The Effects of Insulin Therapy on Mothers' Blood Pressure and Weight in Women with Gestational Diabetes Mellitus

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Research article

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Abstract

Background

The primary mechanism of gestational diabetes mellitus (GDM) was insulin resistance. Effects of insulin as the first - line medicine for GDM women was blurring. This work aims to investigate influences of insulin therapy on GDM mothers.

Methods

This retrospective cohort study recruited 616 GDM women with lifestyle intervention (diet and physician alone) and 92 GDM women with insulin therapy. Comparing the differences of variables (BMI, blood pressure, gestational weight gain, the incidence of macrosomia and so on) between GDM women with insulin and with lifestyle alone with univariate analysis. Employed paired sample test to evaluate the changes of BP from the time of intervention to one week before delivery, and used logistic regression to analyze the relationship between insulin therapy and gestational hypertension (GH).

Results

There were no significant differences in delivery mode, newborn weight and the incidence of macrosomia between GDM women with insulin and with lifestyle alone. Insulin therapy slightly increased mothers' weight despite there were no significant statistically differences in the rate of excessive weight gain comparing to the intervention of lifestyle alone which was attributed to short - term administration (about 12 weeks). In addition, the injection of insulin remarkably enhanced the incidence of gestational hypertension (GH). furthermore, the effect still existed after matching the time of insulin therapy, and from starting insulin usage to delivery systolic blood pressure significantly elevated 6mmHg (*vs* 4mmHg lifestyle alone, $P = 0.529$) and diastolic blood pressure 9mmHg (*vs* 5mmHg lifestyle alone, $P = 0.032$). Correlation analysis implied blood pressure near the delivery had significant positive correlation with BMI, 1 hour blood glucose, HbA1c, area under the blood glucose curve and gestational weight gain. Logistic regression analysis with enter selection confirmed that insulin therapy was an independent risk factor for the development of GH.

Conclusions

This work suggested that insulin therapy for short - term usage might slightly increase mothers' weight, but had the marked risk of raising mothers' BP, especially DBP.

Introduction

Background

Gestational diabetes mellitus (GDM) is defined as "diabetes diagnosed in the second or third trimester of [illegible]es prior to gestation."[1] the prevalence of GDM is increasing

globally with a greater prevalence of obesity and sedentary lifestyles. GDM contributed to a higher risk of developing serious complications for the mother (preeclampsia, caesarean section and the mother to development of type 2 diabetes) and the offspring (fetal macrosomia and childhood obesity)[2] [3–6].

GDM development generally associated with overweight or obesity [7], and insulin resistance was the major pathophysiologic feature of women with GDM. So far, three kinds of drugs were recommended for glycemic control in GDM mothers by American Diabetes Association (ADA). Insulin was the first - line medication for treating hyperglycemic in GDM, metformin and glyburide should be used secondarily, as both later can cross the placenta to fetus. Glyburide had higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin [8]. Metformin may lead to nutrient restriction of glucose and amino acids to fetus [9]. Fetal metformin exposure may result in growing up rapidly after birth and had higher body mass index (BMI) by mid - childhood (5–9 years), which were associated with long - term metabolic consequences including obesity, type 2 diabetes, and cardiovascular disease in later life [10]. As insulin does not cross the placenta to a measurable extent, it is safe for babies, so insulin is currently recommended as first - line agents for treating hyperglycemia in GDM. However, the effects of insulin therapy on GDM mothers were not focused on. Furthermore, insulin might have no actions on improve GDM mothers' pathophysiologic features attributed to its two major side effects, firstly the risk of weight gain, secondly water and sodium retention.

This retrospective cohort study aimed to investigate the effects on maternal and neonatal outcomes of insulin therapy. Firstly, we found that insulin therapy was safe for fetus, then it slightly leaded to weight gain for short - term administration and significantly increase the incidence of gestational hypertension (GH).
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Research Design And Methods

This was a retrospective cohort study.

