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Metabolic characteristics and adverse pregnancy outcomes for women with hyperglycaemia in pregnancy as a function of insulin resistance

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Short title: Insulin resistance and hyperglycaemia in pregnancy

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Disclosure summary

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Highlights

- In previous studies, women with pregnancies complicated by hyperglycaemia in pregnancy (HIP) and insulin resistance (IR), but not those without IR, had a greater risk of adverse pregnancy outcomes than those with normoglycaemic pregnancies
- Considering only women with HIP, we found that HOMA-IR index was positively associated with insulin therapy, gestational hypertension, preeclampsia, large-for-gestational-age infants and neonatal hypoglycaemia
- The association between a high HOMA-IR and insulin therapy, hypertensive disorders and large-for-gestational-age infants remained after adjustment for confounders, including body mass index
- On clinical practice, HIP stratification according to presence of IR might help decision makers adapt care to prevent adverse pregnancy outcomes

Abstract

Aim. - Recent studies have shown that women with hyperglycaemia in pregnancy and insulin resistance have a greater risk of adverse pregnancy outcomes than women with normoglycaemic pregnancies. This study aimed to determine adverse pregnancy outcomes of women with hyperglycaemia in pregnancy only as a function of insulin resistance.

Methods. - From a prospective cohort study, we included 1,423 women with hyperglycaemia in pregnancy whose insulin resistance was evaluated using homeostatic model assessment for insulin resistance (HOMA-IR) when care was first provided for this condition. We compared the adverse pregnancy outcomes for different tertiles of HOMA-IR (intertertile range 1.9 and 3.3).

Results. - Increasing HOMA-IR tertiles were positively associated with the rate of insulin therapy (tertile 1, 2 and 3: 32.7, 47.0 and 58.7%, $P < 0.0001$), caesarean section (23.7, 26.0 and 32.2%, respectively, $P < 0.01$), gestational hypertension (1.3, 2.8 and 5.4% respectively, $P < 0.01$), preeclampsia (1.5, 2.8 and 4.5% respectively, $P < 0.05$), large-for-gestational-age infant (13.3, 10.4 and 17.6% respectively, $P < 0.05$), and neonatal hypoglycaemia (0.8, 1.5 and 3.2% respectively, $P < 0.05$). Women in the 3rd HOMA-IR tertile were more likely to have insulin therapy (odds ratio 2.09 (95% interval confidence 1.61-2.71)), hypertensive disorders (2.26 (1.42-3.36)), and large-for-gestational-age infant (1.42 (1.01-1.99)) than those in the 1st and 2nd tertiles combined in multivariable logistic regression analyses adjusted for gestational age at HOMA-IR measurement, glycaemic status, age, body mass index, family history of diabetes, parity and ethnicity.

Conclusion. - Despite suitable care and increased rates of insulin therapy during pregnancy, higher insulin resistance in women with hyperglycaemia in pregnancy was associated with a greater risk of adverse pregnancy outcomes.

Keywords: Diabetes in pregnancy; Gestational diabetes mellitus; HOMA-B, HOMA-IR; Oral glucose tolerance test; Pregnancy outcomes

Abbreviations:

1h-PG: plasma glucose value 1 hour after 75g oral glucose tolerance test

2h-PG: plasma glucose value 2 hours after 75g oral glucose tolerance test

BMI: body mass index

DIP: diabetes in pregnancy

FPG: fasting plasma glucose

GDM: gestational diabetes mellitus

HIP: hyperglycaemia in pregnancy

HOMA-B: homeostatic model assessment of beta cell function

HOMA-IR: homeostatic model assessment for insulin resistance

IADPSG: International Association of Diabetes Pregnancy Study Group

IR: insulin resistance

OGTT: 75-g oral glucose tolerance test

WG: weeks of gestation

WHO: World Health Organisation

Introduction

The term hyperglycaemia in pregnancy (HIP) corresponds to the discovery of one of the three following hyperglycaemic states during pregnancy: early-diagnosed gestational diabetes mellitus (eGDM), gestational diabetes mellitus (GDM) (diagnosed at the end of the 2nd or during the 3rd trimester), and diabetes in pregnancy (DIP). DIP is defined as having glucose values during screening equal to or higher than the thresholds defining diabetes outside pregnancy. DIP diagnosis suggests undiagnosed type 2 diabetes before pregnancy [1–4]. HIP results from elevated insulin resistance (IR) insufficiently balanced by increased insulin secretion (i.e., relative defective insulin secretion) [5,6]. HIP is more frequent in persons diagnosed with overweightness, hypertension, dyslipidaemia and polycystic ovarian syndrome, all these conditions being related to IR [7–9]. The rate of HIP also increases with age [7,8], partly due to a lower capacity of insulin secretion as people get older. IR appears to be the main driver of HIP [10,11].

