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ORIGINAL ARTICLE

# Hypertensive disorders during pregnancy and 3 years after delivery in women with gestational hyperglycemia

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## Abstract

**Aims** Women with gestational hyperglycemia commonly experience hypertensive disorders during pregnancy. More information is needed about how hypertension develops in these patients over time. We investigated the prevalence of hypertension during and 3 years after pregnancy in Caucasian women with gestational hyperglycemia. We also investigated metabolic syndrome presence, glucose tolerance status, insulin sensitivity and insulin secretion levels in the follow-up period.

**Methods** In a prospective longitudinal study with a 3-year follow-up, we assessed hypertension status and clinical-related characteristics of 103 consecutive women with gestational hyperglycemia sub-grouped according to their hypertensive status during and after pregnancy.

**Results** Overall, 29 (28.1%) women had hypertension during pregnancy (24 gestational hypertension; 4 chronic hypertension; 1 preeclampsia). At follow-up 16 (15.5%) women were diagnosed as having hypertension (11 with hypertension in pregnancy; 5 with a normotensive pregnancy). Women with hypertension after pregnancy had higher BMI, metabolic syndrome rate and worse insulin resistance indexes than normotensive women. Weight increase at follow-up (OR 1.17, 95% CI 1.00–1.35) and hypertension in pregnancy (OR 6.72, 95% CI 1.17–38.64) were associated with hypertension after pregnancy.

**Conclusions** Women with gestational hyperglycemia should undergo regular monitoring during and after pregnancy to detect metabolic and clinical impairments and to prevent cardiovascular harm.

**Keywords** Gestational hyperglycemia · Hypertension · Pregnancy · Metabolic syndrome

## Introduction

During normal pregnancy women undergo several metabolic and circulatory changes to meet fetal needs. Hormonal and metabolic factors are involved in determining variations in insulin sensitivity and/or insulin resistance [1]. Blood pressure is maintained in a normal range thanks to the increased blood volume and the reduced vascular resistance typical of pregnancy [2]. When these adjustments fail, pregnant women may experience glucose tolerance impairment, hypertension during pregnancy or both disorders [3]. Glucose tolerance impairment can be represented by gestational diabetes mellitus (GDM) or by minor alterations of glucose metabolism. This status affects the placental and systemic vascular reactivity both of the mother and the fetus via a number of mechanisms, such as insulin resistance or hyperinsulinemia, that may predispose to hypertension triggering a chronic inflammatory response, by increasing sympathetic nerve activity, sodium retention, or altering the function of vascular smooth muscles and the nitric oxide/cyclic-GMP pathway. Finally, long-term diabetic complications, in particular nephropathy, may play an additional important role [4]. Alterations of glucose metabolism are associated with an increased risk of hypertensive disorders in pregnancy along with high risk of type 2 diabetes and

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metabolic syndrome development later in life [4–8]. Ample evidence describes hypertension occurring after a pregnancy complicated by GDM as a significant element of metabolic syndrome [4, 7, 8]. To date, few longitudinal data focused on hypertensive disorders in a mid-term follow-up period are available for women with a history of gestational hyperglycemia complicated or not by hypertension in pregnancy. Especially important, because hypertension during pregnancy is a life-threatening condition and a possible predictor of hypertension after delivery, we need reliable data on these patients sub-grouped according to the time when hypertension is diagnosed. Better information might help in recognizing hypertensive disorders early after delivery before they cause cardiovascular harm.

Our primary objective was to assess hypertension status and patients' clinical-related characteristics according to hypertensive status during pregnancy and in a mid-follow-up period after delivery in women whose pregnancy was complicated by gestational hyperglycemia. Our secondary aim was to explore for metabolic syndrome presence, glucose tolerance status, insulin sensitivity and insulin secretion levels in the follow-up period according to the hypertensive status during and after pregnancy.

## Methods

This prospective observational longitudinal single-center study was conducted between 2003 and 2007 at the Diabetes and Pregnancy Unit at S. Andrea Hospital (Sapienza University) in Rome. All consecutive women diagnosed as having gestational hyperglycemia were invited to participate at the study. Exclusion criteria were: age ≤ 18 years, multiple pregnancy, pre-gestational hypertension, any systemic pathology and/or any medical treatment interfering with glucose levels and blood pressure levels, another pregnancy between the index pregnancy and the final follow-up visit.