From May 2013 to July 2019, we recruited all women with GDM at the Gestational Diabetes Mellitus Care Center of the Fifth People's Hospital of Shanghai, Fudan University.
The health card of all pregnant women was established from gestational 10 weeks to 12weeks. The healthy card obtained information about age, last menstruation, method of conception, parity, obstetric history, family history of diabetes, previous history of GDM, and pre - pregnancy weight. Meanwhile, at the first visit, at the time of performing oral glucose tolerance test (OGTT) and at the time of one week before delivery, routine physical examinations blood pressure (BP), weight, blood count (Sysmex XN9000, Japan), biochemical tests (Cobas 8000, Germany)) were employed. Blood tests were performed in the morning after an overnight fast of at least 8 hours. BP was measured on two occasions 6 hours apart, BMI was calculated as weight in kilograms divided by the square of height in meters. Total gestational weight gain (GWG) and the rate of weight gain during intervention was categorized into three groups by

the 2009 Institute of Medicine recommendations[11]: (1) inadequate weight gain; (2) adequate weight gain; (3) excessive weight gain.

Gestational hypertension (GH) was defined as a systolic blood pressure (SBP) ≥ 140 mmHg and / or a diastolic blood pressure (DBP) ≥ 90 mmHg on two occasions at least 6 hours apart after 20 weeks of gestation in a woman with previously normal blood pressure.

All subjects with the exception of those diagnosed with overt diabetes or GDM in early pregnancy underwent routine screening for GDM at 24–28 weeks' gestation according to a 75g OGTT. A diagnosis of GDM was based on ADA diagnostic criteria.

The values for Homeostatic Model Assessment of Insulin Resistance (HOMA - IR) and Homeostatic Model Assessment of Insulin Sensitivity (HOMA - β) were determined from fasting plasma glucose and insulin concentration (Electrochemiluminescence, Cobas e602, Germany) [12]. Area under blood glucose (BG) curve was roughly calculated as $\frac{1}{2} \times (\mathrm{fasting blood glucose(FBG)} + 1\text{ hour BG}) + \frac{1}{2} \times (1\text{ hour BG} + 2\text{ hours BG})$

Mothers with GDM were recommended to start lifestyle intervention immediately when the diagnosis of GDM was determined until to delivery. The time of GDM diagnosis was defined the initiating intervention pregnant week. GDM women should go quickly for a 30 - min walk every day, at least three days per week, together with a medical nutrition therapy and weight management. If the glycemic control was not aiming for the targets recommended by the Fifth International Workshop - Conference on GDM (Fasting glucose, 5.3 mmol/L or 1 hour postprandial glucose, 7.8 mmol/L or 2 hours postprandial glucose, 6.7 mmol/L) [13], insulin injection was started with continuous lifestyle therapy after one week according to ADA recommendations. Changes of weight and blood pressure were observed from the time of GDM diagnosis to one week before delivery.

After delivery, details including gestational age at delivery, treatment protocol for lowering glycemia, birth weight, and gender of the neonate were recorded by medical staff.

Women were excluded from the study for any of the following: pre-existing DM; chronic hypertension; renal disease history; multiple gestation; (5) serious liver dysfunction (alanine transaminase above 2.5 times upper limitation) and renal dysfunction (estimated Glomerular Filtration Rate below 90 ml/min/1.73m^2). Finally, 708 GDM women were entered in the analysis. Retrospective analysis processes were shown in Fig. 1.

Statistical analysis

Descriptive statistics for studied variables are presented as mean ± standard deviation (SD) for normally distributed variables, median (interquartile range (IQR)) for non - normally distributed variables, and frequency (percentage) for categorical variables. Student's t - test or Mann - Whitney U tests were used to

HOMA - IR and HOMA - β were log transformed previously for

t tests. In order to eliminate the confounder of the initiated time of controlling glycemia, a case - control matching method was employed to match variables of OGTT gestational weeks. Matching tolerance was 1 (week). Linear correlation between BP and other continuous variations were assessed by Pearson correlation analysis. Logistic regression analysis was performed with GH classified in a binary manner (presence / absence) as the dependent variable. Insulin therapy (categorized by whether or not) and other possible risk factors were entered into logistic regression analysis. Effect estimates are reported along with *OR* value, 95% *CI* and *P* value. The changes of BP after intervention (from the time of GDM diagnosis to one week before delivery) were subjected to paired sample test. Calculating difference of BP and comparing with student's *t* test. All analyses were performed using SPSS 24.0 (IBM SPSS Inc, Chicago, IL, USA). Two - tailed $P < 0.05$ was considered to indicate statistical significance.