Several studies have recently shown that HIP may display different characteristics and have a different prognosis depending on the presence or not of IR and insulin secretion capacity [12]. More specifically, their results highlighted that women with IR required insulin treatment more often than those without IR, with higher insulin doses being prescribed [13,14]. Furthermore, compared with normoglycaemic pregnancies, HIP pregnancies were more complicated for women with IR [10,14–16] and for those with both IR and defective insulin secretion [17,18], but not for those who only had the latter condition. Most all studies [15–18] but two [14,19] were unable to compare, only in women with HIP, adverse pregnancy outcomes according to IR and/or defective insulin secretion. The latter two studies did not have multi-ethnic cohorts, and included only Chinese women [14,19]. Although they explored a small number of outcomes, they did not study the core set of outcomes for HIP studies proposed by the INSPIRED research group [20].

In this context, we conducted a multi-ethnic prospective French cohort study, which aimed to investigate whether HIP pregnancies have a poorer prognosis if IR is also present, after adjustment for confounders.

Material and methods

- Data collection

This observational prospective cohort study was conducted in Jean Verdier University hospital in Bondy, a suburb of Paris, France. Analyses were based on the hospital's data from routine electronic medical records of maternal and neonatal events at birth which occurred between January 2012 and December 2018 [8,21–23]. In addition, we collected data on HIP screening for all the women who gave birth during this period. In Jean Verdier hospital and in general in the other Public Assistance Hospitals in Paris, all patients are informed at admission that their medical records may be used for research, unless they indicate their opposition [8,21–23]. Data were analysed anonymously. Our database was declared to the French Committee for computerized data (CNIL: Commission Nationale de l'Informatique et des Libertés, number 1704392v0).

- HIP screening and care

In Jean Verdier University hospital, we follow French recommendations for HIP screening, diagnostic criteria and care [4], except that we perform universal rather selective screening. Screening is performed both at the beginning of women's pregnancies and after 24 weeks of gestation (WG) when prior screening is not performed or returns a normal result. Early screening during pregnancy is based on fasting plasma glucose (FPG) measurement. Women with an FPG level between 5.1 and 6.9 mmol/l are diagnosed with eGDM, and those with an

FPG \geq 7.0 mmol/l with DIP. Women diagnosed with either of these two hyperglycaemic states in early pregnancy are promptly provided care for HIP.

Women who are not diagnosed early with HIP undergo a 75g oral glucose tolerance test (OGTT) between 24 and 28 WG, with measurement of plasma glucose at fasting, and then 1 and 2 hours after OGTT (1h-PG and 2h-PG, respectively) [4]. The International Association of Diabetes Pregnancy Study Group (IADPSG) [1] / World Health Organisation (WHO) recommendations [2] are used to diagnose HIP, as these guidelines are endorsed in France [4]. Accordingly, GDM is defined as FPG 5.1-6.9 mmol/l and/or 1h-PG \geq 10.0 mmol/l and/or 2h-PG 8.5-11.0 mmol/l in OGTT, whereas DIP is defined as FPG \geq 7.0 and/or 2-h PG \geq 11.1 mmol/l.

- Selection criteria for the present study

Inclusion criteria for the present study were as follows: HIP diagnosis but no known diabetes before pregnancy, aged 18 to 50 years old, single foetus pregnancy, no personal history of bariatric surgery, IR level measurement using the homeostasis model assessment (HOMA) method (HOMA-IR) (performed when care was first provided for HIP) (Flow chart in [Figure S1](#); see supplementary materials associated with this article on line).

- Evaluation of IR and insulin deficiency

The levels of IR and insulin secretion (beta-cell function) were evaluated using the HOMA-IR and beta-cell function (HOMA-B) methods, based on FPG and insulin levels on the day care was first provided for HIP [24]. Therefore, no woman was insulin-treated at the time of measurement. Moreover, our routine had no selection criteria to measure insulin level. The following formulas were used to measure the respective levels: HOMA-IR = fasting plasma insulin concentration (mIU/ml) \times FPG (mmol/l) / 22.5, and HOMA-B = 20 \times fasting plasma

insulin concentration (mIU/ml) / (FPG [mmol/l] - 3.5). HOMA-B could only be calculated for women with FPG > 3.5 mmol/l. Higher HOMA-IR values indicated higher levels of IR.

- Data collection

Pre-pregnancy weight and waist circumference (classified into three categories: < 80, 80-88 and > 88 cm) were self-reported. Height was measured. Gestational weight gain was defined as weight measured before delivery minus self-reported pre-pregnancy weight. Ethnicity was self-reported as European, North African, Sub-Saharan African, Indian-Pakistan-Sri Lankan, Caribbean, or Other.

