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RESEARCH ARTICLE

Fibroblast growth factor 23 is associated with the development of gestational diabetes mellitus

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Abstract

Background: Besides its established impact on bone and mineral metabolism, it was suggested that fibroblast growth factor 23 (FGF23) might play an important role in the pathogenesis of type 2 diabetes. The impact of FGF23 on gestational diabetes mellitus (GDM), however, is not well understood. iFGF23 ELISAs measure the intact FGF23 molecule, whereas cFGF23 assays measure intact FGF23 as well as degradation products of FGF23.

Objectives: The aim of this study is to compare the association of maternal and foetal cFGF23 and iFGF23 with GDM in a German birth cohort.

Methods: cFGF23 and iFGF23 were analysed in 826 random mother/child pairs from the Berlin Birth Cohort.

Results: Mothers who developed GDM had higher concentrations of iFGF-23 compared to mothers who did not suffer from GDM (19.73 vs. 13.23 pg/mL, $p < 0.0001$), but not higher concentrations of cFGF-23. Multivariant regression analyses showed that gestational diabetes is associated with iFGF23 independently of confounding factors such as age, BMI, ethnic background, family history of diabetes, smoking during pregnancy, and recurrent pregnancy loss. This, however, was only seen when using an iFGF23 ELISA measuring just the full length FGF23 and not in addition FGF23 fragments. No differences in both iFGF23 and cFGF23 concentrations between the GDM and non-GDM groups were detected in cord blood samples of the offspring.

Conclusions: This study of a representative German birth cohort showed that maternal but not foetal iFGF23 is independently associated with GDM.

KEYWORDS
birth cohort study, cFGF23, FGF23, gestational diabetes mellitus, iFGF23

1 | INTRODUCTION

FGF-23, a 32kDa protein composed of 227 amino acids, is secreted by osteocytes and is an essential regulator of phosphate and vitamin D homoeostasis. FGF-23 stimulates the excretion of phosphate by the kidneys. The role of FGF-23 is to keep blood phosphate levels constant despite varying dietary phosphate intake. Increased blood levels of FGF-23 lead to decreased blood phosphate levels, decreased production of $1,25(OH)_2$ vitamin D, and osteomalacia. Decreased blood levels of FGF-23 result in increased blood phosphate levels (hyperphosphatemia), increased production of $1,25(OH)_2$-vitamin D, soft tissue calcification, excessive bone formation (hyperostosis), and decreased life expectancy. FGF-23 binds to the FGF receptor 1c and the co-receptor Klotho. Activation of this receptor complex in the proximal tubule of the kidney inhibits phosphate re-absorption from the primary urine and thus has a phosphoruric and hypophosphatemic effect. Specifically, the activation of the receptor results in reduced expression of the sodium-phosphate cotransporters NaPi-IIa and NaPi-IIc.[1–3]

Besides its established impact on bone and mineral metabolism, it was suggested that fibroblast growth factor 23 (FGF23) might likewise play an important role in the pathogenesis of type 2 diabetes mellitus.[4] This hypothesis was based on observational clinical studies. These studies provided evidence that FGF23 is associated with markers of obesity, metabolic syndrome, insulin levels, and HOMA-IR index. Moreover, a positive association between diabetes and serum FGF23 levels was described.[5–15] However, a recent study published in PNAS provided evidence that insulin/IGF1-dependent PI3K/PKB/Akt/FOXO1 signalling is a potent suppressor of FGF23 production in vitro in mice and humans. The clinical part of this study had the advantage that other factors potentially influencing FGF23 were almost absent.[16] The discrepancy with previous studies, where insulin-resistant individuals had higher FGF23 serum levels, might be due to other coexisting pathophysiological factors such as inflammation, preexisting chronic kidney disease or coronary heart disease, obesity, high nutritional phosphate intake, and high leptin levels. To minimise the potential effects of these main confounding factors on serum FGF23 concentrations, we thus analysed women with and without gestational diabetes coming from a random but huge subgroup of the Berlin Birth Cohort study, a population where most of these confounding factors were absent or played a minor role.[17–24]

In addition, we used both currently existing types of FGF23 ELISA assays. On the one hand, a C-terminal FDF23 ELISA assay that recognises the full-length FGF23 and its degradation products was employed. On the other, an intact FGF23 ELISA assay that merely detects full-length FGF23. Both assays were used since there is evidence from head-to-head comparisons of both ELISA types in clinical studies that clinical associations may depend on the ELISA type used.[25–27]

2 | METHODS

2.1 | Study population

The Institutional Review Board of the University Hospital of Charité Berlin, Germany, approved the study. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. Data were collected from 2000 to 2008. This observational study (Berlin Birth Cohort) included 826 random samples from mothers delivering at the Charité Obstetrics Department and their respective newborns. We analysed this random subset of the Berlin Birth Cohort due to budget restrictions for this project. The Berlin Birth Cohort was described in detail previously.[17–24]

After written consent was obtained, a structured medical history was taken. The following data were extracted into our database: age, ethnicity, body height, body weight at the begining of the pregnancy, diabetes mellitus, hypertension during pregnancy, systolic and diastolic blood pressure (BP) measurements recorded during pregnancy, smoking during pregnancy, and mode of delivery. Biometric data of the newborns were collected during the routine postnatal examination: birth weight, birth length, head circumference, and child sex; gestational age at delivery was based on the last menstrual period and anamnestically assessed during the first pregnancy examination. Midwives collected maternal blood from the cubital vein in the delivery room. Foetal blood samples were collected from the umbilical cord within 10 min after delivery. Blood was centrifuged at 2750 G immediately after its withdrawal, and the obtained serum was stored at −80°C until measurements were performed. Obtained serum samples were used for metabolomic analyses and additionally to measure glucose and insulin concentrations. GDM was screened for and assessed according to the practice guidelines of the German Diabetes Association (DDG) and the German Association for Gynaecology and Obstetrics (DGGG).[28]

2.2 | cFGF23, iFGF23 and sclerostin measurements

cFGF23 and iFGF23 were always measured in duplicate in maternal and cord blood samples as recently described[25] with a commercially available cFGF23 specific ELISA (cat. no. BI-20702, Biomedica, Austria) and an iFGF23 specific ELISA (cat. no.BI-20700, Biomedica, Austria) according to the instructions of the manufacturer. The average intra-and inter-assay coefficients of variation were ≤12% and ≤10% for the cFGF23 assay (described in detail on https://www.bmgrp.com/wp-content/uploads/2019/03/bi-20702-fgf23-elisa-validation-data-150306.pdf), and ≤8 and ≤6% for iFGF23 assay (described in detail on https://www.bmgrp.com/wp-content/uploads/2022/05/BI-20700-FGF23-Intact-ELISA-Validation-Data-RUO-220524.pdf). Sclerostin concentration was measured both in maternal and cord blood samples using the commercial ELISA (BI-20492, Biomedica Medizinprodukte GmbH, Vienna, Austria), according to

the manufacturer's instructions (https://www.bmgrp.com/wp-content/uploads/2022/05/BI-20492-Sclerostin-ELISA-IFU-220524.pdf). All samples were measured in duplicate and all assays were subjected to regular quality control.

