transferrin receptor; TfR, transferrin receptor.

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the second trimester and an increased risk of sPTB[1,10–15]. Potential mechanisms resulting in elevated ferritin levels being linked to the risk of sPTB include the following: intra-uterine infection; failure of the maternal plasma volume to expand; infection and inflammation[6]. Ferritin production is increased with infection and inflammation as part of the acute-phase response; therefore, interpretation of these studies is challenging. Results are conflicting, with studies differing in their definition of sPTB and in the cut-off values used for high ferritin levels (>50th, >75th and >90th centiles)[1,10–15]. The majority of these studies do not adjust for confounding factors, such as age and parity, and lack information on inflammatory or Fe biomarkers other than serum ferritin. Therefore, the aim of the present study was to examine the association between Fe biomarkers, including serum ferritin concentrations, and the risk of total, early and moderate-to-late sPTB.

Subjects and methods

Study design and population

The study population included women with a singleton infant with a birth weight of at least 400 g or at least 20 weeks of gestation, who attended first-trimester Down's syndrome screening between January and October 2007, and had results analysed by Pathology North, a state-wide public screening service in New South Wales (NSW), Australia. Serum samples that were archived and stored at −80°C were thawed and used for subsequent biochemical analysis.

Biochemical analysis

Serum samples for the present study were thawed and analysed for the levels of serum ferritin (μg/l), soluble transferrin receptor (sTfR, nmol/l) and C-reactive protein (CRP, mg/dl but reported as mg/l) using commercial assays. Serum ferritin level was measured using a solid-phase direct sandwich ELISA method (Calbiotech, Inc.) with an inter-assay CV of 6·2 %. sTfR level was measured using an ELISA method (Quantikine IVD, Human sTfR Immunoassay; R&D Systems) with an inter-assay CV of 6·4 %. CRP level was measured using the quantitative sandwich enzyme immunoassay technique (Quantikine™; R&D Systems, Inc.) with an inter-assay CV of 13·3 %.

Data sources

Laboratory records and the results of each woman's Fe biomarker analyses were linked to electronic birth and hospital records sourced from the NSW Perinatal Data Collection and the NSW Admitted Patients Data Collection (APDC), respectively, to obtain pregnancy and birth information. The Perinatal Data Collection is a statutory population-based collection of all births in NSW of at least 400 g birth weight or at least 20 weeks of gestation, and includes information on maternal and infant characteristics, pregnancy, labour, delivery and infant characteristics at birth. The APDC is a census of all admissions in NSW public and private hospitals. Up to fifty diagnoses for each separation are coded according to the tenth revision of the International Classification of Diseases, Australian Modification[16]. Validation studies of the Perinatal Data Collection and the APDC have shown an excellent level of agreement with the hospital medical record and low rates of missing data[17,18]. Reporting in both datasets has high specificity (>99 %), indicating few false positive reports. Only variables known to be reliably reported in birth and/or hospital data were included in the analysis. The NSW Centre for Health Record Linkage (CHeReL) performed probabilistic record linkage between the three datasets[19]. The CHeReL assesses linkage quality for each study, and for the present study reported <5/1000 missed links and <2/1000 false positive links. Only de-identified data were provided to the researchers. The present study was approved by the NSW Population and Health Services Research Ethics Committee (HREC/09/CIPHS/52).

Variables and definitions

The primary outcome was sPTB defined as births <37 weeks of gestation after the onset of spontaneous labour or preterm premature rupture of the membranes (PPROM), and subdivided into early (<34 weeks) and moderate-to-late (34–36) preterm births[2]. Data on serum ferritin concentrations were examined continuously and as quartiles. Low ferritin level was defined using the established definition for Fe deficiency (serum ferritin levels <12 μg/l)[20]. There is no standard cut-off value for high ferritin levels; therefore, commonly used cut-off values in the literature were assigned at the 50th, 75th and 90th percentiles[1,10–15]. As sTfR is an intercellular Fe-carrier protein, concentrations are inversely related to intracellular body Fe concentrations. Data on transferrin receptor (TfR) were examined continuously and also as Fe deficient (TfR levels ≥21·0 nmol/l), according to the manufacturer's guidelines, and as high Fe[21]. Again, similar to ferritin, there are not standard cut-off values for high TfR levels; therefore, cut-off values that corresponded to those used for ferritin were used for TfR (<50th, <25th and <10th percentiles).