FPG concentration was assessed using the enzymatic reference method with hexokinase (Cobas c 501 analyzer, Roche Diagnostics, France). Insulin level was measured in serum samples using the Roche Cobas® electrochemiluminescence immunometric assay (Cobas e 601 analyzer, Roche Diagnostics, France). The intra-assay coefficient of variation (repeatability) was 3.7% and the inter-assay coefficient of variation (reproducibility) was 4.6%.

- Outcomes

In order to examine the association of IR level on adverse pregnancy outcomes, we considered the following set of outcomes, entitled ‘maternal’ and ‘neonatal’ outcomes by the INSPIRED research group (the same terms are used in the Results section below): maternal outcomes included HIP diagnosis, hypertensive disorders, pharmacological therapy for HIP (i.e., only insulin in France), gestational weight gain, and mode of birth; neonatal outcomes included birth weight, large-for-gestational-age (LGA), small-for-gestational-age, gestational age at birth, preterm birth, neonatal hypoglycaemia, neonatal death and stillbirth [20].

Gestational hypertension was defined by the onset of hypertension (blood pressure \geq 140 mmHg systolic or \geq 90 mmHg diastolic) at or after 20 WG, in the absence of proteinuria and without biochemical or haematological abnormalities. When earlier blood pressure values were unknown, they were considered to be normal. Preeclampsia was defined as having blood pressure \geq 140/90 mmHg for two measurements four hours apart, and proteinuria of at least 300 mg/24 hours or a 3+ level with dipstick testing in a random urine sample, and/or evidence of maternal acute kidney injury, liver dysfunction, neurological features, haemolysis or thrombocytopenia, and/or foetal growth restriction. Hypertensive disorders were defined as gestational hypertension or preeclampsia. We also considered selective and emergency (before or during delivery) caesarean sections.

LGA and small-for-gestational-age were defined as a birth weight greater than the 90th percentile and lower than the 10th percentile for a standard French population, respectively [25]. Preterm birth was defined as occurring before 37 WG [8,21–23] and neonatal hypoglycaemia as at least one blood glucose measurement under 2.5 mmol/l during the first two days of life. Blood glucose levels were measured at one hour and three hours of life and then every six hours. Finally, we also considered intrauterine foetal and neonatal death (in the first 24 hours of life).

All women diagnosed with HIP were referred to our multidisciplinary team comprising a diabetologist, an obstetrician, a midwife, a dietician and a nurse educator. Care was provided in accordance with French recommendations. These women received individually tailored dietary advice and instructions on how to perform self-monitoring of blood glucose levels six times a day. They were seen by the diabetologist every two to four weeks. In accordance with French guidelines, they received insulin therapy when pre-prandial and 2-hour post-prandial glucose levels were greater than 5.0 and 6.7 mmol/l, respectively [4]. For information, oral hypoglycaemic agents are not currently used during pregnancy in France. The obstetrical care

provided also followed French recommendations [4]. More specifically, a 37-week ultrasound scan was used for foetal weight estimation to discuss the timing and mode of delivery with the patient and obstetric staff. During the 39th gestational week, labour induction (using prostaglandin E2 or oxytocin infusion) or caesarean section was decided according to obstetric history, maternal condition, and estimated foetal weight. Labour was induced in case of LGA foetus. Elective Caesarean section was planned if estimated foetal weight was > 4,250 to 4,500 g.

- Statistical analyses

Baseline continuous variables were expressed as mean \pm standard deviation (SD). Categorical variables were expressed as frequencies (percentages). No data replacement procedure was used for missing data. To control for selection bias, baseline metabolic characteristics of the women included were compared with those of the women not included ([Table S1; see supplementary materials associated with this article on line](#)). Student's t test and the chi-squared (χ^2) test were used to compare continuous variables, while Fisher's exact test was used to compare categorical variables. Metabolic characteristics of the study sample and adverse pregnancy outcomes were compared according to HOMA-IR tertiles ([Table I](#)) with ANOVA and the χ^2 test for continuous variables, and Fisher's exact test for categorical variables. We performed a post hoc analysis to make inter-group comparisons of the characteristics of women in the three different tertiles using Bonferroni's alpha risk correction for multiplicity. Because IR varies throughout pregnancy – with an increase in the latter part of the 2nd trimester [11] – we performed a sensitivity analysis considering only women who had HOMA-IR measured after 22 WG ([Table S2; see supplementary materials associated with this article on line](#)).

We also compared the rates of insulin therapy, caesarean section, hypertensive disorders, LGA infant, small-for-gestational-age infant, and preterm delivery in women in the 3rd tertile of HOMA-IR with those for women in the 1st and 2nd tertiles (combined) using multivariable logistic regression analyses adjusted for the following confounders: model 1=unadjusted; model 2=adjusted for body mass index (BMI) and gestational age at HOMA-IR measurement; model 3=adjusted for maternal age and gestational age at HOMA-IR measurement; model 4=adjusted for HOMA-B and gestational age at HOMA-IR measurement; model 5=adjusted for glycaemic status, age, BMI, family history of diabetes, parity, ethnicity and gestational age at HOMA-IR measurement; model 6=model 5 + adjusted for HOMA-B; model 7=model 6 + adjusted for gestational weight gain and model 8=model 7 + adjusted for insulin therapy during pregnancy (Table II).