2.3 | Statistical analysis

Descriptive statistics for continuous parameters are shown as medians (interquartile ranges), and categorical data are shown as numbers (%). Statistical differences between groups were analysed as appropriate by Mann-Whitney U, Kruskal-Wallis, or Chi-square test. To assess the prognostic value of iFGF-23 concentrations for the presence of gestational diabetes mellitus (GDM), a recipient operating characteristic (ROC) curve was conducted. Spearman's rank correlation analysis was performed to assess the correlation between the presence of GDM and selected parameters. Binary logistic regression analysis was then performed with GDM as the dependent variable and other co-factors affecting the presence of GDM as independent variables. Model 1 consisted of age, body mass index (BMI), ethnic background, and iFGF-23 concentrations. Model 2 consisted of age, BMI, ethnic background, diabetes in the family, smoking during pregnancy, and iFGF-23 concentrations. Model 3 consisted of age, BMI, ethnic background, diabetes in the family, smoking during pregnancy, recurrent pregnancy loss (two or more miscarriages), gestational age, and iFGF-23 concentration. All statistical analyses were performed using SPSS 25.0 software (SPSS, Chicago, IL, USA). The level of significance was set at $p < 0.05$.

2.4 | Data and resource availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

3 | RESULTS

3.1 | Participant characteristics

Table 1 presents descriptive statistics of mothers and their newborns in detail and descriptive statistics of the cohort classified by the presence or absence of GDM. The median age of the mothers was 31 (26, 35) years, and the median BMI before pregnancy was 22.5 (20.4, 26.0) kg/m^2. 88.6% of all mothers were European, 5.3% were Asian, 1.2% were African, and 4.8% were of unknown ethnicity. The median concentration of iFGF-23 was 14.66 (8.38, 23.49) pg/mL. The incidence of GDM was 7.7% (64/826). Mothers who developed GDM were significantly older (34 vs. 30 years old, $p < 0.0001$), heavier (68.0 vs. 64.0 kg, $p = 0.003$), and displayed an increased prevalence of previous miscarriage (25.4% vs. 12.0%, $p = 0.002$). Regarding FGF23, mothers who developed GDM had a significantly higher concentration of iFGF-23 compared to mothers who did not suffer from GDM (19.73 vs. 13.23 pg/mL, $p < 0.0001$), but no higher cFGF-23 concentration (Figure 1). In addition, the ROC curve assessed the prognostic value of iFGF-23 concentration for the presence of GDM, with an area under the curve of 0.66 (95% CI, 0.59–0.73, $p < 0.0001$), and once again, no such significant prognostic value was found for cFGF-23 concentration. Sclerostin, as a key hormone being important for the control of bone metabolism, was also measured. Its concentrations did not differ significantly between GDM and non-GDM ($p = 0.72$ in maternal blood and $p = 0.07$ in cord blood) (Table 1). To further clarify associations between iFGF-23 concentration and other factors, including the presence of GDM, we grouped iFGF-23 and cFGF-23 into quintiles separately and performed comparisons among these groups (Table 2, Supporting Information S1: Table S1). Consistent with the above finding, the incidence of GDM increased significantly with increasing iFGF-23 concentration. At iFGF 23 concentrations not greater than 6.07 pg/mL, the incidence of GDM was 3.3%, but as the concentration of iFGF 23 increased to over 24.72 pg/mL, this incidence escalated to 13.2%. In addition, iFGF-23 concentrations were associated with hypertension during pregnancy, age, BMI, and cFGF-23 concentration.

3.2 | Association of iFGF-23 concentrations with clinical parameters

Spearman's correlation analyses between maternal iFGF-23 concentrations and other clinical parameters are shown in Table 3 iFGF-23 concentrations were significantly and positively correlated with cFGF-23 concentrations (Spearman's rho = 0.350, $p < 0.0001$), the presence of GDM (Spearman's rho = 0.146, $p < 0.0001$), and negatively correlated with BMI at the beginning of pregnancy (Spearman's rho = −0.207, $p < 0.0001$). Furthermore, iFGF-23 concentrations showed a weak but still significant positive correlation with age (Spearman's rho = 0.155, $p < 0.0001$), second-trimester body weight (Spearman's rho = 0.080, $p = 0.036$), hypertension during pregnancy (Spearman's rho = 0.112, $p = 0.003$), last measured DBP (Spearman's rho = 0.101, $p = 0.016$), and history of miscarriage (Spearman's rho = 0.091, $p = 0.016$).

After that, binary logistic regression analysis models were performed to better characterise the relationship between iFGF-23 concentrations and GDM. Three different models adjusted for various confounders of GDM (age, BMI, ethnic background, diabetes in the family, smoking during pregnancy, recurrent pregnancy losses, and intrauterine delivery) showed that iFGF-23 concentrations are independently associated with the presence of GDM (Table 4); however, this association was not found with cFGF-23 nor sclerostin concentrations (Supporting Information S1: Tables S2 and S3).

Then, we divided the cohort into two BMI groups according to the WHO classification of weight status, underweight (BMI <18.5 kg/m^2) or not (BMI ≥18.5 kg/m^2). Within these subgroups, we again performed binary logistic regression analysis using the same three models. iFGF-23 is significantly associated with GDM in women

TABLE 1 Descriptive data of all mother/child pairs. Data are given as median and interquartile range (IQR) or number (%).