Explanatory variables in the analysis included the following: maternal age; parity; gestational age and maternal body weight, both obtained at the time of blood test; country of birth; smoking during pregnancy; socio-economic status; gestational diabetes; hypertensive disorders in pregnancy. Electronic records from the laboratory database provided information on maternal body weight and gestational age at the time of screening (mean gestational age 12·0 (SD 0·9) weeks). Postcode was used to derive an indicator of socio-economic status using an Index of Relative Disadvantage produced by the Australian Bureau of Statistics, and categorised into quintiles[22]. Hospital data were used to identify PPROM and gestational diabetes mellitus (GDM) based on diagnosis by the attending clinician[18,23,24]. Pregnancy-induced hypertensive disorders included gestational hypertension, pre-eclampsia and eclampsia in women with the onset of hypertension from 20 weeks of gestation[25]. Missing data were infrequent with the following missing records excluded from the analyses: maternal age (*n* 16 records, 0·80 %); smoking status (*n* 11, 0·55 %); country of birth (*n* 29, 1·5 %); socio-economic disadvantage (*n* 12, 0·60 %).

Statistical analysis

Maternal, pregnancy, and other Fe and inflammatory biomarker characteristics were examined by serum ferritin quartiles, and differences were assessed using the χ^2 test for categorical variables and the Kruskal–Wallis test for continuous variables. *Post hoc* comparisons between serum ferritin quartiles and explanatory variables were also made, and Bonferroni correction was used to obtain an adjusted P value of 0·00 125 as the cut-off for statistical significance for each of the *post hoc* tests. When examined continuously, serum ferritin and CRP concentrations were log-transformed. Multivariate logistic regression analysis was performed to take into account any potential confounding with explanatory variables included in the full model. Separate models were run to examine serum ferritin as a continuous variable, as quartiles, as low ferritin (<12 μg/l) and as high ferritin using three cut-offs (>50th, >75th and >90th percentiles). These cut-offs for elevated serum ferritin levels were examined to allow comparison with the cut-offs used in previous studies[1,10–15]. Separate models were also run to examine the association between sPTB and sTfR treated as a continuous variable and dichotomous variables for low and high sTfR levels.

Final models were determined using backward stepwise selection, with variables of least significance progressively dropped from each model until all the remaining covariates were statistically significant (two-tailed, $P<0·05$). Variables not selected were then added back into the selected model, one at a time, to assess whether they were confounders (i.e. changed the effect by more than 10 %), and the final model was determined. Statistical analysis was performed using SAS for Windows version 9.3 (SAS Institute, Inc.).

Results

A total of 2254 women with spontaneous labour or PPROM were included in the analysis. Women had a mean gestational age of 12·0 (SD 0·9) weeks at the time of blood collection. The median serum ferritin concentration for the total study population was 25·4 (25th–75th 14·5–42·8) μg/l. The association between quartiles of serum ferritin concentrations and maternal and pregnancy characteristics is provided in Table 1. The analyses examining the correlation between serum ferritin concentrations and maternal and pregnancy characteristics found significant correlations with maternal age (r 0·09, $P<0·0001$), country of birth (r 0·04, $P=0·03$), nulliparity (r 0·11, $P<0·0001$), gestational age at blood sampling (r −0·04, $P=0·05$) and gestational diabetes (r 0·07, $P=0·0009$). Very small but significant correlations were found between serum ferritin and sTfR concentrations (r −0·05, $P=0·03$) and between serum ferritin and CRP concentrations (r 0·06, $P=0·006$). Serum ferritin concentrations were not significantly correlated with maternal weight quintiles (r 0·02, $P=0·39$), smoking during pregnancy (r 0·01, $P=0·65$), socio-economic disadvantage quintiles (r 0·03, $P=0·10$) and hypertensive disorders in pregnancy (r 0·004, $P=0·86$). *Post hoc* comparisons found that first serum ferritin quartile concentrations (<15 μg/l) were significantly more likely among younger maternal age (<25 years, $P<0·0001$) and less likely among nulliparous women ($P<0·0001$) and those with gestational diabetes ($P=0·0002$). *Post hoc* comparisons also found that women in the fourth serum ferritin quartile (≥43 μg/l) were more likely to have higher maternal age (≥35 years, $P=0·0002$) and be nulliparous ($P=0·0002$). None of the other tests was significant.

