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Review Article

Effect of metformin combined with insulin aspart on β-HCG and PAPP-A in gestational diabetes mellitus

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Abstract: Objective: This study set out to study the effect of metformin combined with insulin aspart on gestational diabetes mellitus and its effect on β-HCG and PAPP-A. Methods: Seventy-five patients with gestational diabetes mellitus from June 2018 to August 2019 in Qinhuangdao Seaport Hospital's obstetrics and gynecology department were selected and divided into group A and group B. Among them, 35 cases were in group A and insulin aspart was injected, while 40 cases were in group B, taking metformin orally. The related blood glucose indexes and biochemical indexes after treatment were observed, and so were the case results of postpartum maternal and infant testing and outcomes. Results: The average hospitalization time in group B was shorter than that in group A ($P < 0.05$). The FBG and 2h-PG indexes in group B were lower than those in group A ($P < 0.05$). The biochemical indexes in group B were lower than those in group A ($P < 0.05$). The incidence of complications and adverse maternal and infant outcomes in group B were lower than those in group A ($P < 0.05$). After treatment, the PAPP-A index level in group B was higher than that in group A ($P < 0.05$), and the β-HCC index level in group B was lower than that in group A ($P < 0.05$). Conclusion: Metformin combined with insulin aspart reduces β-HCG and increases PAPP-A in gestational diabetes mellitus patients.

Keywords: Metformin, insulin aspart, gestational diabetes mellitus, β-HCG, PAPP-A

Introduction

Gestational diabetes mellitus is usually considered as the onset of the disease in women between 24 and 28 weeks of pregnancy, and is first identified by having glucose intolerance [1]; however, it usually disappears after delivery [2]. It is the most common metabolic dysfunction during pregnancy. About 15% of pregnant women in the world are affected [3]. If not treated in time, it will increase the risk of complications. It can also lead to fetal overgrowth and cause problems during childbirth with both mother and child; including birth injury, caesarean section and neonatal period [4]. In addition, according to demographics, the incidence of gestational diabetes mellitus is expected to increase in the future [5]. Traditionally, insulin has been considered as the management standard for gestational diabetes mellitus when diet and exercise cannot achieve strict maternal glucose control without the risk of insulin trans-placental transfer [6]. However, it is worrying that insulin therapy may lead to changes in placental and umbilical vessels as well as in the fetuses and newborns [7]. It can lead to increased storage of fetal pancreas, heart, liver and fat as well as changes in nutritional components [8]. Metformin is a widely used drug, which has clear benefits in glucose metabolism and diabetes-related complications [9]. In recent years, more and more studies have shown that oral hypoglycemic drugs, such as glibenclamide and metformin, can be used to treat gestational diabetes mellitus [10]. As metformin may have advantages over glibenclamide as a first-line therapeutic drug, we chose it in this study [11]. It has been increasingly recognized as a substitute for insulin in the treatment of gestational diabetes mellitus and has strong evidence for its effectiveness and safety [12]. Therefore, this study is to explore the effect of metformin combined with insulin aspart on gestational diabetes mellitus and its effect on β-HCG and PAPP-A.

Materials and methods

General information

From June 2018 to August 2019, 75 patients with gestational diabetes mellitus in Qinhuangdao Seaport Hospital's Obstetrics and Gynecology Department were selected and divided into group A and group B. Among them, 35 patients were in group A and were injected insulin aspart, and the gestational age was (22.46±1.34) weeks; 40 patients were in group B, taking metformin orally and the gestational age was (22.69±1.43) weeks.

Exclusion and inclusion criteria

Inclusion criteria were as follows: fasting plasma glucose (FPG) > 5.6 mmol/l in all parturients, blood glucose two hours after meal ≥ 7.8 mmol/l, complete clinical data. This study was approved by the Ethics Committee of Qinhuangdao Seaport Hospital and pregnant women and their families signed informed consent forms.

Exclusion criteria were as follows: Patients with communication disorders; patients with severe hepatic and renal insufficiency; patients with drug allergy; patients with major infectious diseases; or patients with mental disorders.

Methods

Patients in the two groups had the same diet and received appropriate healthy exercise. Patients in group A received subcutaneous insulin aspart (SFDA Approval No. S20133006, China Novonordisk Pharmaceutical Co., Ltd.) 0.1 U/kg half an hour before eating three meals a day. Patients in group B took metformin (0.5 g, SFDA Approval No. H20050699, Shanghai Sine Pharmaceutical Co., Ltd.) orally, one tablet each time, twice a day. Patients in both groups were given drugs until delivery, and their blood glucose changes were closely monitored during the medication period.