Characteristics	All (*N* = 826)	GDM (*N* = 64)	Non-GDM (*N* = 762)	*p* value
Mother				
Age (years)	31 (26, 35)	34 (30, 38)	30 (26, 35)	<0.0001
BMI begin pregnancy (kg/m^2)	22.5 (20.4, 26.0)	23.3 (20.6, 28.6)	22.5 (20.3, 25.9)	0.14
Ethnic background				0.523
Caucasian	732	57 (89.1%)	675 (88.6%)	
Asian	44	3 (4.7%)	41 (5.4%)	
Unclear	40	2 (3.1%)	38 (5.0%)	
African	10	2 (3.1%)	8 (1.0%)	
1st trimester body weight (kg)	64.4 (58.0, 72.5)	68.0 (60.5, 85.3)	64.0 (58.0, 71.1)	0.003
2nd trimester body weight (kg)	67.5 (60.8, 76.0)	71.8 (64.5, 90.8)	67.3 (60.7, 75.0)	0.001
3rd trimester body weight (kg)	75.0 (68.0, 84.2)	81.1 (71.0, 93.6)	74.7 (67.7, 83.2)	0.004
Smoking during pregnancy (yes/no)	89/586	10 (15.6%)	78 (12.8%)	0.529
Hypertension during pregnancy (yes/no)	70/749	8 (12.7%)	61 (8.1%)	0.208
1st trimester SBP (mmHg)	114 (105, 120)	118 (105, 123)	113 (105, 120)	0.545
2nd trimester SBP (mmHg)	113 (106, 121)	113 (107, 121)	113 (106, 122)	0.822
3rd trimester SBP (mmHg)	114 (108, 121)	115 (108, 121)	114 (108, 122)	0.748
Last measured SBP (mmHg)	130 (120, 138)	130 (120, 140)	130 (120, 137)	0.453
1st trimester DBP (mmHg)	70 (60, 75)	70 (65, 75)	70 (60, 75)	0.233
2nd trimester DBP (mmHg)	67.5 (62, 73)	69 (65, 75)	68 (62, 73)	0.123
3rd trimester DBP (mmHg)	70 (64, 75)	69 (65, 75)	70 (64, 75)	0.707
Last measured DBP (mmHg)	70 (65, 80)	70 (65, 80)	70 (65, 80	0.913
History of miscarriage (yes/no)	104/698	16 (25.4%)	88 (12.0%)	0.002
25OHD (nmol/L)	13.0 (5.0, 27.0)	10.5 (5.8, 17.3)	14.0 (5.0, 28.0)	0.233
Sclerostin (pmol/L)	23.9 (18.0, 30.9)	20.6 (16.7, 34.2)	24.0 (18.1, 30.6)	0.716
Newborn				
APGAR 5 min	8 (8, 10)	9 (8, 10)	9 (9, 10)	0.042
APGAR 10 min	9 (8, 10)	10 (9, 10)	10 (9, 10)	0.016
Birthweight (g)	3330 (2960, 3675)	3360 (2807, 3647)	3328 (2965, 3680)	0.727
Gestational age (week)	39 (38, 40)	38 (37, 39)	39 (38, 40)	<0.0001
Umbilical cord Ph	7.28 (7.23, 7.32)	7.27 (7.23, 7.34)	7.28 (7.22, 7.32)	0.61
25OHD (nmol/L)	15.0 (8.0, 24.0)	23.0 (16.0, 45.0)	15.0 (8.0, 24.5)	0.095
Sclerostin (pmol/L)	44.9 (36.5, 56.3)	42.1 (29.6, 51.0)	45.3 (37.3, 57.4)	0.069

Note: Descriptive statistics for continuous parameters are shown as medians (interquartile ranges), and categorical data are shown as numbers (%). Statistical differences between groups were analysed as appropriate by Mann-Whitney U, or Chi-square test. Gestational age refers to the week of gestation at the time of birth.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

having normal or elevated body weight at the beginning of pregnancy, but not in underweight pregnant women (BMI <18.5 kg/m^2) (Table 5). Moreover, similar results were also seen in the BMI subgroups, which are divided according to ROC analysis-determined cut-off values (18.1 kg/m^2). The association of iFGF-23 concentration with the development of GDM was just seen in women with BMI above the ROC-curve-determined cut-off (Supporting Information S1: Table S5).

Newborn cord blood FGF23 (both iFGF23 and cFGF23) were similar in the GDM and non-GDM groups (Supporting Information S1: Figure S1).

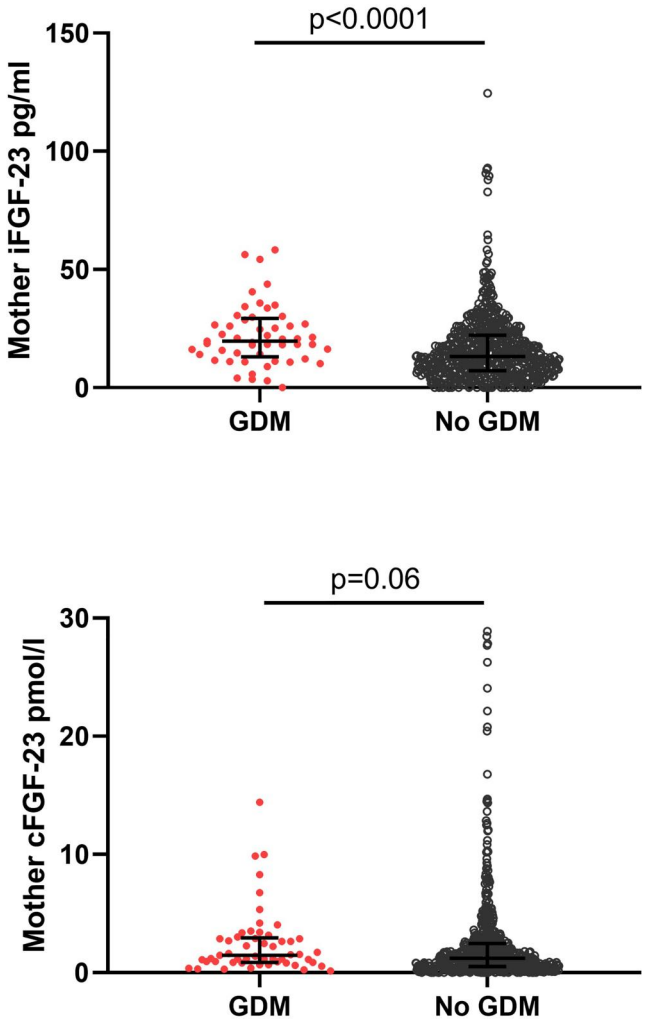

FIGURE 1 Plots of serum iFGF-23 and cFGF-23 concentrations in mothers with and without GDM (gestational diabetes mellitus). All plots display median with interquartile range. Median serum iFGF-23 was significantly higher in mothers with GDM (19.73 [13.09, 29.26] versus 13.23 [7.19, 22.22] pg/mL, $p < 0.001$).

4 | DISCUSSION

The current study showed that the prevalence of gestational diabetes in a European birth cohort is associated with FGF23 independent of confounding factors such as age, BMI, ethnic background, history of diabetes in the family, smoking during pregnancy, and recurrent pregnancy loss. However, this independence was only seen when using an ELISA for FGF23, which measures the intact FGF23 molecule. Using an ELISA recognising intact and degraded fragments of FGF23 did not show this relationship. Furthermore, concentrations of both iFGF23 and cFGF23 in cord blood were not significantly different between the GDM and non-GDM groups.