We included women with GDM and those in whom an oral glucose tolerance test (OGTT) during pregnancy yielded only one abnormal value (OAV).

GDM or OAV were diagnosed between the 24th and 28th gestational week. According to Carpenter and Coustan criteria and to the Fourth International Workshop Conference on Gestational Diabetes Mellitus recommendations GDM diagnosis was made in the presence of two pathologic blood glucose levels at OGTT. In women with one or more known risk factors for GDM, the OGTT was performed as soon as possible [9]. Hypertension was defined as antihypertensive treatment started in pregnancy or blood pressure values ≥ 140/90 mmHg. According to the National High Blood Pressure Education Program Working Group on Blood Pressure in Pregnancy, hypertension was classified as chronic hypertension or gestational hypertension if diagnosed before or after the 20th week of gestation, respectively. Preeclampsia was defined as the simultaneous presence of gestational hypertension and proteinuria (0.3 g/24 h). Arterial blood pressure was measured with a sphygmomanometer in standard conditions (3 times/each visit, every 5′ on the non-dominant arm), during the late morning (between 10 and 12 a.m.). The fifth Korotkoff sound was considered to determine the diastolic blood pressure value. A standard arm cuff was used when the upper arm circumference was < 32 cm; an appropriate-size cuff was used for larger arms [10]. Women with hypertensive disorders were treated with antihypertensive drugs. Treatment consisted of alfa-metil dopa (750–1500 mg) in women with gestational hypertension whilst Amlodipina (5–10 mg) was given to women with gestational hypertension in agreement with gynecologist prescription or added on alfa-metil dopa in case of preeclampsia in whom blood pressure targets were not yet reached. Waist circumference was measured midway between the anterior superior iliac spine and the costal arch, in the standing position. All women underwent similar clinical and therapeutic management, as usual care.

During pregnancy, information on the following demographic and clinical parameters was recorded: parity, pre-gestational BMI, smoking habits, first-degree family history of diabetes mellitus and cardiovascular diseases, weight gain during pregnancy, glycated hemoglobin, gestational week and type of delivery, insulin treatment need. No other antidiabetic treatment was given such as metformin and/or inositols. Pre-pregnancy BMI was calculated as the ratio of reported pre-gestational weight in kg/(height in m)$^2$. At the last visit in pregnancy, we planned periodic post-partum assessments after 3, 6 months and then yearly. Given the risk of diabetes development after a pregnancy complicated by glucose impairment, patients received general recommendations about healthy lifestyle according to ADA guidelines [11] and Italian Standards of Care [12]. All the women who missed an appointment were contacted by telephone and encouraged to participate in follow-up assessments, whenever possible.

During follow-up visits, information on parity, BMI, smoking habits, blood pressure levels, family history of diabetes and cardiovascular disease, drug therapy (including antihypertensive drugs) was collected; furthermore, the presence of glucose tolerance impairment, metabolic syndrome and hypertension was investigated. Three years after delivery a standard 2-h 75-g OGTT with glucose and insulin assay (samples at 0′, 30′, 60′, and 120′) was performed to check for diabetes in all women except those with fasting glucose levels already indicative of having diabetes (≥ 7.0 mmol/L at least twice). Glucose tolerance and metabolic syndrome were defined according to ADA criteria [13] and Adult Treatment Panel III criteria [14], respectively. At the time of the OGTT, blood samples were collected and centralized to

the same laboratory to assay total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apo B, apo A1, HbA1c, uric acid, the inflammatory variables fibrinogen and high-sensitivity C-reactive protein (hs-CRP), the prothrombotic marker homocysteine, and the cardiovascular risk index microalbuminuria. Insulin resistance and insulin secretion indexes were estimated starting from plasma glucose and insulin levels sampled during the OGTT. Insulin resistance was quantified using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index [15]. Insulin secretion index (ISI) was derived from the OGTT as proposed by Matsuda and DeFronzo [16]. HOMA-IR and ISI reflect hepatic and whole-body insulin resistance levels, respectively. To study beta-cell secretory capacity, we calculated the oral disposition index [17] and the insulinogenic index, expressed as ΔIns30/ΔGlu30, a surrogate for first-phase insulin secretion [18]. All blood samples were analyzed by the same laboratory in our university hospital.

All the women attending our outpatients' clinic at the first visit in pregnancy gave a written informed consent which was later confirmed when they attended for the final postpartum visit. The institutional review board gave us permission to use anonymous data extracted from our patient's clinical reports.