Results

1. Characteristics of subjects between lifestyle intervention group and insulin therapy group in all GDM women

12.9% GDM women were supplemented with insulin in additional to lifestyle intervention whereas the majority women (87.1%) simply needed lifestyle intervention. Women treated with insulin were more likely to have family history of diabetes than women with lifestyle intervention alone, and they also had much higher BG, area under BG curves and earlier time of OGTT performing (24.3 ± 4.8 *vs* 25.8 ± 2.9 weeks, $P = 0.042$), but lower HOMA - β (94.90 (52.05–259.19) *vs* 295.85 (162.47–663.78), $P < 0.001$) than lifestyle intervention mothers. There were no significant differences in pre - pregnancy BMI, HOMA - IR, serum lipid parameters, SBP and DBP at baseline between two groups. At one week before delivery, we found that women treated with insulin had much higher BMI (30.9 ± 4.5 *vs* 28.4 ± 3.5 kg/m^2, $P = 0.002$), SBP (131 ± 13 *vs* 124 ± 13 mmHg, $P = 0.005$), DBP (80 ± 8 *vs* 74 ± 9 mmHg, $P = 0.007$), and higher incidence of GH (31.0% *vs* 11.7%, $P = 0.001$). However, the ratio of excessive weight gain had no significant differences despite higher in GDM women with insulin than with lifestyle alone. (*Table 1*). There were statistically significant changes of DBP in GDM women with insulin therapy. DBP was changed from 70 ± 8 mmHg to 80 ± 8 mmHg, increased 9mmHg (95% CI: 6–12 mmHg, $P < 0.001$), and SBP from 124 ± 11 mmHg to 131 ± 13 mmHg, increased 6 mmHg (95% CI: 1–11 mmHg, $P = 0.015$). On the other hand, in women with lifestyle intervention alone SBP increased 4mmHg (95% CI: 2–6 mmHg, $P < 0.001$) and DBP increased 5 mmHg (95% CI: 4–7 mmHg, $P < 0.001$). Difference of changes in DBP (9 mmHg *vs* 5 mmHg, $P = 0.032$) other than SBP (6 mmHg *vs* 4mmHg, $P = 0.529$) was significant between women with insulin and without. (Fig. 2). Finally, there were no difference of intervention time frame for high glycemia (12.6 ± 3.1 weeks *vs* 12.3 ± 1.6 weeks, $P = 0.628$), delivery mode, preterm, newborn weight, and the incidence of macrosomia between women with insulin and without (*Table 1*).

2. Comparing parameters between women with lifestyle intervention alone and with insulin therapy after matched

OGTT gestational weeks

Generally, women who had family history of DM performed OGTT and initiated insulin therapy earlier than those without. In order to eliminate the confounder of the initiating time of insulin therapy, a case - control matching method was employed to match variables of gestational weeks at the time of performing OGTT. After matching, we found that there were no significant differences in intervention time frame for glycemic control, the ratio of excessive weight gain, delivery mode, newborn weight and incidence of macrosomia between women with different intervention ways. However, there were still higher BMI, incidence rate of GH (29.3% *vs* 16.7%, $P = 0.038$), SBP (135 ± 13 mmHg *vs* 128 ± 13 mmHg, $P = 0.045$) and DBP (82 ± 8 mmHg *vs* 75 ± 11 mmHg, $P = 0.044$) when near the time of delivery in women with insulin therapy than those with lifestyle intervention. (*Table 1*).

3. Comparing parameters of subjects between women with GH and without

To investigate the risk factor for GH incidence, parameters were compared between women with GH and without. As shown in *Table 2*, comparing to women without GH, GH mother had higher rate of family history of hypertension (22.8% *vs* 6.0%, $P = 0.017$), pre - pregnancy BMI ($P = 0.006$), BMI at the time of one week before delivery ($P < 0.001$), the ratio of excessive weight gain during the whole pregnancy (66.7% *vs* 16.3%, $P < 0.001$) and during the time of intervention (80.0% *vs* 45.0%, $P = 0.036$) and 2 h BG (9.50 ± 1.42 *vs* 8.20 ± 1.62mmol/L, $P = 0.001$). We found that women developing GH had much higher level of SBP and DBP in the first and second trimester though they were in the normal range. Furthermore, GH women had higher insulin usage rate than those without (43.5% *vs* 11.2%, $P < 0.001$). There were no significant differences of newborn weight, incidence of macrosomia, preterm and delivery mode between women with GH and without.