Prior evidence indicates that FGF-23 is not only involved in the bone and mineral disorders but also acts as a "hormone-like" factor in the metabolism of glucose and lipids, including insulin resistance, visceral adiposity, and dyslipidemia.[5,29,30] FGF-23 is elevated in patients with type 2 diabetes, especially those with impaired renal function compared to those without diabetes.[14,31] However, the association between FGF23 and glucose metabolism in pregnant women is still less reported. So far, there are only three small studies ($n < 100$) investigating the potential association between FGF23 and GDM.[32–34] The results were conflicting most like due to the small sample size of these studies making change findings possible. Moreover, there are currently two types of assays for the determination of FGF23 concentrations in human. Intact FGF23 (iFGF23) assay binds two epitopes flanking the proteolytic cleavage site that lays between amino acids 179 and 180, and thus presumably detects only biologically active, full-length FGF23 (~32 kDa),[35] whereas the C-terminal FGF23 (cFGF23) assay binds to epitopes within the C-terminal region of the FGF23 protein and therefore measures both degraded and non-degraded FGF23 fragments (~14 kDa).[36] There is evidence from head-to-head comparisons of both ELISA types in clinical studies that clinical associations may depend on the ELISA type used.[25] In above three studies, they did not compare intact FGF23 with C-terminal FGF23, nor analysed both maternal and cord-blood levels of FGF23. Only one study corrected their analysis for a limited number of confounding factors[34] (Supporting Information S1: Table S4). In the present study, we used both types of FGF23 ELISA assay, and further considered co-founding factors that might be associated with GDM, that is, age, BMI, ethnic background, diabetes in the family, smoking during pregnancy, recurrent pregnancy loss, and gestational age in regression analysis, which makes our findings more convincing. Therefore, for the first time, we found that maternal (but not foetal) intact FGF23 (but not cFGF23) is associated with GDM. This difference in measurements might have two consequences. First, the amount of intact FGF23 is diluted using cFGF23 ELISAs, which might increase the non-specific background noise of the signal in any clinical study. Second, and probably more importantly, FGF23 fragments might be bioactive by blocking the FGF23 receptors, thus competing with the intact FGF23 molecule for receptor binding.[37]

The study population in our study was created randomly by selecting 826 mother/child pairs from the Berlin Birth Cohort. Random selection of the subset was necessary due to budget restrictions. The prevalence of GDM in the subset was 7.7%. Mothers with GDM were older than those without GDM, had a more frequent history of miscarriage, and delivered earlier. Hence, although GDM mothers delivered earlier, birthweight was slightly numerically higher (Table 1). These are typical characteristics of a central European birth cohort[38–40]; thus, our cohort is representative of a European birth cohort.

A correlation between iFGF23 serum levels and body composition, blood pressure, selected glucose parameters, and insulin and fat metabolism has been studied in a group of 68 non-insulin-resistant, nondiabetic adolescents with mild obesity.[6] In this study, authors found negative correlations between circulating iFGF23, fasting insulin level, and HOMA-IR ($r = -0.3$ and $r = -0.29$, respectively; $p < 0.05$ for both).[6] Consistent with these findings, we published in 2018[16] a clear negative correlation of plasma insulin with FGF23 in a group of healthy (in particular nondiabetic) pregnant women

TABLE 2 Parameters according to quintiles of maternal iFGF-23 concentration.

	iFGF-23 ≤ 6.07 (pg/mL)	6.07 < iFGF-23 ≤ 11.12 (pg/mL)	11.12 < iFGF-23 ≤ 16.72 (pg/mL)	16.72 < iFGF-23 ≤ 24.72 (pg/mL)	iFGF-23 > 24.72 (pg/mL)	*p* value
GDM						
Yes	5	5	9	15	19	0.003
No	147	140	136	132	125	
% within quintile	3.3%	3.6%	6.2%	10.2%	13.2%	
Ethnic background						
Caucasian	139	126	127	126	125	0.996
Asian	6	10	9	8	8	
Unclear	6	3	8	10	46	
African	1	1	1	3	7	
Smoking during pregnancy						
Yes	26	17	17	21	21	0.881
No	126	123	128	126	123	
% within quintile	16.9%	12.2%	11.7%	14.3%	14.6%	
Hypertension during pregnancy						
Yes	10	6	12	10	21	0.019
No	142	133	133	137	123	
% within quintile	6.6%	4.3%	8.3%	6.8%	14.6%	
History of miscarriage						
Yes	10	16	21	23	23	0.078
No	142	124	124	124	121	
% within quintile	6.6%	11.4%	14.5%	15.6%	16.0%	
Age (years)	28 (25, 32)	30 (25, 34)	31 (27, 36)	32 (27, 36)	31 (26, 35)	<0.0001
BMI (kg/m^2)	25.6 (22.2, 28.7)	23.4 (20.7, 27.2)	21.5 (19.8, 24.7)	22.0 (20.1, 24.1)	22.2 (20.3, 24.8)	<0.0001
1st trimester body weight (kg)	63.9 (57.1, 71.2)	64.9 (59.3, 71.0)	64.0 (57.5, 72.0)	64.0 (57.3, 70.0)	65.0 (58.0, 73.5)	0.637
2nd trimester body weight (kg)	66.7 (60.0, 75.2)	68.0 (61.0, 76.0)	65.3 (60.0, 73.7)	67.7 (60.4, 74.7)	69.1 (63.0, 78.8)	0.132
3rd trimester body weight (kg)	74.3 (65.6, 84.4)	76.0 (68.3, 84.3)	73.8 (66.1, 83.0)	75.0 (67.6, 81.6)	76.7 (70.1, 87.1)	0.064
1st trimester SBP (mmHg)	112 (105, 120)	115 (105, 120)	115 (106, 120)	113 (103, 120)	114 (105, 125)	0.597
2nd trimester SBP (mmHg)	115 (107, 121)	115 (106, 124)	113 (105, 120)	112 (106, 120)	115 (107, 123)	0.542
3rd trimester SBP (mmHg)	115 (108, 122)	114 (109, 123)	114 (108, 120)	115 (108, 121)	115 (108, 122)	0.954
Last measured SBP (mmHg)	125 (120, 137)	125 (120, 134)	130 (120, 140)	130 (120, 139)	130 (120, 140)	0.125
1st trimester DBP (mmHg)	70 (60, 75)	68 (60, 73)	70 (60, 80)	70 (60, 73)	70 (61, 78)	0.465
2nd trimester DBP (mmHg)	68 (61, 73)	68 (63, 74)	68 (62, 73)	67 (63, 73)	69 (63, 75)	0.657
3rd trimester DBP (mmHg)	70 (64, 76)	70 (65, 76)	69 (64, 75)	70 (65, 75)	71 (65, 74)	0.910
Last measured DBP (mmHg)	70 (65, 80)	70 (65, 80)	70 (60, 80)	73 (64, 80)	70 (64, 80)	0.495
Maternal 25OHD (nmol/L)	11 (5, 26)	15 (4, 21)	12 (4.0, 28)	15.0 (6.0, 35.0)	14.0 (6.0, 26.3)	0.559
Maternal sclerostin (pmol/L)	19.5 (17.2, 25.5)	23.8 (17.0, 29.7)	25.8 (19.7, 33.3)	25.6 (18.4, 34.4)	22.7 (17.5, 30.9)	0.716
Maternal cFGF-23 (pmol/L)	0.42 (0.13, 1.19)	1.01 (0.32, 2.20)	1.33 (0.69, 2.39)	1.70 (1.01, 3.36)	1.76 (1.03, 3.12)	<0.0001