### Statistical analyses

The National database on the Italian general population [19] reported a hypertension rate of 5.5% in women in childbearing age, whereas studies on GDM reported a hypertension rate of 7% after a mid-follow-up period [4]. The minimum sample size needed to estimate the prevalence of hypertension was therefore 75–100 women (estimated with the sample size calculator http://www.raosoft.com/samplesize.html, calculated for a 5% margin of error and 95% confidence interval). Participants were sub-grouped according to whether hypertensive disorders occurred during and after pregnancy, during pregnancy alone, after pregnancy alone or never. BMI was considered as a continuous measure or in classes: normal weight (BMI < 25 kg/m$^2$), overweight (BMI 25–29.9 kg/m$^2$) and obesity (BMI ≥ 30.0 kg/m$^2$).

Continuous variables were expressed as median (25–75th centile) or mean ± standard deviation (SD) according to their distribution, and categorical variables as numbers (percentage). Mann–Whitney or Kruskal–Wallis test or unpaired *t* test for continuous variables was used as appropriate to compare women's characteristics and Fisher exact test or Chi-square test (*p* value and odds ratio) for categorical variables. Bonferroni post hoc test was used to analyze multiple mean and median values in patients sub-grouped according to when hypertension was diagnosed. Multiple logistic regression with relative risk (RR) and 95% confidence intervals (CI) was performed to assess possible association between hypertension after pregnancy and weight increase at follow-up (weight difference between pregnancy and the last follow-up visit), fasting glucose levels at the follow-up OGTT and hypertensive status in pregnancy. A two-sided *p* value < 0.05 was considered to indicate statistical significance. Data were processed with the software program SPSS IBM version 20.1.

## Results and discussion

### Characteristics of the studied sample

Overall, out of a total of 179 Caucasian women to whom the study was proposed, 103 of them (78% with GDM; 22% with OAV) completed the study attending the 3-year follow-up visit, 51 dropped out and 25 were excluded because of a new pregnancy during the follow-up period. No difference was found for clinical and demographic characteristics between women who dropped out compared to those who completed the study (data not shown), apart from a higher insulin treatment rate in the latter (48.7 vs. 68.7%, $p < 0.0001$). The median follow-up period was of 33 (interquartile range 15–45) months.

Differences in general characteristics between baseline and the last study visit are reported in Table 1. At the end of the study women obviously had higher parity [2 (1–3) pregnancies] and were older than before pregnancy; furthermore, they had a similar number of first-degree relatives with diabetes or with cardiovascular diseases, higher BMI (particularly, a great number of obese women after delivery was detected) and more often smoked compared to the pre-pregnancy period.

**Table 1** Demographic and clinical characteristics of the 103 women with gestational hyperglycemia at baseline and 3 years after delivery

| | Baseline | 3 years after delivery |
|---|---|---|
| Age (years) | 33.3 ± 4.2 | 37.2 ± 4.6 |
| Body mass index (kg/m$^2$) | 23.6 (21.8–27.3) | 24.7 (21.9–28.9) |
| Normal weight (%) | 64 (62.1) | 57 (55.3) |
| Overweight (%) | 26 (25.2) | 28 (27.2) |
| Obese (%) | 13 (12.7) | 18 (17.5) |
| Smoking habits (%) | 0 (0) | 27 (26.2) |
| Family history of diabetes mellitus in first-degree relatives *n* (%) | 53 (51.4) | 55 (53.4) |
| Family history of cardiovascular disease in first-degree relatives *n* (%) | 64 (62.1) | 68 (66.0) |

Data are expressed as mean ± SD or as median and 25th–75th centile according to distribution

### Hypertensive status during and after pregnancy

Looking at hypertension rates during and after pregnancy, which was our primary outcome, we found that the majority of participants (66.9%) was normotensive during and after the index pregnancy; women with hypertension diagnosed in pregnancy which was present also after the delivery accounted for 10.6%; almost one in five women was hypertensive in pregnancy and normotensive after (17.5%); finally, a small but considerable number of women (4.8%) had a normotensive pregnancy but developed hypertensive disorders after the pregnancy.

Clinical and metabolic characteristics of these four groups are reported in Table 2. Groups were different in BMI levels both before pregnancy and at follow-up, women with hypertension during and after pregnancy showing the highest BMI increase. BMI remained almost unchanged at follow-up only in the group of women who were hypertensive during pregnancy and normotensive thereafter.