4. Association between blood pressure and metabolic parameters

As shown in table 3, BP level at weeks of performing OGTT was closely associated with HOMA - IR ($r = 0.25$, $P = 0.026$) and pre - pregnancy BMI ($r = 0.21$, $P = 0.039$). BP at the time of delivery had significant positive correlation with 1 hour BG ($r = 0.24$, $P = 0.010$), HbA1c ($r = 0.25$, $P = 0.010$), area under BG curve ($r = 0.35$, $P < 0.001$), BMI ($r = 0.39$, $P < 0.001$), and total GWG ($r = 0.22$, $P = 0.029$).

5. Insulin therapy was an independent risk factor for the development of GH

Logistic regression analysis with enter selection showed that insulin therapy was an independent risk factor for the development of GH (*OR* = 6.33; 95%CI, 1.17 to 34.09 *vs* the lifestyle intervention, $P = 0.032$) corrected by history of hypertension, 2 h BG and total GWG, the same result occurred when the rate of weight gain during intervention instead of total GWG entered the model (*OR* = 6.65; 95%CI, 1.14 to 38.65 *vs* the lifestyle intervention, $P = 0.035$). (*Table 4*).

Discussion

Insulin is recommended as first - line agents for treating hyperglycemia in GDM by ADA and many other associations. However, insulin might not be the best choose for GDM women which can't improve the pathophysiology of GDM women. In this retrospective cohort study, we assessed the effect of insulin injection on mothers with GDM and fetus. Insulin therapy for about 12 weeks had mild effect on mothers' weight. Otherwise, the injection of insulin markedly enhanced the incidence of GH, furthermore, the effect of insulin therapy on mothers' BP still existed after matching the time of initiating intervention.

Previous studies have evaluated the effects between insulin and oral anti - diabetic drugs for GDM treatment. Compared to oral anti - diabetic drugs, insulin was associated with higher weight gain in GDM women [14,15]. For the infant, there was no significantly difference between groups for the risk of perinatal death, being born large - for - gestational age [16,17] and serious neonatal outcomes [18,19] between women who had been treated with insulin and those treated with oral anti - diabetic pharmacological therapies. As we know, insulin resistance mostly attributed to obesity, in addition that were the vital physiological character of GDM. Obviously, insulin therapy was efficacy for glycemic control, but could not improve the physiology of GDM.

A Few studies had compared the effects on mothers and/or fetus between insulin and life style intervention in GDM patients, which did not show difference of weight gain between two intervention ways. Our study retrospectively analyzed the effects on maternal and neonatal outcomes of insulin therapy and we found that women with GDM had slightly higher the ratio of excessive weight gain who used insulin for glycemic control than diet and physician alone. There were no difference of delivery mode, preterm, and being born macrosomia which were consistence with other studies. [20,21].

It is generally considered that insulin therapy may induce weight gain in diabetic patients. Insulin induced weight gain was attributed that insulin may promote glucose movement from circulation into cells and inhibit glycogen production and release from liver. In addition, Insulin suppresses lipolysis, proteolysis, and it also stimulates gluconeogenesis, protein synthesis. All these excess energies are deposited by the style of fat. In our cohort study, the short time of insulin treatment frame was only about 12 weeks in GDM women, which result in the mild effect of insulin therapy on weight, but if the administration of insulin was longer than 12 weeks, the adverse effect might be aggravated.