Note: Descriptive statistics for continuous parameters are shown as medians (interquartile ranges), and categorical data are shown as numbers (%). Comparisons between groups were assessed by the Kruskal-Wallis test.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

TABLE 3 Correlation analysis between maternal iFGF-23 concentrations with clinical parameters.

Characteristics	Spearman's rho	*p* value
Age (years)	0.155	<0.0001
BMI begin pregnancy (kg/m^2)	−0.207	<0.0001
Ethnic background	−0.013	0.729
1st trimester body weight (kg)	0.03	0.464
2nd trimester body weight (kg)	0.080	0.036
3rd trimester body weight (kg)	0.069	0.07
GDM (yes/no)	0.146	<0.0001
Smoking during pregnancy (yes/no)	0.014	0.729
Hypertension during pregnancy (yes/no)	0.112	0.003
1st trimester SBP (mmHg)	0.033	0.429
2nd trimester SBP (mmHg)	0.025	0.511
3rd trimester SBP (mmHg)	0.008	0.831
Last measured SBP (mmHg)	0.037	0.381
1st trimester DBP (mmHg)	0.015	0.723
2nd trimester DBP (mmHg)	−0.005	0.89
3rd trimester DBP (mmHg)	−0.006	0.881
Last measured DBP (mmHg)	0.101	0.016
History of miscarriage (yes/no)	0.091	0.016
Maternal 25OHD (nmol/L)	0.047	0.350
Maternal sclerostin (pmol/L)	0.106	0.064
Maternal cFGF-23 (pmol/L)	0.350	<0.0001

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus; SBP, systolic blood pressure.

without manifest IR or hyperinsulinemia. In vitro and in vivo mouse data in this study supported the suppressive effect of insulin on FGF23.[16]

Due to unknown reasons, in patients with diabetes, the opposite observations have been reported, that is, a positive correlation between insulin resistance (HOMA-IR) and FGF23 and higher FGF23 serum concentrations in patients with diabetes as compared to nondiabetic controls.[5–15] These studies are in line with a recent study in humans where insulin was infused. The authors investigated serum FGF23 during a euglycemic-hyperinsulinemic clamp in both lean and glucose-tolerant obese healthy individuals and patients with type 2 diabetes. They did not find any differences in baseline levels of serum FGF23, but after the clamp, there was a significant increase in serum FGF23 in the diabetic patients only.[41]

Why findings in young healthy subjects[6,16] are different from those with diabetes type or GDM as seen in the present study with regard to FGF23 response to insulin remains unknown. It was suggested that confounding factors such as inflammation or impaired kidney function (factors that stimulate FGF23) are often seen in

TABLE 4 Binary logistic regression analysis models for gestational diabetes.

	OR	β	S.E.	Wald	*p* value
Model 1					
(Constant)	0.001	−7.227	1.349	28.707	<0.0001
Age (years)	1.109	0.103	0.027	15.055	0.0001
BMI (kg/m^2)	1.079	0.076	0.024	10.431	0.001
Ethnic background (unclear)	Ref.	Ref.	Ref.	4.062	0.255
Ethnic background (Caucasian)	0.414	−0.882	0.811	1.181	0.277
Ethnic background (African)	1.584	0.460	1.136	0.164	0.686
Ethnic background (Asian)	0.714	−0.337	1.005	0.112	0.738
Maternal iFGF-23 (pg/mL)	1.015	0.015	0.006	7.090	0.008
Model 2					
(Constant)	0.001	−6.584	1.414	21.667	<0.0001
Age (years)	1.102	0.097	0.028	12.149	0.0005
BMI (kg/m^2)	1.101	0.096	0.024	15.609	<0.0001
Ethnic background (unclear)	Ref.	Ref.	Ref.	3.040	0.386
Ethnic background (Caucasian)	0.551	−0.597	0.858	0.484	0.486
Ethnic background (African)	1.926	0.656	1.173	0.312	0.576
Ethnic background (Asian)	0.920	−0.083	1.047	0.006	0.937
Diabetes in family (no)	0.932	−0.070	0.327	0.046	0.831
Smoking during pregnancy (no)	0.388	−0.948	0.425	4.968	0.026
Maternal iFGF-23 (pg/mL)	1.011	0.011	0.005	5.148	0.023
Model 3					
(Constant)	0.557	−0.585	2.494	0.055	0.814
Age (years)	1.089	0.085	0.029	8.422	0.004
BMI (kg/m^2)	1.094	0.090	0.025	13.261	0.003
Ethnic background (unclear)	Ref.	Ref.	Ref.	4.009	0.260
Ethnic background (Caucasian)	0.546	−0.605	0.913	0.439	0.508
Ethnic background (African)	2.642	0.972	1.226	0.628	0.428
Ethnic background (Asian)	0.896	−0.110	1.100	0.010	0.920
Diabetes in family (no)	0.945	−0.057	0.336	0.028	0.866

(Continues)

TABLE 4 (Continued)

	OR	β	S.E.	Wald	*p* value
Smoking during pregnancy (no)	0.425	−0.855	0.453	3.558	0.059
Recurrent pregnancy loss (no)	0.666	−0.407	0.409	0.988	0.320
Gestational age (weeks)	0.872	−0.137	0.052	7.011	0.008
Maternal iFGF-23 (pg/mL)	1.011	0.011	0.005	4.345	0.037

Note: BMI, body mass index, was calculated at the beginning of the pregnancy. Recurrent pregnancy loss: two or more miscarriages. Gestational age refers to the week of gestation at the time of birth.

patients with diabetes and may account for these differences. However, our data do not favour this hypothesis since these confounding factors that are known to stimulate FGF23 do not play a key role in a general birth cohort.