No difference was found among the four groups for family history of hypertension and cardiovascular disease or for inflammatory and prothrombotic markers (data not showed). The group of normotensive women during pregnancy but hypertensive after had the highest fasting glucose, total cholesterol and LDL cholesterol levels at follow-up. Insulin resistance indexes were higher in women who had hypertension at follow-up than in those with a normotensive follow-up, and peaked in women who were hypertensive during pregnancy and thereafter. No statistically significant differences were observed in insulin secretion indexes among the four sub-groups. Women who remained normotensive during and after pregnancy showed the best clinical and metabolic profiles.

Overall, 29 women (28.1%) were hypertensive in pregnancy: chronic hypertension was diagnosed in early pregnancy in 4 women (none of whom had a history of pre-gestational hypertension); 24 women had gestational hypertension and only one developed preeclampsia. When comparing women who were hypertensive in pregnancy with normotensive women, the first had a higher pre-gestational BMI [25.2 (24–31.4) vs. 22.6 (21.4–25.8) kg/m$^2$, $p = 0.001$]. There were no differences between groups for age, parity,

**Table 2** Clinical and metabolic characteristics of women with gestational hyperglycemia sub-grouped according to the presence of hypertension in and after pregnancy

| | Hypertensive in and after pregnancy (HH) | Normotensive in pregnancy and hypertensive after (NH) | Hypertensive in pregnancy and normotensive after (HN) | Normotensive in and after pregnancy (NN) | *p* |
|---|---|---|---|---|---|
| Number of subjects | 11 | 5 | 18 | 69 | |
| Body mass index before pregnancy (kg/m$^2$) | 31.7 (28.4–34.8) | 22.5 (21.0–26.1) | 25.0 (22.8–29.9) | 22.6 (21.4–25.8) | 0.001^<br>0.009† |
| Body mass index at follow-up (kg/m$^2$) | 34.9 (27.1–39.2) | 23.7 (22.3–26.1) | 24.9 (22.8–28.8) | 24 (21.7–27.7) | 0.041^<br>0.03† |
| Weight gain at follow-up (kg) | 4.78 ± 5.89 | 7.70 ± 7.61 | 1.09 ± 7.6 | 2.21 ± 4.96 | ns |
| Fasting glucose (mmol/L) | 5.4 ± 1.0 | 5.7 ± 1.4 | 5.2 ± 1.1 | 4.8 ± 0.5 | 0.008^ |
| Total cholesterol at follow-up (mmol/L) | 4.4 ± 0.8 | 5.9 ± 1.0 | 5.2 ± 0.8 | 4.9 ± 1.0 | 0.046^ |
| High-density lipid cholesterol at follow-up (mmol/L) | 1.1 ± 0.3 | 1.4 ± 0.3 | 1.4 ± 0.3 | 1.5 ± 0.4 | 0.028^<br>0.028† |
| Low-density lipid cholesterol at follow-up (mmol/L) | 2.8 ± 0.8 | 4.0 ± 0.9 | 3.4 ± 0.7 | 2.9 ± 1.0 | 0.025^ |
| Homeostasis model assessment insulin resistance at follow-up | 4.2 (1.3–7.9) | 1.9 (1.5–5.7) | 1.0 (0.8–2.4) | 1.0 (0.7–1.6) | 0.001^<br>0.001†<br>0.004° |
| Metabolic syndrome at follow-up *n* (%) | 7 (63.6) | 1 (20) | 3 (16.8) | 6 (8.7) | 0.0002χ |
| Abnormal glucose tolerance at follow-up *n* (%) | 5 (45.4) | 4 (80) | 6 (33.3) | 16 (23.2) | 0.05χ |
| Diabetes mellitus (*n*) | 2 | 2 | 2 | 4 | |
| Impaired fasting glucose (*n*) | 2 | 0 | 3 | 7 | |
| Impaired glucose tolerance (*n*) | 1 | 2 | 2 | 5 | |

Data are expressed as mean ± SD or as median and 25th–75th centile according to distribution

*p* significant: † HH vs NN; ° HH vs HN

^Bonferroni post hoc, χ Chi-square test

smoking habits, weight gain in pregnancy, insulin requirement rate and HbA1c levels (data not shown). Notably, significant differences between groups were detected in two of the main pregnancy outcomes, women with hypertension in pregnancy delivering at earlier gestational week (37.8 ± 2.0 vs. 38.9 ± 1.7, respectively, $p = 0.01$) and having a higher Cesarean section rate (79.3 vs. 48.7%, respectively, $p = 0.008$).