Niromanesh et al[22] found that insulin therapy had higher BP and weight gain than metformin in pregnancy women. Our study showed that insulin therapy increased the incidence of GH, DBP increased much more significantly than SBP. BP was positively associated with BMI and HOMA-IR. Furthermore, insulin therapy was an independent risk factor for the development of GH in GDM women corrected by family history of hypertension, 2 h BG and total GWG or the rate of weight gain during the time of intervention. Insulin injection might accelerate hyperinsulinemia/insulin resistance of GDM pregnant women which may aggravate the incidence of GH. Wang F *et al* [23] demonstrated that insulin resistance or elevated fasting insulin concentrations is independently associated with an exacerbated risk of erinsulinemia / insulin resistance may induce sodium

reabsorption by the distal nephron segments[24], resulting increased release of angiotensin II, which was the main effector peptide of the renin - angiotensin system [25], enhanced sympathetic activity, vascular resistance [26,27], and endothelial dysfunction [25]. Finally, data demonstrate the changes of DBP were more remarkable than SBP, it might be attribute to the increasement volume, vessels spasm and aggravated peripheral vascular resistance during pregnancy.

The results implied that clinician should take note of the side effects on mothers, and it might be necessary to develop a new pharmaceutical which not only can improve the pathophysiology of GDM women but also does not cross the placenta.

Conclusions

In summary, our study indicated that insulin therapy was safe for fetus and had slight effect on mothers' weight if short - term usage of insulin, but which warned us about the adverse effect if for longer time than 12 weeks. In addition, the administration of insulin might have the risk of raising mothers' BP, especially DBP.

Abbreviations

GDM, gestational diabetes mellitus

ADA, American Diabetes Association

BMI, body mass index

GH, gestational hypertension

OGTT, oral glucose tolerance test

BP, blood pressure

GWG, Total gestational weight gain

SBP, systolic blood pressure

DBP, diastolic blood pressure

HOMA - IR, Homeostatic Model Assessment of Insulin Resistance

HOMA - β, Homeostatic Model Assessment of Insulin Sensitivity

BG, blood glucose

Declarations

Ethics approval and consent to participate

The Ethics Committee of Shanghai Fifth People's Hospital has approved this study (Number: 2020 Ethics Approval. No. 154). This work is a retrospective study. Only clinical data of patients were analyzed, hereby be applicable for exemption of informed consent. These are appliance with the rule of ethics committee of Shanghai Fifth People's Hospital.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

SZ researched data. TS wrote the manuscript and researched data. LZ and JL reviewed/edited the manuscript. FW and SZ contributed to discussion and reviewed/edited manuscript. FM, YL, RZ, ZY and XH contributed to data collection. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Tables

Due to technical limitations, table 1 to 4 is only available as a download in the Supplemental Files section.