All tests were two-sided. Analyses were conducted using R 3.6.3 software (R foundation, Vienna, Austria, <https://cran.r-project.org>).

Results

- Study population's metabolic characteristics

Among the 2,686 women who met the inclusion criteria (Figure S1; see supplementary materials associated with this article on line), the 1,423 who had a HOMA-IR measurement were included (study sample). Table S1 (see supplementary materials associated with this article on line) compares the study sample with the 1,263 eligible women with no HOMA-IR measurement. Women in the study sample were more likely to have eGDM, to have had HIP in previous pregnancies, and a family history of diabetes. They were also older (on average +1 year) and had higher BMI (+0.7 kg/m²) and parity (+0.15).

Table I shows the metabolic characteristics of the study population.

- Metabolic characteristics of women in study sample with HIP according to HOMA-IR tertiles

Increasing tertiles of HOMA-IR were positively associated with the following metabolic characteristics: plasma glucose levels during HIP screening; glycaemic status; pre-pregnancy BMI; waist circumference; family history of diabetes; HIP, macrosomia, and hypertensive disorders all during previous pregnancies (three separate variables); and non-European ethnicity (Table I).

- Maternal outcomes according to increasing HOMA-IR tertile

Table I shows that each consecutively higher HOMA-IR tertile was associated with a higher percentage for the following adverse pregnancy outcomes: insulin treatment during pregnancy, caesarean section, gestational hypertension, and preeclampsia. In contrast, gestational weight gain was similar for all three tertiles.

In the multivariable regression analyses, women in the 3rd tertile were more likely to need insulin therapy than those in the 1st and 2nd tertiles (combined) for all models, including model 7 (i.e., adjusted for glycaemic status, age, BMI, family history of diabetes, parity, ethnicity, HOMA-B, gestational age at HOMA-IR measurement and gestational weight gain: odds ratio (OR) 2.02 [95% confidence interval 1.54-2.67]). They were also more likely to have both a higher rate of caesarean section after adjustment for gestational age at HOMA-IR measurement and BMI (OR 1.05 [1.03-1.07]), and age (OR 1.44 [1.13-1.83]), and HOMA-B (OR 1.44 [1.13-1.85]) and hypertensive disorders for all models including model 8 (i.e., model 7 + adjusted for insulin therapy (OR 2.05 [1.26-3.38]) (Table II).

- Neonatal outcomes according to HOMA-IR tertile

Table I also shows that women in the third HOMA-IR tertile gave birth to the heaviest newborns, with an increasing rate of LGA infant as a function of increasing HOMA-IR tertile in the study sample. Likewise, the higher the HOMA-IR tertile, the higher the rate of neonatal hypoglycaemia.

In the multivariable regression analyses, women in the 3rd tertile of HOMA-IR had a higher rate of LGA infant than women in the 1st and 2nd tertiles (combined), after adjustment for all models but model 8 (considering gestational weight gain). The OR in model 7 was 1.45 [1.02-2.07] (Table II).

- Sensitivity analysis considering women with a HOMA-IR measurement at 22 WG or later
Mean HOMA-IR in the 1,190 women who had their HOMA-IR measured at 22 WG or later (3.13 ± 2.67 (inter-tertile range 1.93 and 3.26)) was similar to that in the 233 women with a measurement before 22 WG (3.14 ± 0.56 (inter-tertile range 2.01 and 3.28)). We explored metabolic characteristics and adverse pregnancy outcomes by tertiles of HOMA-IR in the former group. The results were similar to those for the whole study sample ([Table S2; see supplementary materials associated with this article on line](#)).

Discussion

This study shows that the presence of IR in women with HIP was associated with a poorer adverse metabolic profile, including abdominal obesity, higher glycaemic values at HIP screening, and HIP, macrosomia and hypertensive disorders during previous pregnancies. IR was also associated with a greater risk of adverse pregnancy outcomes despite suitable care, and in particular, higher rates of insulin therapy during pregnancy. Interestingly, after

adjusting for numerous confounders, including BMI, IR remained positively associated with insulin therapy, hypertensive disorders and LGA infant.