Outcome measures

Fasting blood glucose (FBG) and 2 h postprandial blood glucose (2hPG) of patients in the two groups before delivery were measured by a blood glucose monitor (Henan Zeyuan Medical Device Sales Co., Ltd.).

The fasting blood of patients in the two groups was collected in the morning. After standing for 20 min, the serum was separated by centrifuge (10×g at 4°C for 15 min, Beijing BMH Instrument Co., Ltd.) and quickly frozen in liquid nitrogen and stored at -80°C for standby. Glycosylated hemoglobin (HbAlc) was determined by turbidimetric inhibition immunoassay, total cholesterol (TC) and total bilirubin (TBil) were monitored by a full-automatic biochemical analyzer, and PAPP-A (pregnancy-related plasma protein A) and β-HCG (β-human chorionic gonadotropin) levels were detected by ELISA (Suzhou ELSBIO Biotechnology Co., Ltd.).

The complications of the patients were as follows: gestational hypertension, hypoglycemia, ketoacidosis, proteinuria, urinary tract infection, pre-eclampsia.

Statistical analysis

SPSS 21.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. The measurement data were expressed by ($\bar{x}$ ± sd), and comparison of those data between groups was performed with at test; the counting data were expressed by [n (%)], and comparison of those data between groups was done with the chi-square test. $P < 0.05$ was considered to be a statistically significant difference.

Results

General information of patients in the two groups

There was no difference between the two groups in general data such as self-condition and basic symptoms ($P > 0.05$) (**Table 1**).

Comparison of maternal and infant testing results between the two groups

The average hospitalization time of group A and group B was (5.35±1.54) d and (4.03±0.57) d, respectively. The blood glucose of infants in group A and group B were (3.63±0.36) mmol/L and (3.79±0.53) mmol/L, respectively. The birth weight of infants in group A and group B were (3.42±0.65) kg and (3.57±0.45) kg, respectively. The average hospitalization time in group B was shorter than that in group A ($P < 0.05$). There was no difference between the other factors in the two groups ($P > 0.05$). More details were shown in **Figure 1**.

Table 1. General data table of patients in the two groups ($\bar{x} \pm sd$) [n (%)]

Classification	Group A (n=35)	Group B (n=40)	t/χ^2 value	*P* value
Age (years)	28.48±4.29	29.23±4.21	0.762	0.448
Height (cm)	162.57±3.26	163.58±3.11	1.372	0.174
Weight (kg)	73.57±5.35	74.63±5.24	0.865	0.389
Gestational age (week)	22.46±1.34	22.69±1.43	0.476	0.715
Place of residence			0.001	0.947
Countryside	13 (37.14)	15 (37.50)		
Cities and towns	22 (62.86)	25 (62.50)		
Education background			0.135	0.712
Below high school	10 (28.57)	13 (32.50)		
Above high school	25 (71.43)	27 (67.50)		
Nationality			0.266	0.605
Han	28 (80.00)	30 (75.00)		
Ethnic minorities	7 (20.00)	10 (25.00)		
Economic level			0.116	0.943
Difficulty	8 (22.86)	9 (22.50)		
Well-to-do	16 (45.71)	17 (42.50)		
Rich	11 (31.43)	14 (35.00)		
Stay up all night			0.455	0.499
Yes	14 (40.00)	13 (32.50)		
No	21 (60.00)	27 (67.50)		
Exercise			0.023	0.877
Yes	19 (54.29)	21 (52.50)		
No	16 (45.71)	19 (47.50)		
Obesity			0.062	0.802
Yes	15 (42.86)	16 (40.00)		
No	20 (57.14)	24 (60.00)		
Parity			0.030	0.861
< 2	26 (74.26)	29 (72.50)		
≥ 2	9 (25.71)	11 (27.50)		
Mode of production			0.303	0.581
Eutocia	24 (68.57)	25 (62.50)		
Cesarean births	11 (31.43)	15 (37.50)		

Comparison of blood glucose indexes between the two groups

FBG indexes of group A and group B were (5.56±0.86) mmol/L and (4.13±0.75) mmol/L, respectively. The 2h-PG indexes of group A and group B were (8.68±1.23) mmol/L and (5.79±1.02) mmol/L, respectively. The FBG and 2h-PG indexes in group B were lower than those in group A ($P < 0.05$). More details were shown in **Figure 2**.