During follow-up 18 women having hypertensive problems in pregnancy (17 with gestational hypertension and 1 with preeclampsia) became normotensive; 16 women (15.5%) were conversely found hypertensive. Among the latter, 11 women were hypertensive also in pregnancy (4 with chronic hypertension and 7 with gestational hypertension) and 5 women were normotensive in pregnancy becoming hypertensive at follow-up.

Hypertension after pregnancy was associated with weight increase at follow-up (OR 1.17, 95% CI 1.00–1.35) but not with fasting glucose levels at the follow-up OGTT (OR 1.01, 95% CI 0.97–1.06); having hypertension in pregnancy was associated with a more than sixfold high risk of hypertension after pregnancy (OR 6.72, 95% CI 1.17–38.64).

## Comparison between women with hypertension after pregnancy and women with normal blood pressure after pregnancy

When comparing women with hypertension after pregnancy with women with normal blood pressure after pregnancy (Table 3) the first had higher fasting glucose levels, triglycerides levels, pre-gestational BMI, BMI recorded at last follow-up visit, weight gain after 3 years, although both groups had a similar weight gain in pregnancy (10.87±4.3 vs. 9.43±9.6 kg, respectively, $p$ = ns). No differences between groups were detected for age, parity, first-degree family history of diabetes mellitus or cardiovascular disease, smoking habits, others lipid profile parameters, inflammatory and prothrombotic markers, microalbuminuria, HbA1c levels, follow-up length and severity of hyperglycemia in pregnancy (data not shown). When considering glucose homeostasis indexes, a statistically significant between-group difference was shown for insulin-resistance and insulin-sensitivity indexes, women with hypertension after pregnancy having higher HOMA-IR levels and lower Matsuda ISI compared with normotensive women. The two groups did not differ for insulinogenic and oral disposition indexes.

## Secondary outcomes assessment

Laboratory testing performed at last follow-up visit disclosed abnormal glucose tolerance in 31 (30.1%) women. Specifically, 10 women developed diabetes, 11 women had impaired fasting glucose, 9 women impaired glucose tolerance and one woman both impaired fasting glucose and impaired glucose tolerance. No significant differences were found for the main clinical and metabolic features tested (including the severity of hyperglycemia during pregnancy) between women with normal or abnormal glucose tolerance, apart from higher BMI in the latter group (Table 4). HOMA-IR was higher in the impaired glucose tolerance group but borderline significant.

When considering the whole sample according to the time when hypertension occurred, the group of normotensive in pregnancy but hypertensive after showed the highest prevalence of glucose impairment (Table 2).

Metabolic syndrome was present in 17 (16.5%) subjects. It was diagnosed in a larger percentage among hypertensive (8/16, 50%) than normotensive (9/87, 10.3%) women ($p = 0.002$). The only variable that differed significantly between hypertensive women without and with metabolic

**Table 3** Clinical characteristics of studied women sub-grouped according to the presence or absence of hypertensive disorders at follow-up

| | Hypertensive patients ($n = 16$) | Normotensive patients ($n = 87$) | $p$ |
|---|---|---|---|
| Body mass index (kg/m$^2$) | | | |
| Pre-gestational | 27.9 (22.5–34.3) | 23.5 (21.7–26) | 0.02§ |
| At follow-up | 29.0 (23.3–38.2) | 24.6 (21.8–28.1) | 0.009§ |
| Fasting glucose at follow-up (mmol/L) | 5.5 ± 1.1 | 4.9 ± 0.7 | 0.01* |
| Abnormal oral glucose tolerance *n* (%) | 10 (62.59) | 23 (27.5) | 0.06χ |
| Triglycerides at follow-up (mmol/L) | 1.12 (0.97–1.38) | 0.76 (0.61–1.20) | 0.005§ |
| Homeostasis model assessment insulin resistance at follow-up | 4.2 (1.4–7.0) | 1.0 (0.7–1.7) | 0.0003§ |
| Matsuda insulin sensitivity index at follow-up | 4.0 (2.6–7.2) | 7.3 (5.3–19.0) | 0.01§ |
| Insulinogenic index at follow-up | 13.0 (6.8–22.7) | 9.3 (6.5–17.2) | ns§ |
| Oral disposition index at follow-up | 1.4 (0.8–2.2) | 2.2 (1.1–4.2) | ns§ |