- Metabolic characteristics associated with IR

Obesity is constantly reported as a determinant of IR in women with HIP [10,13–16,26]. Our study confirms this and suggests that abdominal obesity is particularly to blame. Indeed, we found that the larger the pregravid waist circumference the higher the level of IR. Similarly, high blood pressure [15], high triglyceride and low HDL-cholesterol levels [14], and glucose values [14,15] have all been shown to be higher in case of IR. We also observed the association between glucose levels and the presence of IR in our study, with women who had the latter being more likely to have DIP. It has been suggested that women who are diagnosed with DIP already have abnormal glucose metabolism [27] and a higher baseline IR before they become pregnant than women diagnosed with GDM [28,29]. This would mean that their IR levels would increase even further during pregnancy because of the 60% decrease in insulin sensitivity [11]. Our results show that ethnicity and a family history of diabetes were also associated with higher IR, something which would suggest a genetic predisposition.

- IR and care for HIP

We did not find any association between IR and gestational weight gain, which reflects findings in two studies of pregnant women with and without HIP [10,15]. However, other studies found a positive association in Caucasian [13] and Chinese women with HIP [14,17]. In line with most [13,14], but not all [15,18] other studies, we found that women with HIP who had higher IR were more likely to have insulin therapy during pregnancy.

- IR and adverse pregnancy outcomes

A recent study showed that IR is a determinant of adverse pregnancy outcomes in a large cohort of women, irrespective of glycaemic status [10]. In that study, IR and insulin secretion measurements, combined with basic clinical variables, appeared to be superior to using HIP to predict pregnancy outcomes [10]. Furthermore, several studies have found that adverse pregnancy outcomes – especially LGA infant – were more frequent in pregnancies complicated by HIP than in normoglycaemic pregnancies, but only when IR was present, whether alone [10,14–16] or combined with defective insulin secretion [17,18]. However, unlike our present study, none of those studies had enough statistical power to compare the prognosis for HIP pregnancies where IR was present with HIP pregnancies where IR was not present [15–18].

Two recent studies, which like us, only included women with HIP according to IADPSG/WHO criteria, showed that higher IR was associated with a higher LGA infant rate [14,19]. In one of the two, this association disappeared after adjustment for age, BMI and gestational weight gain before HIP diagnosis [14], while in the other, it remained significant after adjustment for confounders including BMI [19]. IR was not associated with caesarean section, preterm delivery and small-for-gestational-age infant in the first study [14], whereas only LGA/macrosomia was investigated in the second [19]. To note in our study, the increase in neonatal hypoglycaemia and in caesarean section in women with IR was probably due in part to a higher rate of LGA infant in these women.

Importantly, our results highlight that women in the 3rd HOMA-IR tertile of our study sample had a higher rate of hypertensive disorders than those in the 1st and 2nd tertiles combined. Another study highlighted that women who developed preeclampsia have more adverse metabolic and biochemical profiles (including HOMA-IR index) than those without preeclampsia over mid- to long-term follow-up [30].

- Possible explanations for our results and implications for clinicians

Obesity is usual in case of IR and is associated with adverse pregnancy outcomes [7,8], independent of hyperglycaemia [8,31]. However, adjustment for BMI did not attenuate the association between IR and most adverse pregnancy outcomes in our study and others [15,16]. HOMA-IR was not associated with LGA infant any more in the multivariable model that included the need for insulin during pregnancy (model 8), suggesting that the increase in the rate of LGA infant could be partly due to difficulties to obtain good glycaemic control through diet alone in women with a high HOMA-IR. Inflammation [11], lipid disorders [14,32] and changes in adipocytokines [16] related to IR may explain the adverse pregnancy outcomes described in this work. It is known that visceral adipose tissue, which is partly responsible for IR, combined with the placenta produce a similar pattern of cytokines [33]. In clinical practice, when providing care to women with HIP, those identified with higher IR levels should be monitored for the possible onset of hypertensive disorders, and be prescribed suitable physical activity, as well as probiotic [34,35] and myo-inositol supplements [36,37]. Indeed, these products appear to reduce IR and therefore might improve pregnancy outcomes.

- Study strengths and limitations

The strengths of our study include *i*) a large study sample; *ii*) a multi-ethnic cohort, which suggests that our results are transferrable for different populations; and *iii*) a pragmatic guidance-based approach. With regard to the latter, the prospectively collected standardised data provided a robust investigational data set, enabling us to adjust our results for a large set of confounders. Among the latter, we considered a marker of insulin secretion, namely HOMA-B, which has previously been shown to be a predictor of adverse pregnancy outcomes [10]. We did not stratify the women with HIP according to either IR or defective insulin secretion or both, as performed in some studies [10,16–18]. Having said that, elsewhere

women with HIP and both IR and defective insulin secretion were found to have the highest HOMA-IR values [17]. Furthermore, HOMA-IR, but not HOMA-B, appears to be associated with adverse pregnancy outcomes in women with HIP [19]. Finally, insulin therapy may have attenuated the impact of IR on adverse pregnancy outcomes [10]; however, results were adjusted for insulin therapy.