One small study conducted in patients from Malaysia with GDM showed contrary results to the current study: lower FGF23 concentrations. Three factors might explain this discrepancy: the sample size was several times smaller, multivariable analyses were not performed, and the ethnic background of the study population was different, with genetic and dietary implications for FGF23 homoeostasis.[34] Further research has to be done to understand why the relationship of insulin to FGF23 changes substantially when an individual gets diabetes using a well-designed basic science study.

TABLE 5 Subgroup binary logistic regression analysis models for gestational diabetes.

	OR	β	S.E.	Wald	*p* value
A. Women with BMI below 18.5 kg/m^2					
Model 1					
(Constant)	<0.0001	−49.509	40,192.968	<0.0001	0.999
Age (years)	1.091	0.087	0.120	0.525	0.469
BMI (kg/m^2)	39.857	3.685	2.643	1.944	0.163
Ethnic background (unclear)	Ref.	Ref.	Ref.	0.040	0.980
Ethnic background (Caucasian)	<0.0001	−23.213	40,192.938	<0.0001	>0.999
Ethnic background (Asian)	<0.0001	−22.873	40,192.938	<0.0001	>0.999
Maternal iFGF-23 (pg/mL)	1.044	0.043	0.031	1.903	0.168
Model 2					
(Constant)	<0.0001	−61.478	40,192.995	<0.0001	0.999
Age (years)	1.318	0.276	0.275	1.010	0.315
BMI (kg/m^2)	63.257	4.147	3.398	1.490	0.222
Ethnic background (unclear)	Ref.	Ref.	Ref.	0.703	0.704
Ethnic background (Caucasian)	<0.0001	−23.376	40,192.943	<0.0001	>0.999
Ethnic background (Asian)	<0.0001	−21.410	40,192.943	<0.0001	>0.999
Diabetes in family (no)	0.028	−3.574	3.775	0.896	0.344
Smoking during pregnancy (no)	0.056	−2.888	3.125	0.854	0.355
Maternal iFGF-23 (pg/mL)	1.085	0.082	0.067	1.507	0.220
Model 3					
(Constant)	<0.0001	−75.086	48,090.451	<0.0001	0.999
Age (years)	1.311	0.271	0.275	0.972	0.324
BMI (kg/m^2)	41.590	3.728	3.365	1.227	0.268
Ethnic background (unclear)	Ref.	Ref.	Ref.	0.538	0.764
Ethnic background (Caucasian)	<0.0001	−23.734	40,192.962	<0.0001	>0.999
Ethnic background (Asian)	<0.0001	−21.941	40,192.962	<0.0001	>0.999
Diabetes in family (no)	0.038	−3.271	3.725	0.771	0.380

TABLE 5 (Continued)

	OR	β	S.E.	Wald	*p* value
Smoking during pregnancy (no)	0.049	−3.023	3.190	0.898	0.343
Recurrent pregnancy loss (no)	38,522,939.235	17.467	26,404.796	<0.0001	0.999
Gestational age (weeks)	1.117	0.111	0.337	0.108	0.743
Maternal iFGF-23 (pg/mL)	1.095	0.090	0.075	1.453	0.228
B. Women with BMI equal or above 18.5 kg/m^2					
Model 1					
(Constant)	0.0002	−8.486	1.610	27.779	<0.0001
Age (years)	1.119	0.113	0.028	15.822	<0.0001
BMI (kg/m^2)	1.087	0.083	0.024	11.691	0.001
Ethnic background (unclear)	Ref.	Ref.	Ref.	2.913	0.405
Ethnic background (Caucasian)	0.884	−0.123	1.084	0.013	0.909
Ethnic background (African)	3.547	1.266	1.347	0.883	0.347
Ethnic background (Asian)	1.318	0.276	1.308	0.045	0.833
Maternal iFGF-23 (pg/mL)	1.015	0.015	0.006	6.649	0.010
Model 2					
(Constant)	0.0003	−8.043	1.715	21.994	<0.0001
Age (years)	1.109	0.103	0.029	12.229	0.0005
BMI (kg/m^2)	1.111	0.105	0.026	16.941	<0.0001
Ethnic background (unclear)	Ref.	Ref.	Ref.	2.506	0.474
Ethnic background (Caucasian)	1.320	0.278	1.139	0.059	0.807
Ethnic background (African)	4.785	1.565	1.397	1.255	0.263
Ethnic background (Asian)	1.749	0.559	1.362	0.169	0.681
Diabetes in family (no)	1.129	0.122	0.348	0.123	0.726
Smoking during pregnancy (no)	0.397	−0.925	0.445	4.322	0.038
Maternal iFGF-23 (pg/mL)	1.011	0.011	0.005	5.169	0.023
Model 3					
(Constant)	0.134	−2.007	2.789	0.518	0.472
Age (years)	1.091	0.087	0.031	8.051	0.005
BMI (kg/m^2)	1.104	0.099	0.026	14.594	0.0001
Ethnic background (unclear)	Ref.	Ref.	Ref.	3.613	0.306
Ethnic background (Caucasian)	1.518	0.417	1.239	0.113	0.736
Ethnic background (African)	7.504	2.015	1.497	1.812	0.178
Ethnic background (Asian)	1.862	0.622	1.460	0.181	0.670
Diabetes in family (no)	1.170	0.157	0.357	0.194	0.659
Smoking during pregnancy (no)	0.439	−0.824	0.475	3.005	0.083
Recurrent pregnancy loss (no)	0.604	−0.504	0.416	1.465	0.226
Gestational age (weeks)	0.872	−0.137	0.055	6.082	0.014
Maternal iFGF-23 (pg/mL)	1.011	0.011	0.005	4.448	0.035

Note: BMI, body mass index, was calculated at the beginning of the pregnancy. Recurrent pregnancy loss: two or more miscarriages. Gestational age refers to the week of gestation at the time of birth.

Foetal or blastocyst-related factors might contribute to the development of GDM in mothers.[42–44] However, this was not the case in our study regarding foetal FGF23 (Supporting Information S1: Figure S1).

This study has several strengths and limitations. A study strength is that we analysed iFGF23 and cFGF23 in mothers and their newborns. However, this cross-section analysis cannot further draw conclusion on causality; serial measurements of these parameters in the mothers would have also been of interest. Furthermore, since the prevalence of GDM depends significantly on the ethnic background, it is a limitation that we mainly analysed European women.