Data are expressed as mean ± SD or as median + 25–75th centile (according to their distribution)

*$t$ test, § Mann–Whitney, χ Chi-square test

**Table 4** Clinical and metabolic characteristics of the studied women according to glucose tolerance status at follow-up

| | Impaired glucose tolerance ($n = 34$) | Normal glucose tolerance ($n = 69$) | $p$ |
|---|---|---|---|
| Age (years) | 38.1 ± 4.8 | 36.7 ± 4.4 | 0.46* |
| Follow-up length (months) | 35.3 ± 23.4 | 30.7 ± 18.4 | 0.15* |
| Number of pregnancies | 2 (1–3) | 2 (1–3) | 0.13* |
| Body mass index (kg/m$^2$) | 27.7 (24–31.6) | 23.9 (21.8–27.3) | 0.01* |
| Systolic blood pressure (mmHg) | 117.1 ± 14.4 | 108.8 ± 13.4 | 0.59* |
| Diastolic blood pressure (mmHg) | 75.5 ± 10.6 | 69.6 ± 6.5 | 0.38* |
| Homeostasis model assessment insulin resistance at follow-up | 1.53 (0.8–3.5) | 1.15 (0.7–1.6) | 0.07§ |
| Matsuda insulin sensitivity index at follow-up | 5.5 (3.8–9.1) | 7.53 (5.4–10.9) | 0.72§ |
| Insulinogenic index at follow-up | 7.6 (4.1–15.3) | 10.8 (7.4–17.4) | 0.60§ |
| Triglycerides (mmol/L) at follow-up | 0.97 (0.7–1.48) | 0.75(0.6–1.2) | 0.98§ |
| Total cholesterol (mmol/L) at follow-up | 5.12 ± 1.19 | 4.94 ± 0.85 | 0.10* |
| Low-density lipid cholesterol (mmol/L) at follow-up | 3.23 ± 1.01 | 2.92 ± 0.88 | 0.40* |
| High-density lipid cholesterol (mmol/L) at follow-up | 1.29 ± 0.3 | 1.47 ± 0.39 | 0.36* |

Data are expressed as mean ± SD or as median and 25th–75th centile according to distribution

*$t$ test, § Mann–Whitney

syndrome was parity [3 (1–3) vs. 2 (1–3) pregnancies per woman, $p = 0.03$].

No difference was observed between normotensive and hypertensive women in the clinical and metabolic variables investigated. When considering the whole sample according to the time when hypertension occurred, the group of hypertensive in and after pregnancy showed the highest prevalence of metabolic syndrome (Table 2).

None of the women who were found to have diabetes, impaired fasting glucose, impaired glucose tolerance, hypertension or metabolic syndrome at follow-up was symptomatic or aware of their clinical condition.

## Discussion

In this prospective longitudinal study conducted in a single academic center and enrolling women whose pregnancy was complicated by GDM or gestational hyperglycemia, hypertension rates during pregnancy matched those reported for a similar age-matched Italian general population [19]. Although about one-third of our population had blood pressure readings compatible with hypertension, this condition left maternal and perinatal outcomes unchanged possibly because these patients underwent strict blood pressure monitoring. In four women, hypertension was classified as chronic because it manifested first in early pregnancy and persisted at follow-up. Measuring blood pressure from early pregnancy onwards could, therefore, give physicians the first chance to diagnose otherwise undetected moderate or severe pre-gestational hypertension, given that blood pressure levels tend to decrease in pregnancy as vascular resistance decreases [20].

When we studied our patients' mid-term outcome we identified hypertension in nearly 16% of the same relatively young cohort 3 years after delivery. We found higher levels of insulin resistance when comparing women with hypertensive disorders after pregnancy with normotensive women, being insulin secretion indexes not different between groups. This conclusion is in line with evidence that insulin resistance, a known pathogenetic factor responsible for hypertension in pregnancy, increases 5.6-fold the RR for hypertension later in life. By acting on the nitric oxide pathway, hyperinsulinemia stimulates sympathetic drive, smooth-muscle growth, and salt and water retention [21, 22].