Although the hyperinsulinaemic euglycaemic glucose clamp is the gold standard for determining IR, it is a complex and time-consuming procedure. Instead, we used as others [14,18,19] the HOMA-IR index which is based on a single measurement of glucose and insulin in the blood [24] and strongly correlates with clamp data [38]. Additionally, HOMA-IR has already been proven to be a robust clinical epidemiological tool in describing the pathophysiology of diabetes [39]. Other studies during pregnancy have used Matsuda index [10,15–18], which was not possible here because its calculation is also based on non-fasting glucose and insulin values. However, HOMA-IR and Matsuda index have shown to similarly correlate with clamp even during late pregnancy [40].

Finally, HOMA-IR measurements are known to increase during pregnancy, especially during the latter part of the 2nd trimester [41]. Our sensitivity analysis, which considered only those women with a HOMA-IR measured at 22 WG or later, showed that our results did not differ for this subpopulation. Furthermore, HOMA-IR values were similar before and after 22 WG in our cohort and adjustment for gestational age at HOMA-IR measurement did not change the result of the association between HOMA-IR and adverse outcomes in the multivariable analyses.

Conclusions

Our study suggests that HIP can be considered a heterogeneous disease in that its severity depends on the level of concomitant IR. Indeed, our results from this large French-based

multi-ethnic cohort of women with HIP showed an independent association between IR and gestational hypertension, preeclampsia, caesarean section, LGA infant and neonatal hypoglycaemia. Identifying women with HIP who also have IR might be useful to improve their surveillance (especially of hypertensive disorders during pregnancy), and help in the implementation of specific interventions to improve pregnancy outcomes. Tailor-made therapeutic studies are essential to evaluate this hypothesis.

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Author contributions.

EC supervised the study and wrote the first draft of the manuscript; EC, CN and HB designed the study; CN designed and performed the statistical analyses; EV and HB co-supervised the study; all authors contributed to the data collection, and especially EF and AS for biological data collection; all authors reviewed and edited the manuscript and approved its submission for publication. EC and LC are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Table I: Metabolic characteristics and adverse pregnancy outcomes according to HOMA-IR tertiles

	Available data	First tertile of HOMA-IR	Second tertile of HOMA-IR	Third tertile of HOMA-IR	Total	P-value
		n=469	n=470	n=484	n=1,423	
Insulin resistance and secretion indexes						
HOMA-IR [min-max]	n=1,423	0.035 - 1.937	1.943 - 3.262	3.264 - 36.60	0.035 - 36.60	
HOMA-IR	n=1,423	1.33 (0.44)*†	2.55 (0.374) ‡	5.44 (3.41)	3.13 (2.65)	< 0.001
HOMA-B	n=1,364	293 (345) *†	354 (391)	374 (381)	342 (375)	0.004
Gestational age at HOMA-IR measurement	n=1,423	28.29 (6.41)	28.00 (6.43)	27.66 (6.38)	27.63 (6.40)	0.286
Screening for HIP before 22 WG						
Fasting plasma glucose (mmol/L)	n=912	5.11 (0.70) †	5.12 (0.59) ‡	5.37 (1.08)	5.20 (0.82)	< 0.001
Gestational age at HIP screening (WG)	n=912	12.25 (7.67)	12.29 (4.31)	12.44 (4.50)	12.33 (5.68)	0.907
Screening with OGTT at 22 WG or later						
Fasting plasma glucose (mmol/L)	n=992	4.88 (0.63) *†	5.05 (0.61) ‡	5.38 (0.84)	5.11 (0.73)	< 0.001
1-hour plasma glucose (mmol/L)	n=913	9.37 (1.99) †	9.36 (2.02) ‡	9.92 (1.88)	9.55 (1.98)	< 0.001
2-hour plasma glucose (mmol/L)	n=922	8.08 (1.96) †	8.13 (1.88) ‡	8.63 (2.06)	8.28 (1.98)	0.001
Gestational age at OGTT (WG)	n=992	27.42 (3.02)	27.34 (3.17)	26.96 (3.12)	27.24 (3.11)	0.108
Glycaemic status during pregnancy						
Early-diagnosed gestational diabetes mellitus	n=1,423	148 (31.6%)	142 (30.2%)	141 (29.1%)	431 (30.3%)	0.001
Gestational diabetes mellitus		302 (64.4%)	298 (63.4%)	289 (59.7%)	889 (62.5%)	
Diabetes in pregnancy		19 (4.1%)	30 (6.4%)	54 (11.2%)	103 (7.2%)	
Metabolic characteristics						
Age (years)	n=1,423	33.22 (5.49) *†	32.63 (5.02) ‡	32.85 (5.49)	32.90 (5.34)	0.229
Pre-pregnancy body mass index (kg/m ²)	n=1,411	25.22 (4.75) *†	27.23 (5.26) ‡	29.67 (6.02)	27.40 (5.67)	< 0.001
Pre-pregnancy obesity	n=1,411	78 (16.8%)*†	132 (28.2%)‡	215 (45.0%)	425 (30.1%)	< 0.001
Pre-pregnancy waist circumference	n=1,073					< 0.001
<80 cm		282 (86.2%)	256 (69.2%)	223 (59.3%)	761 (70.9%)	
80-88 cm		39 (11.9%)	98 (26.6%)	126 (33.5%)	263 (24.5%)	
>88 cm		6 (1.8%)	16 (4.3%)	27 (7.2%)	49 (4.6%)	
Family history of diabetes	n=1,423	140 (29.9%)†	169 (36.0%)	199 (41.1%)	508 (35.7%)	0.001
Employment at beginning of pregnancy	n=1,420	167 (35.6%)	180 (38.3%)	159 (33.1%)	506 (35.6%)	0.241
Parity	n=1,423	2.36 (1.25)	2.30 (1.30)	2.44 (1.35)	2.36 (1.30)	0.259
Previous pregnancy(ies)						
History of HIP	n=1,423					0.02§