5 | CONCLUSION

In conclusion, our study in a representative European birth cohort provides robust evidence indicating that maternal (not foetal) intact FGF23 (not cFGF23) is associated with GDM.

AUTHOR CONTRIBUTIONS

Carl-Friedrich Hocher measured samples, researched data and wrote the manuscript. Xin Chen and Jiao Zuo researched data. Katarina Horvathova measured samples. Berthold Hocher and Bernhard K. Krämer contributed to the discussion. Chang Chu researched data, wrote and reviewed the manuscript. Dr. Chang Chu is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

The authors have nothing to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The ethics committee of the Charité - Universitätsmedizin Berlin approved this study (No.: EA1/175/08).

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PEER REVIEW

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REFERENCES

1. Rausch S, Foller M. The regulation of FGF23 under physiological and pathophysiological conditions. *Pflugers Arch*. 2022;474(3):281-292. https://doi.org/10.1007/s00424-022-02668-w
2. Bar L, Stournaras C, Lang F, Foller M. Regulation of fibroblast growth factor 23 (FGF23) in health and disease. *FEBS Lett*. 2019; 593(15):1879-1900. https://doi.org/10.1002/1873-3468.13494
3. Lang F, Leibrock C, Pandyra AA, Stournaras C, Wagner CA, Foller M. Phosphate homeostasis, inflammation and the regulation of FGF-23. *Kidney Blood Press Res*. 2018;43(6):1742-1748. https://doi.org/10.1159/000495393
4. Donate-Correa J, Martin-Nunez E, Gonzalez-Luis A, et al. Pathophysiological implications of imbalances in fibroblast growth factor 23 in the development of diabetes. *J Clin Med*. 2021;10(12):2583. https://doi.org/10.3390/jcm10122583
5. Mirza MA, Alsio J, Hammarstedt A, et al. Circulating fibroblast growth factor-23 is associated with fat mass and dyslipidemia in two independent cohorts of elderly individuals. *Arterioscler Thromb Vasc Biol*. 2011;31(1):219-227. https://doi.org/10.1161/atvbaha.110.214619
6. Wojcik M, Dolezal-Oltarzewska K, Janus D, Drozdz D, Sztefko K, Starzyk JB. FGF23 contributes to insulin sensitivity in obese adolescents - preliminary results. *Clin Endocrinol*. 2012;77(4):537-540. https://doi.org/10.1111/j.1365-2265.2011.04299.x
7. Garland JS, Holden RM, Ross R, et al. Insulin resistance is associated with fibroblast growth factor-23 in stage 3-5 chronic kidney disease patients. *J Diabetes Complicat*. 2014;28(1):61-65. https://doi.org/10.1016/j.jdiacomp.2013.09.004
8. Hanks LJ, Casazza K, Judd SE, Jenny NS, Gutierrez OM. Associations of fibroblast growth factor-23 with markers of inflammation, insulin resistance and obesity in adults. *PLoS One*. 2015;10(3):e0122885. https://doi.org/10.1371/journal.pone.0122885
9. Vervloet MG, van Zuilen AD, Heijboer AC, et al. Fibroblast growth factor 23 is associated with proteinuria and smoking in chronic kidney disease: an analysis of the MASTERPLAN cohort. *BMC Nephrol*. 2012;13(1):20. https://doi.org/10.1186/1471-2369-13-20
10. Schoppet M, Hofbauer LC, Brinskelle-Schmal N, et al. Serum level of the phosphaturic factor FGF23 is associated with abdominal aortic calcification in men: the STRAMBO study. *J Clin Endocrinol Metab*. 2012;97(4):E575-E583. https://doi.org/10.1210/jc.2011-2836
11. Hu X, Ma X, Luo Y, et al. Elevation in fibroblast growth factor 23 and its value for identifying subclinical atherosclerosis in first-degree relatives of patients with diabetes. *Sci Rep*. 2016;6(1):34696. https://doi.org/10.1038/srep34696
12. Wahl P, Xie H, Scialla J, et al. Earlier onset and greater severity of disordered mineral metabolism in diabetic patients with chronic kidney disease. *Diabetes Care*. 2012;35(5):994-1001. https://doi.org/10.2337/dc11-2235
13. Donate-Correa J, Martin-Nunez E, Hernandez-Carballo C, et al. Fibroblast growth factor 23 expression in human calcified vascular tissues. *Aging*. 2019;11(18):7899-7913. https://doi.org/10.18632/aging.102297
14. Gateva A, Assyov Y, Tsakova A, Kamenov Z. Prediabetes is characterized by higher FGF23 levels and higher prevalence of vitamin D deficiency compared to normal glucose tolerance subjects. *Horm Metab Res*. 2019;51(2):106-111. https://doi.org/10.1055/a-0813-3164
15. Fernandez-Real JM, Puig J, Serrano M, et al. Iron and obesity status-associated insulin resistance influence circulating fibroblast-growth factor-23 concentrations. *PLoS One*. 2013;8(3):e58961. https://doi.org/10.1371/journal.pone.0058961
16. Bar L, Feger M, Fajol A, et al. Insulin suppresses the production of fibroblast growth factor 23 (FGF23). *Proc Natl Acad Sci U S A*. 2018; 115(22):5804-5809. https://doi.org/10.1073/pnas.1800160115