Relative to women with term births, women with a sPTB <37 weeks were more likely to be heavier ($P=0·05$) and have GDM ($P=0·007$) (Table 2). These women also had significantly higher median concentrations of ferritin (25·3 *v.* 26·5 μg/l, $P=0·05$) and CRP (7 *v.* 10 mg/l; $P=0·01$). There was no difference in sTfR concentrations among women with a sPTB *v.* term birth ($P=0·61$).

The univariate analysis found significant associations between elevated serum ferritin concentrations (defined >75th and >90th percentiles) and sPTB (Table 3). No associations were found between elevated sTfR percentiles and sPTB, or between low Fe levels and sPTB using either serum ferritin or sTfR. The multivariate analyses indicated increased odds of sPTB for serum ferritin concentrations >75th percentile (≥43 μg/l) and >90th percentile (≥68 μg/l) of 1·49 (95 % CI 1·06, 2·10) and 1·92 (95 % CI 1·25, 2·96), respectively (Table 3).

The univariate analysis examining the association between low and elevated serum ferritin and sTfR concentrations stratified by early and moderate-to-late sPTB is presented in online Supplementary Table S1. For early sPTB, women with serum ferritin concentrations >90th percentile had a 2·54 increased odds of early sPTB (95 % CI 1·36, 4·76), and this association remained significant in the fully adjusted analyses (OR 2·50, 95 % CI 1·32, 4·73).

The univariate analysis indicated increased odds of moderate-to-late sPTB for serum ferritin concentrations >75th and >90th percentiles (see online Supplementary Table S1). The multivariate analysis found that women with serum ferritin concentrations >75th percentile had a 1·56 increased odds of moderate-to-late sPTB (95 % CI 1·03, 2·37). The association between serum ferritin concentrations >90th percentile and moderate-to-late sPTB did not reach statistical significance in the fully adjusted analyses (OR 1·62, 95 % CI 0·93, 2·84).

sTfR concentrations by specific cut-off values were not associated with increased odds of early sPTB. The significant association found between sTfR and moderate-to-late sPTB in the univariate analysis (OR 1·03, 95 % CI 1·00, 1·06) was no longer significant in the fully adjusted analysis (OR 1·02, 95 % CI 0·99, 1·06).

Discussion

Preterm birth is a major public health concern. The present study found that serum ferritin concentrations in early pregnancy are significantly elevated in pregnant women with subsequent spontaneous preterm labour or PPROM. We also found that women with a sPTB had significantly higher first-trimester CRP concentrations, and that there was no association between sTfR concentrations (a biomarker of Fe supplied to tissues) and sPTB. These results suggest that serum ferritin levels are elevated as part of the acute-phase

Table 1. Maternal serum ferritin quartiles by maternal and pregnancy characteristics and biochemical indices in women who had a spontaneous onset of labour or preterm premature rupture of the membranes

(Number of subjects and percentages; median values and 25th–75th percentiles)