First child		135 (28.8%)	148 (31.5%)	142 (29.3%)	425 (29.9%)	
No		264 (56.3%)	246 (52.3%)	238 (49.2%)	748 (52.6%)	
Yes		70 (14.9%)†	76 (16.2%)	104 (21.5%)	250 (17.6%)	
History of macrosomia	n=1,423					0.017§
First child		135 (28.8%)	148 (31.5%)	142 (29.3%)	425 (29.9%)	
No		316 (67.4%)	293 (62.3%)	302 (62.4%)	911 (64.0%)	
Yes		18 (3.8%)†	29 (6.2%)	40 (8.3%)	87 (6.1%)	
History of hypertensive disorders	n=1,423					0.001§
First pregnancy		88 (18.8%)	86 (18.3%)	76 (15.7%)	250 (17.6%)	
No		373 (79.5%)	369 (78.5%)	377 (77.9%)	1119 (78.6%)	
Yes		8 (1.7%)†	15 (3.2%)	31 (6.4%)	54 (3.8%)	
History of fetal death	n=1,423					0.985§
First pregnancy		88 (18.8%)	86 (18.3%)	76 (15.7%)	250 (17.6%)	
No		366 (78.0%)	369 (78.5%)	392 (81.0%)	1119 (78.6%)	
Yes		8 (1.7%)	15 (3.2%)	31 (3.2%)	54 (3.8%)	
Ethnicity	n=1,420					0.003
North African		182 (38.8%)	159 (33.8%)	167 (34.7%)	508 (35.8%)	
European		106 (22.6%)	92 (19.6%)	69 (14.3%)	267 (18.8%)	
Sub-Saharan African		70 (14.9%)	70 (14.9%)	91 (18.9%)	231 (16.3%)	
Indian-Pakistan-Sri Lankan		66 (14.1%)	86 (18.3%)	95 (19.8%)	247 (17.4%)	
Caribbean		12 (2.6%)	24 (5.1%)	29 (6.0%)	65 (4.6%)	
Other		33 (7.0%)	39 (8.3%)	30 (6.2%)	102 (7.2%)	
Maternal outcomes						
Gestational weight gain (kg)	n=1,284	9.63 (5.01)	9.27 (5.40)	9.50 (6.21)	9.46 (5.57)	0.636
Insulin therapy during pregnancy	n=1,423	163 (34.8%)*†	230 (48.9%)‡	304 (62.8%)	697 (49.0%)	< 0.001
Caesarean section	n=1,423	111 (23.7%)†	122 (26.0%)	156 (32.2%)	389 (27.3%)	0.009
Hypertension in pregnancy	n=1,423	6 (1.3%)†	14 (3.0%)‡	32 (6.6%)	52 (3.7%)	< 0.001
Preeclampsia	n=1,423	7 (1.5%)†	13 (2.8%)	23 (4.8%)	43 (3.0%)	0.012
Hypertensive disorders during pregnancy	n=1,423	13 (2.8%)†	27 (5.7%)‡	55 (11.4%)	95 (6.7%)	< 0.001
Neonatal outcomes						
Birthweight (g)	n=1,423	3,312 (520)	3,297 (481) ‡	3,381 (563)	3,330 (524)	0.031
Large-for-gestational-age infant	n=1,423	59 (12.6%)	45 (9.6%)‡	87 (18.0%)	191 (13.4%)	0.001
Small-for-gestational-age infant	n=1,423	41 (8.7%)	49 (10.4%)	42 (8.7%)	132 (9.3%)	0.576
Gestational age at birth (WG)	n=1,423	39.6 (1.6)	39.6 (1.5)	39.4 (1.6)	39.5 (1.6)	0.06
Preterm delivery (<37 WG)	n=1,423	28 (6.0%)	26 (5.5%)	33 (6.8%)	87 (6.1%)	0.700