Figures

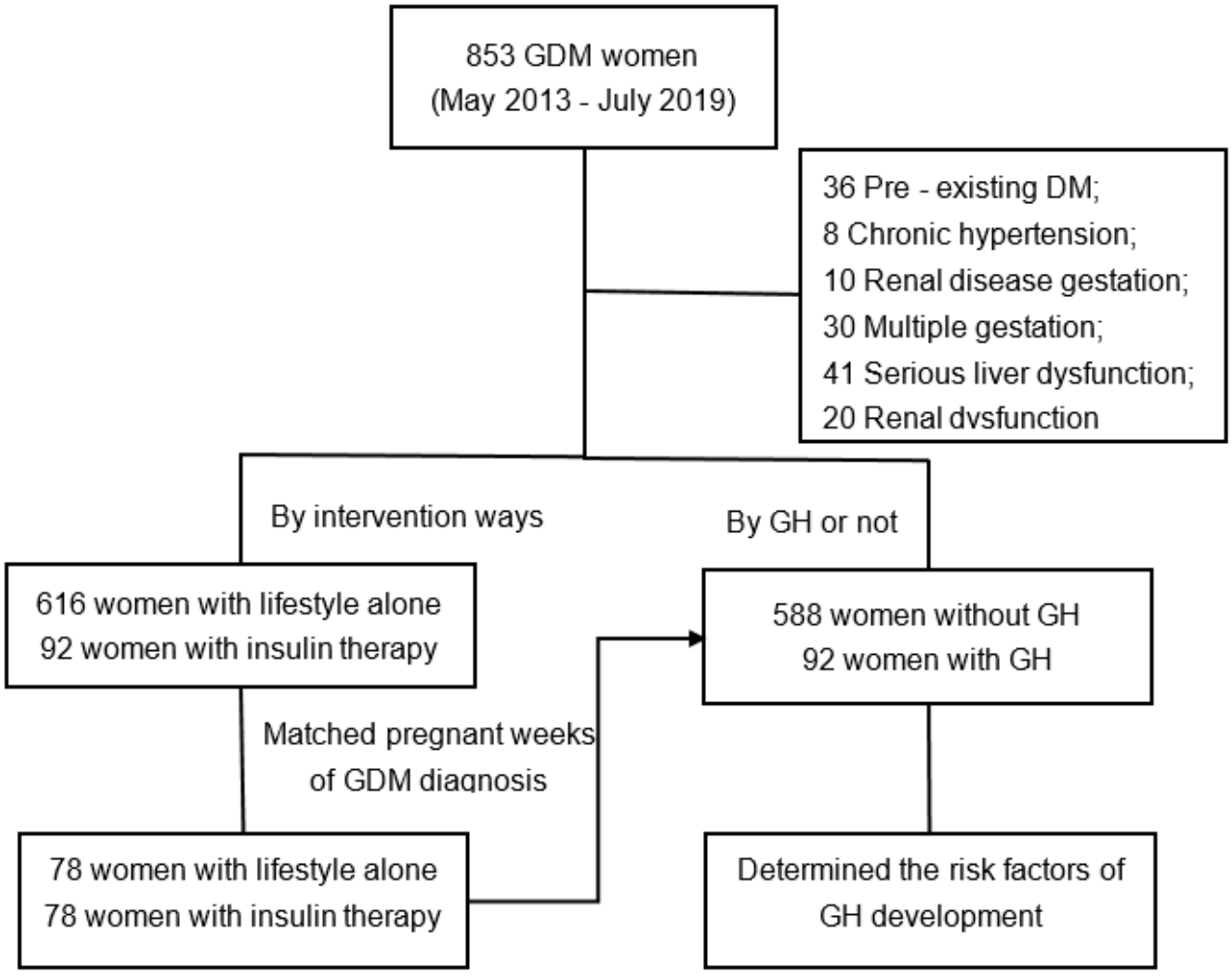

Figure 1

Loading [MathJax]/jax/output/CommonHTML/jax.js l diabetes mellitus; GH, gestational hypertension

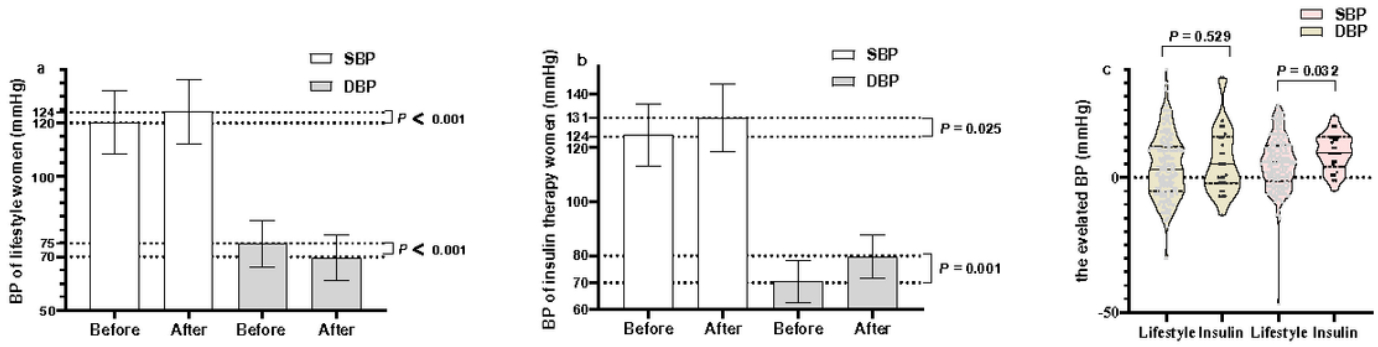

Figure 2

Comparing the changes of BP before and after intervention in GDM women Figure a was the changes of BP in women with lifestyle alone; Figure b was the changes of BP in women with insulin therapy; Figure c was the comparison of the elevated BP between women with lifestyle alone and with insulin therapy. GDM, gestational diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TablesSun.xlsx