	Serum ferritin quartiles								
	<15 μg/l		15–24 μg/l		25–42 μg/l		≥43 μg/l		
	n 580		*n* 536		*n* 578		*n* 560		
	n	%	*n*	%	*n*	%	*n*	%	*P**
Maternal characteristics									
Maternal age (years)									
<25	78	13·6	49	9·2	41	7·2	27	4·9	<0·0001
25–34	342	59·5	344	64·5	391	68·5	353	63·8	
≥35	155	27·0	140	26·3	139	24·3	173	31·3	
Country of birth									
Australia	373	64·3	343	64·0	362	62·6	344	61·4	0·88
New Zealand, North and South Americas	18	3·10	15	2·8	19	3·3	17	3·0	
Europe	46	7·9	30	5·6	43	7·4	38	6·8	
Middle East and Africa	26	4·5	32	6·0	19	3·3	29	5·2	
South and Southeast Asia	56	9·7	58	10·8	59	10·2	61	10·9	
Northeast Asia	41	7·1	41	7·7	54	9·3	47	8·4	
Other	20	3·5	17	3·2	22	3·8	24	4·3	
Maternal weight quintiles (kg)†									
<55	87	17·7	93	19·7	89	18·0	100	20·1	0·04
55–59	106	21·5	75	15·9	88	17·8	85	17·1	
60–65	102	20·7	127	26·9	116	23·4	96	19·3	
66–73	97	19·7	88	18·6	112	22·6	93	18·7	
≥74	101	20·5	90	19·0	90	18·2	123	24·8	
Smoking during pregnancy	39	6·8	31	5·8	44	7·7	35	6·3	0·64
Socio-economic disadvantage quintiles									
1 (most disadvantage)	119	20·5	113	21·2	110	19·3	130	23·3	0·32
2	115	19·8	84	15·7	99	17·4	91	16·3	
3	133	22·9	126	23·6	116	20·4	107	19·2	
4	102	17·6	111	20·8	115	20·2	116	20·8	
5 (least disadvantage)	111	19·1	100	18·7	130	22·8	114	20·4	
Pregnancy characteristics									
Nulliparous	268	46·2	292	54·5	315	54·5	340	60·7	<0·0001
Gestational age at blood sampling (weeks)									
9–10	41	12·1	36	11·0	52	14·2	64	16·1	0·33
11	115	34·0	125	38·2	139	37·9	145	36·4	
12–14	182	53·9	166	50·8	176	48·0	189	47·5	
Gestational diabetes	2	0·3	17	3·2	18	3·1	17	3·0	0·003
Hypertensive disorders in pregnancy	23	4·0	24	4·5	17	2·9	25	4·5	0·51
Biochemical indices									
Soluble transferrin receptor (nmol/l)									0·01
Median	15·6		14·5		15·0		15·3		
25th–75th percentile	12·2–19·5		11·6–18·3		12·0–18·0		12·5–18·4		
C-reactive protein (mg/l)									0·13
Median	7		7		8		8		
25th–75th percentile	3–14		3–14		3–16		3–18		

* *P* values were determined by using the Kruskal–Wallis test.

† Data on maternal body weight were collected by the health care professional referring women for Down's syndrome screening.

response, and that the inflammatory process associated with sPTB is apparent from the first trimester of pregnancy.

Interestingly, the present study found that greater maternal body weight and GDM were both independently associated with elevated ferritin levels and sPTB, and thus included as confounders in the adjusted analyses. Both overweight and GDM are inflammatory conditions. While there is some evidence that maternal overweight and obesity during pregnancy is associated with increased risks of preterm birth[26], the association between GDM and sPTB is inconsistent and controversial[27].

Results from previous studies examining the association between elevated ferritin concentrations and preterm birth have been inconsistent[1,10–15]. Only one other study has measured serum ferritin levels in the first trimester in a small sample of thirty cases and ninety controls, and found no significant difference in the proportion of women with ferritin levels >75th percentile in early preterm *v.* term delivery groups (36·7 *v.* 25·6 %, $P=0·251$)[28]. Thresholds for elevated serum ferritin levels have varied as either >50th, 75th or 90th percentile[1,10–15]. To compare the present study with previous findings, we examined all three of these thresholds. We found that serum ferritin levels >75th percentile (≥43 μg/l) were associated with increased odds of sPTB (<37 weeks) and the subcategory moderate-to-late sPTB (34–36 weeks). However, only the higher threshold (>90th percentile)

Table 2. Maternal characteristics, pregnancy characteristics and biochemical indices in women who had a spontaneous onset of labour or preterm premature rupture of the membranes and delivered a preterm or term infant

(Number of subjects and percentages; median values and 25th–75th percentiles)