Comparison of biochemical indexes between the two groups

HbAlc indexes of group A and group B were (6.46±1.43)% and (5.25±1.14)%, respectively. The TC indexes of group A and group B were (3.87±0.46) mmol/L and (2.79±0.37) mmol/L, respectively. The TBil indexes of group A and group B were (12.65±1.43) μoml/L and (10.47±1.35) μoml/L, respectively. The related indexes in group B were lower than those in group A ($P < 0.05$). More details were shown in **Figure 3**.

Comparison of complications between the two groups

The total incidence of complications in group A was 45.71%, while that in group B was 17.50%, and the incidence of complications in group B was lower than that in group A ($P < 0.05$), as shown in **Table 2**.

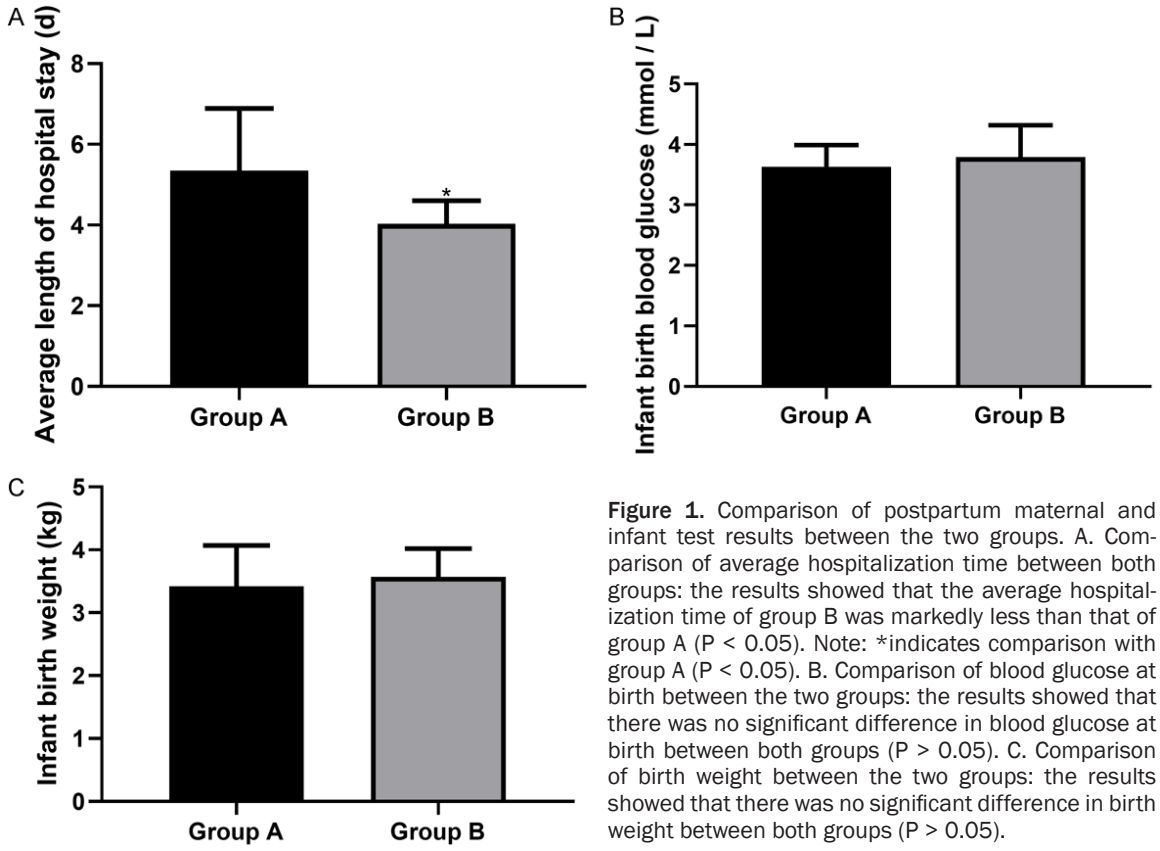

Figure 1. Comparison of postpartum maternal and infant test results between the two groups. A. Comparison of average hospitalization time between both groups: the results showed that the average hospitalization time of group B was markedly less than that of group A ($P < 0.05$). Note: *indicates comparison with group A ($P < 0.05$). B. Comparison of blood glucose at birth between the two groups: the results showed that there was no significant difference in blood glucose at birth between both groups ($P > 0.05$). C. Comparison of birth weight between the two groups: the results showed that there was no significant difference in birth weight between both groups ($P > 0.05$).