When we assessed secondary outcomes, including the presence of metabolic syndrome, glucose tolerance and insulin sensitivity and secretion in the overall population, the prevalence of metabolic syndrome as well as altered glucose tolerance matched that reported in other studies involving woman with GDM with a similar follow-up length [7, 8]. About 10% of our Caucasian women coming from the same urban area and mostly having normal weight manifested overt diabetes. At follow-up, other investigators report a prevalence of type 2 diabetes ranging between 10 and 60% within 5 years after delivery, though ethnicity, length of follow-up, selection criteria, and tests for gestational diabetes and type 2 diabetes varied among studies [6].

A strong point in our study design was that we compared clinical and metabolic features in these women sub-grouped according to whether hypertensive disorders manifested during and after pregnancy, during pregnancy alone, after pregnancy alone or never. This approach underlined that despite

having gestational hyperglycemia and, therefore, belonging to a high-risk population, women whose hypertensive disorders manifested during and also after pregnancy have higher insulin resistance indexes, including BMI, than the other three sub-groups. A prospective population-based study showed that the risk for hypertension 20 years after delivery depended largely on overweight, especially overweight combined with GDM [23]. The multiple logistic regression analysis we performed clearly showed how the role of weight increase confers a high risk of having hypertensive problems after the pregnancy.

A new, unexpected finding was that hypertension manifested at follow-up in five women who remained normotensive throughout gestation, and had the worst glucose tolerance levels and LDL cholesterol lipid profiles [24]. Ample information shows that hyperglycemia has an excitatory effect on the renin–angiotensin–aldosterone system whereas how cholesterol influences this system is less clear [22]. Some evidence shows an inverse and continuous relationship between cholesterol levels and endothelium-dependent vasodilatation, even though cholesterol levels seem partly to explain variance in endothelium-dependent vasodilation [25]. Early treatment improves endothelial function [26]. Equally important, oxidative stress also oxidizes LDL cholesterol, which in turn activates the renin–angiotensin system and angiotensin II [27]. Some studies report increased arterial media-intimal thickness in women with previous gestational hyperglycemia [28]. Finally, women with gestational hyperglycemia in a previous pregnancy who remained normotensive before and after pregnancy showed the best clinical and metabolic profiles.

Why only one of the patients we studied with pregnancy-related hyperglycemia manifested preeclampsia, a severe hypertensive disorder, is hard to explain [29]. In this study we were unable to assess whether preeclampsia and gestational hypertension differentially predict hypertension later in life [30–32], given that we observed only one woman with preeclampsia, a primiparous, normal weight, non-smoker, who remained normotensive until the last follow-up visit after delivery. The few published data concerning hypertension after delivery come from cross-sectional studies, describing preeclampsia related to metabolic syndrome [4]. A large prospective cohort study found that women with a history of GDM had a 26% increased risk of hypertension developing during a 16-year follow-up, even after adjustment for pregnancy hypertension and subsequent type 2 diabetes [33]. However, this study took into account information on hypertension coming from patient reports through questionnaires, this limiting the precision of collected data. In our study we assessed hypertension directly with clinical examination.

A major problem inherent to studies enrolling pregnant women over time is dropout. In this single-center study we had a high dropout rate, this representing a study limitation. Three years after delivery, fewer than 60% of the women we followed in pregnancy respected a post-partum follow-up protocol, this confirming other reports [34]. Because most of these women required insulin treatment in pregnancy they were probably more motivated than dropouts to attend follow-up after delivery. Exploring strategies to reduce dropout and encourage women to attend assessment after delivery Korpi-Hyövälti concluded that the most successful policy is a centralized special call or reminder [35]. Another strategy to improve post-partum participation might be a lifestyle intervention during pregnancy to make women aware that hypertension and diabetes can be prevented or delayed.

Another limitation of the study is that our study population included only Caucasian women. Hence our conclusions need to be confirmed in other ethnic groups. Infrequent events, such as preeclampsia in gestational hyperglycemia, deserve investigation in larger and possibly multicenter studies. Finally, the lack of a control group prevented us from comparing the prevalence of hypertension in pregnancy with a cohort of non-diabetic women.

## Conclusions

Women with a history of gestational hyperglycemia should undergo regular monitoring during and after pregnancy to detect metabolic and clinical impairments. We encourage more and larger studies to explore whether and how new strategies can prevent or delay hypertension and/or hyperglycemia in and out of pregnancy [36]. Detecting promptly hypertension before it could cause irreversible cardiovascular harm should be a strong clinical priority.

### Compliance with ethical standards

**Conflict of interest** On behalf of all authors, the corresponding author states that there is no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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