	Preterm birth (<37 weeks)		Term birth (≥37 weeks)		
	n 175		*n* 2079		
	n	%	*n*	%	*P**
Maternal age (years)					
<25	16	9·3	179	8·7	0·36
25–34	118	68·2	1312	63·7	
≥35	39	22·5	568	27·6	
Nulliparous	105	60·0	1110	53·4	0·09
Country of birth					
Australia	111	63·4	1311	63·1	0·65
New Zealand, North and South Americas	6	3·4	63	3·0	
Europe	15	8·6	142	6·8	
Middle East and Africa	11	6·3	95	4·6	
South and Southeast Asia	16	9·1	218	10·5	
Northeast Asia	9	5·1	174	8·4	
Other	7	4·0	76	3·7	
Gestational age at blood sampling (weeks)					
9–10	19	15·3	174	13·3	0·72
11	42	33·9	482	36·9	
12–14	63	50·8	650	49·8	
Maternal body weight quintiles (kg)					
<55	27	17·9	342	18·9	0·05
55–59	20	13·3	334	18·5	
60–65	38	25·2	403	22·3	
66–73	23	15·2	367	20·3	
≥74	43	28·5	361	20·0	
Smoking during pregnancy	14	8·0	135	6·5	0·27
Socio-economic disadvantage quintiles					
1 (most disadvantage)	35	20·0	437	21·1	0·95
2	30	17·1	359	17·4	
3	40	22·9	442	21·4	
4	32	18·3	412	19·9	
5 (least disadvantage)	38	21·7	417	20·2	
Gestational diabetes	10	5·7	44	2·1	0·007
Hypertensive disorders in pregnancy	11	6·3	78	3·8	0·1
Serum ferritin (μg/l)					0·05
Median	26·5		25·3		
25th–75th percentile	16·2–52·3		14·3–42·1		
Soluble transferrin receptor (nmol/l)					0·61
Median	15·2		15·1		
25th–75th percentile	11·9–19·0		12·1–18·6		
C-reactive protein (mg/dl)					0·01
Median	1·0		0·7		
25th–75th percentile	0·4–1·9		0·3–1·5		

* *P* values were determined by using the χ^2 test.

for serum ferritin levels (≥68 μg/l) was significantly associated with early sPTB in the present study. This is in agreement with a few studies that have found levels >30 μg/l to be associated with preterm birth[11,14]. Inconsistent findings across studies may be related to differences in study populations and the severity of sPTB, reduced numbers of women in certain categories of exposure and/or outcome, and the types of confounders included in adjusted analyses. Previous studies have mostly been cross-sectional and limited to serum ferritin measurements later in pregnancy or at the time of birth[10,11,13–15].

The usefulness of serum ferritin as a marker for sPTB is uncertain. Significant associations between elevated ferritin concentrations and sPTB were not found across all the thresholds or subtypes for sPTB (i.e. early *v.* moderate-to-late). Before routine screening of serum ferritin for the prediction of sPTB can be recommended, further research is needed to establish normative values, to understand the variability in ferritin as an early pregnancy biomarker, and to determine its accuracy, reliability, interpretability and feasibility. While the present study found increased odds of sPTB in association with elevated ferritin concentrations, this does not demonstrate that ferritin will function well as a diagnostic test unless ferritin is shown to be a manifestation of sPTB[29]. Although significant, the overall difference observed in median ferritin concentrations was minimal between women with and without sPTB. Further research is needed to validate our findings in other study populations.

Table 3. First-trimester serum ferritin and soluble transferrin receptor concentrations in women who had a spontaneous onset of labour or preterm premature rupture of the membranes and delivered a preterm *v.* a term infant

(Number of subjects and percentages; odds ratios and 95 % confidence intervals; median values and 25th–75th percentiles)