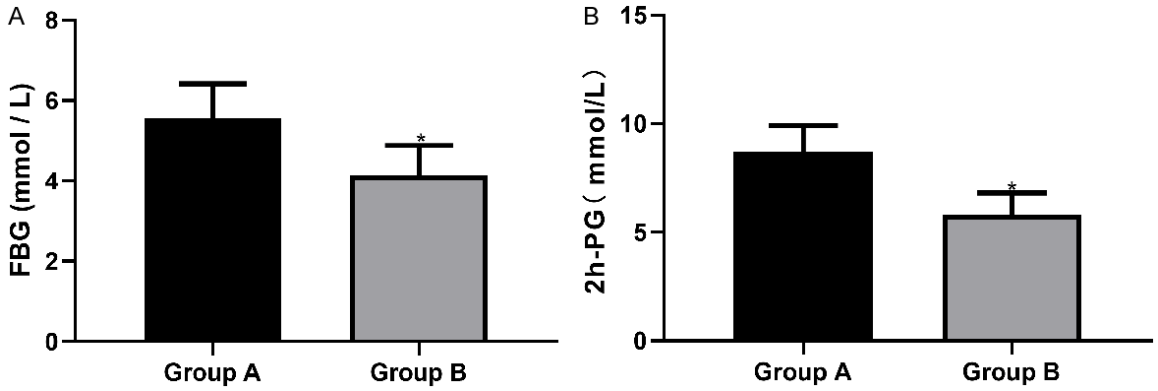

Figure 2. Comparison of blood glucose indexes between the two groups. A. Comparison of FBG index levels between both groups: the results showed that the FBG index level in group B was dramatically lower than that in group A ($P < 0.05$). Note: *indicates comparison with group A ($P < 0.05$). B. Comparison of 2h-PG index level between both groups: the results showed that 2h-PG index level in group B was dramatically lower than that in group A ($P < 0.05$). Note: *indicates comparison with group A ($P < 0.05$).

Comparison of maternal and infant outcomes between the two groups

There were 18 cases of abnormal maternal and infant outcomes in group A, with a total incidence of 51.43%. There were 9 cases of abnormal maternal and infant outcomes in group B, with a total incidence of 22.50%. Abnormal maternal and infant outcomes in group B were lower than those in group A ($P < 0.05$). More details were shown in **Table 3**.

Comparison of PAPP-A indexes between the two groups before and after treatment

The PAPP-A index levels before and after treatment in group A were (20.54±1.53) ng/mL and (22.69±1.45) ng/mL, respectively. The PAPP-A