Neonatal hypoglycaemia	n=1,421	3 (0.6%) [†]	7 (1.5%)	16 (3.3%)	26 (1.8%)	0.007
Neonatal death and stillbirth	n=1,423	2 (0.4%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	0.108

Data are n (%) or mean (standard deviation)

HIP: hyperglycaemia in pregnancy; OGTT: oral glucose tolerance test; WG: weeks of gestation

Symbols inserted only if significant ($P < 0.05$) after Bonferroni adjustment for multiplicity

*: tertile 1 vs tertile 2

†: tertile 1 vs tertile 3

‡: tertile 2 vs tertile 3

§: Yes vs No (no history possible if first child)

Table II: Risk of adverse pregnancy outcomes in women in the 3rd HOMA-IR tertile vs. those in the 1st and 2nd tertiles combined according to each study model

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8
Maternal outcomes								
Insulin therapy	2.35 (1.87-2.94) <i>P</i> < 0.001	2.16 (1.70-2.75) <i>P</i> < 0.001	2.41 (1.91-3.04) <i>P</i> < 0.001	2.37 (1.87-3.00) <i>P</i> < 0.001	2.07 (1.61-2.67) <i>P</i> < 0.001	2.09 (1.61-2.71) <i>P</i> < 0.001	2.02 (1.54-2.67) <i>P</i> < 0.001	-
Caesarean section	1.44 (1.13-1.83) <i>P</i> = 0.003	1.05 (1.03-1.07) <i>P</i> < 0.001	1.44 (1.13-1.83) <i>P</i> = 0.003	1.44 (1.13-1.85) <i>P</i> = 0.003	1.21 (0.93-1.58) <i>P</i> = 0.150	1.22 (0.93-1.60) <i>P</i> = 0.143	1.23 (0.93-1.63) <i>P</i> = 0.143	1.18 (0.89-1.57), <i>P</i> = 0.250
Hypertensive disorders	2.88 (1.89-4.42) <i>P</i> < 0.001	2.25 (1.45-3.53) <i>P</i> < 0.001	2.83 (1.85-4.35) <i>P</i> < 0.001	2.81 (1.83-4.35) <i>P</i> < 0.001	2.30 (1.45-3.65) <i>P</i> < 0.001	2.26 (1.42-3.62) <i>P</i> = 0.001	2.05 (1.26-3.36) <i>P</i> = 0.004	2.05 (1.26-3.38) <i>P</i> = .004
Neonatal outcomes								
Large-for-gestational-age infant	1.76 (1.29-2.39) <i>P</i> < 0.001	1.41 (1.01-1.95) <i>P</i> = 0.042	1.80 (1.32-2.46) <i>P</i> < 0.001	1.75 (1.28-2.40) <i>P</i> < 0.001	1.45 (1.03-2.03) <i>P</i> = 0.031	1.42 (1.01-1.99) <i>P</i> = 0.045	1.45 (1.02-2.07) <i>P</i> = 0.039	1.39 (0.97-1.99) <i>P</i> = 0.070
Small-for-gestational-age infant	0.90 (0.61-1.31) <i>P</i> = 0.576	0.98 (0.65-1.46) <i>P</i> = .930	0.88 (0.60-1.29) <i>P</i> = 0.529	0.95 (0.64-1.41) <i>P</i> = 0.812	0.91 (0.59-1.38) <i>P</i> = 0.654	0.97 (0.62-1.50) <i>P</i> = 0.894	1.08 (0.68-1.71) <i>P</i> = 0.740	1.11 (0.69-1.76) <i>P</i> = 0.672
Preterm delivery	1.20 (0.76-1.87) <i>P</i> = .426	1.22 (0.75-1.95) <i>P</i> = .412	1.18 (0.74-1.84) <i>P</i> = 0.474	1.13 (0.71-1.77) <i>P</i> = 0.607	1.32 (0.79-2.16) <i>P</i> = 0.283	1.26 (0.75-2.08) <i>P</i> = 0.376	1.30 (0.75-2.24) <i>P</i> = 0.347	1.27 (0.72-2.19) <i>P</i> = 0.405

Values are OR (95% confidence interval), *P*-value

Model 1: unadjusted

Model 2: adjusted for body mass index and gestational age at HOMA-IR measurement

Model 3: adjusted for maternal age and gestational age at HOMA-IR measurement

Model 4: adjusted for HOMA-B and gestational age at HOMA-IR measurement

Model 5: adjusted for glycaemic status, age, body mass index, family history of diabetes, parity, ethnicity and gestational age at HOMA-IR measurement

Model 6: model 5 + adjusted for HOMA-B

Model 7: model 6 + adjusted for gestational weight gain

Model 8: model 7 + adjusted for insulin therapy during pregnancy