	Preterm birth (<37 weeks)		Term birth (≥37 weeks)		Unadjusted		Adjusted	
	n	%	*n*	%	OR	95 % CI	OR*	95 % CI
Serum ferritin (μg/l)								
Median	26·5		25·3		1·24†		1·17	
25th–75th percentile	16·2–52·3		14·3–42·1		1·02–1·50		0·96–1·43	
Soluble transferrin receptor (nmol/l)								
Median	15·2		15·1		1·02		1·01	
25th–75th percentile	11·9–19·0		12·1–18·6		0·99–1·04		0·99–1·04	
Elevated Fe								
High serum ferritin levels (μg/l)								
>50th percentile (≥25 μg/l)	95	54·3	1043	50·2	1·18	0·87, 1·61	–	
>75th percentile (≥43 μg/l)	58	33·1	502	24·2	1·56†	1·12, 2·17	1·49†	1·06, 2·10
>90th percentile (≥68 μg/l)	30	17·1	193	9·3	2·02†	1·33, 3·08	1·92†	1·25, 2·96
Low sTfR levels (nmol/l)								
<50th percentile (≤15 nmol/l)	96	54·9	1202	57·8	0·89	0·65, 1·21	–	
<25th percentile (≤12 nmol/l)	50	28·6	663	31·9	0·85	0·61, 1·20	–	
<10th percentile (≤9 nmol/l)	24	13·7	221	10·6	1·34	0·85, 2·10	–	
Fe deficiency								
Serum ferritin (<12 μg/l)	30	17·1	402	19·3	0·86	0·57, 1·30	–	
sTfR (≥21 nmol/l)	29	16·6	318	15·3	1·10	0·73, 1·67	–	

sTfR, soluble transferrin receptor.

* Adjusted for maternal age, parity, gestational diabetes mellitus and C-reactive protein. Empty cells indicate that adjusted analyses were not performed due to no association being found in the univariate analysis.

† $P < 0·05$.

It has been proposed that high ferritin concentrations may be a marker of clinical and subclinical vaginal infection, which, in turn, may be triggers in the preterm delivery pathway[10,13]. There is evidence of an association between vaginal infections and preterm delivery from longitudinal studies[29,30] and a single randomised controlled trial which found that second-trimester antenatal screening and treatment for asymptomatic vaginal infections reduced the rate of preterm births by 50 %[31]. The association between maternal Fe status and vaginal infections in early pregnancy has not been well studied. Studies have observed an increase in various bacterial and non-bacterial infectious diseases in genetic Fe-overload diseases, such as haemochromatosis, where Fe levels in serum are increased. Given that a notable adaptation of bacterial growth is enhanced virulence secondary to acquiring a supply of Fe from the host[32], future studies are needed to examine the relationship between maternal Fe status and early pregnancy infections.

The strengths of the present study include a longitudinal design; one of the largest sample sizes to date, with measurement of serum ferritin concentrations in the first trimester of pregnancy as well as other Fe and inflammatory biomarkers; adjustment for confounders; and a sensitivity analysis using a range of cut-off values for elevated serum ferritin concentrations. While the present study used multiple data sources to analyse serum biomarkers and a range of maternal and pregnancy characteristics, limitations include the lack of data on medical conditions that has an impact on Fe status, such as haemochromatosis, maternal characteristics associated with sPTB, such as ethnicity and BMI, as well as early pregnancy infections and placental Fe biomarkers, such as serum placental isoferritin. There is a paucity of studies on pre-pregnancy BMI for this outcome, especially for moderate and very early preterm birth. Although we only had information on maternal weight, we did find a trend towards increased sPTB with increasing maternal weight. A recent systematic review and meta-analysis has found that being overweight or slightly obese was not associated with the overall risk of preterm birth (<37 weeks of gestation), but that high maternal BMI may have different effects on different subtypes of preterm birth. A notable limitation is the lack of Hb data, which is routinely performed during pregnancy but collected by various individual health care providers and local laboratories. There is some evidence of a U-shaped relationship between Hb concentrations in early pregnancy and the risk of preterm birth; however, the role of maternal Hb in preterm birth remains poorly defined. Another study limitation is the generalisability of the present study population, which does not represent the total state maternity population during the same period, possibly due to a healthier and more affluent group attending first-trimester screening.

In summary, results from the present study provide further support of an association between elevated ferritin concentrations in early pregnancy and the risk of sPTB. Importantly, this suggests that an inflammatory process that is detectable in early pregnancy may be a plausible biological mechanism for this association. Further research investigating the pathophysiological processes between elevated ferritin concentrations and the risk of sPTB, which considers the associations between inflammation, obesity, GDM and vaginal infections, is warranted.

Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S0007114515001932

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None of the authors has a conflict of interest to declare.

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