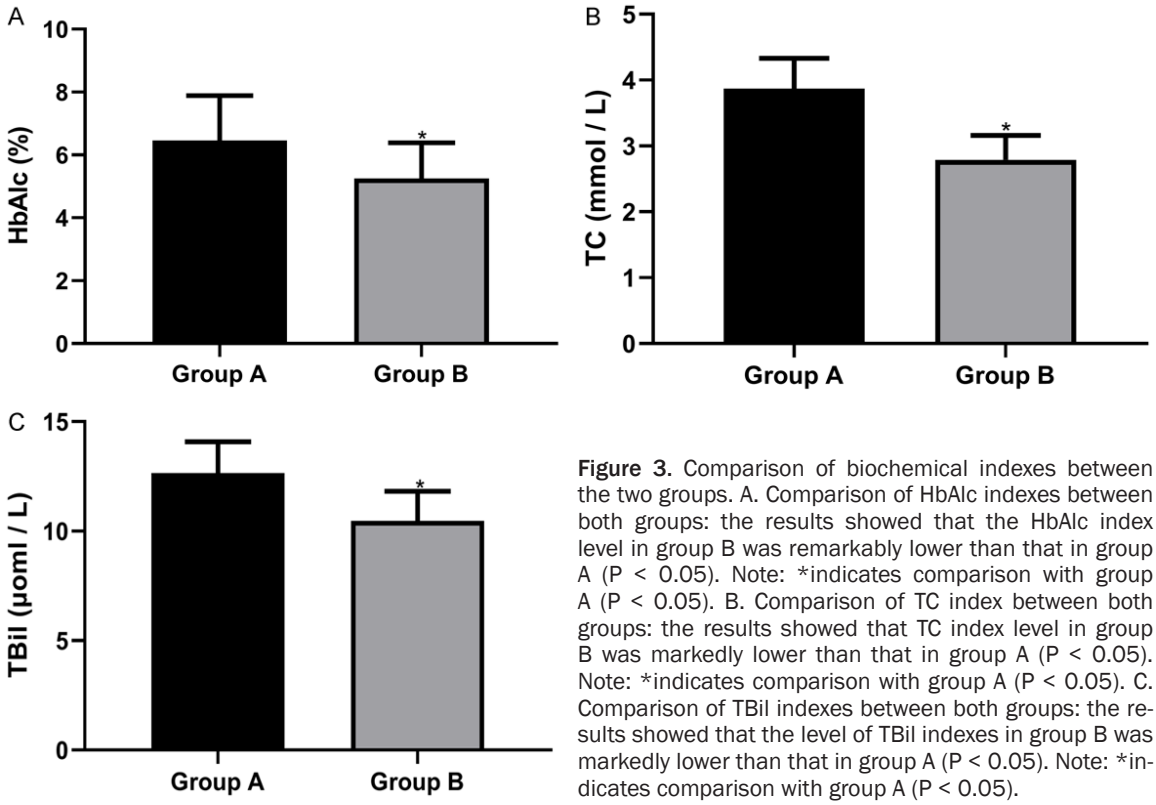

Figure 3. Comparison of biochemical indexes between the two groups. A. Comparison of HbAlc indexes between both groups: the results showed that the HbAlc index level in group B was remarkably lower than that in group A ($P < 0.05$). Note: *indicates comparison with group A ($P < 0.05$). B. Comparison of TC index between both groups: the results showed that TC index level in group B was markedly lower than that in group A ($P < 0.05$). Note: *indicates comparison with group A ($P < 0.05$). C. Comparison of TBil indexes between both groups: the results showed that the level of TBil indexes in group B was markedly lower than that in group A ($P < 0.05$). Note: *indicates comparison with group A ($P < 0.05$).

Table 2. Comparison of complications of patients between the two groups [n (%)]

Complication	Group A (n=35)	Group B (n=40)	X^2	P
Gestational hypertension	2 (5.71)	1 (2.50)	-	-
Hypoglycemia	4 (11.43)	1 (2.50)	-	-
Ketoacidosis	2 (5.71)	1 (2.50)	-	-
Proteinuria	2 (5.71)	1 (2.50)	-	-
Urethral infection	3 (8.57)	2 (5.00)	-	-
Preeclampsia	3 (8.57)	1 (2.50)	-	-
Total incidence	16 (45.71)	7 (17.50)	6.989	0.008

index levels before and after treatment in group B were (20.48±1.49) ng/mL and (25.89±1.22) ng/mL, respectively. Compared with the same group, the PAPP-A index level of the two groups increased after treatment ($P < 0.05$). There was no difference between the two groups before treatment ($P > 0.05$). After treatment, the PAPP-A index level in group B was higher than that in group A ($P < 0.05$). More details were shown in **Figure 4**.

Comparison of β-HCG indexes between the two groups before and after treatment

The β-HCC index levels before and after treatment in group A were (1.47±0.86) MOM and (1.15±0.36) MOM, respectively. The β-HCC index levels before and after treatment in group B were (1.46±0.85) MOM and (0.98±0.24) MOM, respectively. Compared with the same group, the β-HCC index level in both groups decreased after treatment ($P < 0.05$). There was no difference between the two groups before treatment ($P > 0.05$). After treatment, the β-HCC index level in group B was lower than that in group A ($P < 0.05$). More details were shown in **Figure 5**.

Discussion

PAPP-A is one of the four placental proteins found at high concentrations in pregnant women's blood [14]. It is also a member of the metalloprotease superfamily, and enhances the bioavailability of local insulin-like growth factor through proteolysis of insulin-like growth factor binding protein. This is important because the insulin-like growth factor axis plays a crucial role in the growth of the fetus and the growth and function of the placenta during pregnancy [15]. Some studies have shown that PAPP-A is a potential biomarker of gestational diabetes risk, and it seems to be

Table 3. Comparison of maternal and infant outcomes between the two groups [n (%)]

Classification	Group A (n=35)	Group B (n=40)	X^2	P
Giant baby	3 (8.57)	1 (2.50)	-	-
Polyhydramnios	4 (11.43)	2 (5.00)	-	-
Premature delivery	2 (5.71)	2 (5.00)	-	-
Neonatal respiratory distress syndrome (NRDS)	3 (8.57)	1 (2.50)	-	-
Neonatal jaundice	3 (8.57)	2 (5.00)	-	-
Placental abruption	2 (5.71)	1 (2.50)	-	-
Postpartum hemorrhage	1 (2.86)	0 (0.00)	-	-
Total	18 (51.43)	9 (22.50)	6.780	0.009