17. Hocher B, Slowinski T, Stolze T, Pleschka A, Neumayer HH, Halle H. Association of maternal G protein beta3 subunit 825T allele with low birthweight. *Lancet*. 2000;355(9211):1241-1242. https://doi.org/10.1016/s0140-6736(00)02094-8
18. Pfab T, Slowinski T, Godes M, Halle H, Priem F, Hocher B. Low birth weight, a risk factor for cardiovascular diseases in later life, is already associated with elevated fetal glycosylated hemoglobin at birth. *Circulation*. 2006;114(16):1687-1692. https://doi.org/10.1161/circulationaha.106.625848
19. Nair AV, Hocher B, Verkaart S, et al. Loss of insulin-induced activation of TRPM6 magnesium channels results in impaired glucose tolerance during pregnancy. *Proc Natl Acad Sci U S A*. 2012;109(28):11324-11329. https://doi.org/10.1073/pnas.1113811109
20. Putra SED, Reichetzeder C, von Websky K, et al. Association between placental global DNA methylation and blood pressure during human pregnancy. *J Hypertens*. 2022;40(5):1002-1009. https://doi.org/10.1097/hjh.0000000000003103
21. Tsuprykov O, Elitok S, Buse C, Chu C, Kramer BK, Hocher B. Opposite correlation of 25-hydroxy-vitamin D- and 1,25-dihydroxy-vitamin D-metabolites with gestational age, bone- and lipid-biomarkers in pregnant women. *Sci Rep*. 2021;11(1):1923. https://doi.org/10.1038/s41598-021-81452-9
22. Dwi Putra SE, Reichetzeder C, Hasan AA, et al. Being born large for gestational age is associated with increased global placental DNA methylation. *Sci Rep*. 2020;10(1):927. https://doi.org/10.1038/s41598-020-57725-0
23. Lu YP, Reichetzeder C, Prehn C, et al. Fetal serum metabolites are independently associated with gestational diabetes mellitus. *Cell Physiol Biochem*. 2018;45(2):625-638. https://doi.org/10.1159/000487119
24. Warrington NM, Beaumont RN, Horikoshi M, et al. Maternal and fetal genetic effects on birth weight and their relevance to cardio-metabolic risk factors. *Nat Genet*. 2019;51(5):804-814. https://doi.org/10.1038/s41588-019-0403-1
25. Chu C, Elitok S, Zeng S, et al. C-terminal and intact FGF23 in kidney transplant recipients and their associations with overall graft survival. *BMC Nephrol*. 2021;22(1):125. https://doi.org/10.1186/s12882-021-02329-7
26. Enlund-Cerullo M, Hauta-Alus H, Valkama S, et al. Fibroblast growth factor 23 concentrations and modifying factors in children from age 12 to 24 months. *Bone*. 2020;141:115629. https://doi.org/10.1016/j.bone.2020.115629
27. Leaf DE, Siew ED, Eisenga MF, et al. Fibroblast growth factor 23 associates with death in critically ill patients. *Clin J Am Soc Nephrol*. 2018;13(4):531-541. https://doi.org/10.2215/cjn.10810917
28. Kleinwechter H, Schafer-Graf U, Buhrer C, et al. Gestational diabetes mellitus (GDM) diagnosis, therapy and follow-up care: practice guideline of the German diabetes association(DDG) and the German association for gynaecologyand obstetrics (DGGG). *Exp Clin Endocrinol Diabetes*. 2014;122(7):395-405. https://doi.org/10.1055/s-0034-1366412
29. Kharitonenkov A. FGFs and metabolism. *Curr Opin Pharmacol*. 2009;9(6):805-810. https://doi.org/10.1016/j.coph.2009.07.001
30. Nakashima A, Yokoyama K, Kawanami D, et al. Association between resistin and fibroblast growth factor 23 in patients with type 2 diabetes mellitus. *Sci Rep*. 2018;8(1):13999. https://doi.org/10.1038/s41598-018-32432-z
31. Yeung SMH, Bakker SJL, Laverman GD, De Borst MH. Fibroblast growth factor 23 and adverse clinical outcomes in type 2 diabetes: a bitter-sweet symphony. *Curr Diab Rep*. 2020;20(10):50. https://doi.org/10.1007/s11892-020-01335-7
32. Kizilgul M, Kan S, Beysel S, et al. Is fibroblast growth factor 23 a new cardiovascular risk marker in gestational diabetes? *Arch Endocrinol Metab*. 2017;61(6):562-566. https://doi.org/10.1590/2359-3997000000287
33. Tuzun D, Oguz A, Aydin MN, et al. Is FGF-23 an early indicator of atherosclerosis and cardiac dysfunction in patients with gestational diabetes? *Arch Endocrinol Metab*. 2018;62(5):506-513. https://doi.org/10.20945/2359-3997000000070
34. Mosavat M, Omar SZ, Sthanshewar P. Serum FGF-21 and FGF-23 in association with gestational diabetes: a longitudinal case-control study. *Horm Mol Biol Clin Investig*. 2020;41(2). https://doi.org/10.1515/hmbci-2019-0060
35. Wolf M, White KE. Coupling fibroblast growth factor 23 production and cleavage: iron deficiency, rickets, and kidney disease. *Curr Opin Nephrol Hypertens*. 2014;23(4):411-419. https://doi.org/10.1097/01.mnh.0000447020.74593.6f
36. Jonsson KB, Zahradnik R, Larsson T, et al. Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. *N Engl J Med*. 2003;348(17):1656-1663. https://doi.org/10.1056/nejmoa020881
37. Ratsma DMA, Zillikens MC, van der Eerden BCJ. Upstream regulators of fibroblast growth factor 23. *Front Endocrinol*. 2021;12:588096.
38. Garbe C, McLeod GR, Buettner PG. Time trends of cutaneous melanoma in Queensland, Australia and central Europe. *Cancer*. 2000;89(6):1269-1278. https://doi.org/10.1002/1097-0142(20000915)89:6<1269::aid-cncr11>3.0.co;2-c
39. Mareckova K, Klasnja A, Andryskova L, Brazdil M, Paus T. Developmental origins of depression-related white matter properties: findings from a prenatal birth cohort. *Hum Brain Mapp*. 2019;40(4):1155-1163. https://doi.org/10.1002/hbm.24435
40. McBride D, Keil T, Grabenhenrich L, et al. The EuroPrevall birth cohort study on food allergy: baseline characteristics of 12,000 newborns and their families from nine European countries. *Pediatr Allergy Immunol*. 2012;23(3):230-239. https://doi.org/10.1111/j.1399-3038.2011.01254.x
41. Winther K, Nybo M, Vind B, Pedersen SM, Hojlund K, Rasmussen LM. Acute hyperinsulinemia is followed by increased serum concentrations of fibroblast growth factor 23 in type 2 diabetes patients. *Scand J Clin Lab Invest*. 2012;72(2):108-113. https://doi.org/10.3109/00365513.2011.640407
42. Hocher B, Schlemm L, Haumann H, et al. Offspring sex determines the impact of the maternal ACE I/D polymorphism on maternal glycaemic control during the last weeks of pregnancy. *J Renin Angiotensin Aldosterone Syst*. 2011;12(3):254-261. https://doi.org/10.1177/1470320310387843
43. Hocher B, Schlemm L, Haumann H, et al. Interaction of maternal peroxisome proliferator-activated receptor gamma2 Pro12Ala polymorphism with fetal sex affects maternal glycemic control during pregnancy. *Pharmacogenet Genomics*. 2010;20(2):139-142. https://doi.org/10.1097/fpc.0b013e3283357337
44. Chen H, Li J, Cai S, et al. Blastocyst transfer: a risk factor for gestational diabetes mellitus in women undergoing in vitro fertilization. *J Clin Endocrinol Metab*. 2022;107(1):e143-e152. https://doi.org/10.1210/clinem/dgab594

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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