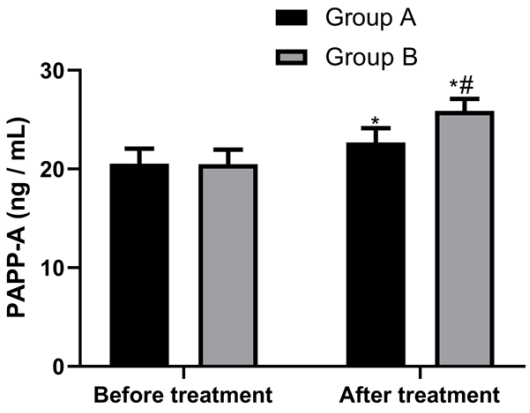

Figure 4. Comparison of PAPP-A index between the two groups before and after treatment. In the same group, the PAPP-A index level of both groups after treatment increased compared with that before treatment ($P < 0.05$); there was no difference between the two groups before treatment ($P > 0.05$). After treatment, the PAPP-A index level in group B was higher than that in group A ($P < 0.05$). Note: *indicates comparison with the same group before treatment ($P < 0.05$); #indicates comparison with group A ($P < 0.05$).

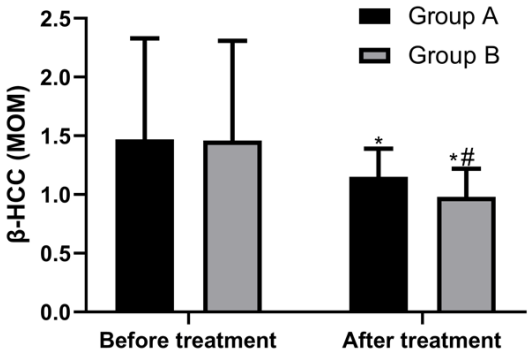

Figure 5. Comparison of β-HCG indexes between the two groups before and after treatment. In the same group, the β-HCC index level of both groups after treatment decreased compared with that before treatment ($P < 0.05$); there was no difference between the two groups before treatment ($P > 0.05$). After treatment, the β-HCC index level in group B was lower than that in group A ($P < 0.05$). Note: *indicates comparison with the same group before treatment ($P < 0.05$); #indicates comparison with group A ($P < 0.05$).

tied to changes in insulin sensitivity in pregnancy [16]. In addition, some studies have shown that the reduction of serum PAPP-A level of pregnant women in early pregnancy not only predicts chromosomal abnormalities, but also predicts adverse pregnancy outcomes [17]. This indicates that the reduction of serum PAPP-A level may increase the risk of adverse pregnancy outcomes. In this experiment, we found that metformin combined with insulin increased serum PAPP-A level more clearly than insulin alone. Some studies have also shown a remarkable reduction in multiple of median of PAPP-A in gestational diabetes. Early pregnancy screening with PAPP-A can effectively identify high-risk women with gestational diabetes [18]. β-HCG is produced by normal trophoblast tissue in placenta [19], which is a pregnancy-specific hormone and regulates placental development. Its abnormal concentration is relevant to adverse pregnancy outcomes, including fetal growth restriction [20]. It can also be used to diagnose and monitor pregnancy [21]. Some studies have signified that low PAPP-A content and high β-hCG content may affect pregnancy outcome [22]. In this study, we found that metformin combined with insulin reduced serum β-hCG content more dramatically than insulin alone. All of these can explain that metformin combined with insulin affects PAPP-A and β-hCG contents and may improve adverse pregnancy outcomes. Therefore, we observed the related complications and maternal and infant outcomes in this test. Gestational diabetes is concerned with pregnancy and adverse maternal and infant outcomes during their

long-term health [23]. Some studies have shown that gestational diabetes of any severity increases the risk of fetal macrosomia, and is also related to the increased frequency of maternal hypertension and the need for cesarean section [24]. Other studies have shown that women with gestational diabetes have increased risks of hypertension and preeclampsia, proteinuria and swelling during pregnancy, and may increase the gestational age of infants [25]. Moreover, maternal hyperglycemia associated with gestational diabetes mellitus leads to fetal hyperglycemia as well as fetal hyperinsulinemia and change L-arginine transport and nitric oxide synthesis, namely endothelial dysfunction [26]. In this study, the incidence of complications and adverse maternal and infant outcomes in group B were markedly lower than those in group A, which indicated that the combined use of metformin and insulin reduced the incidence of related complications and adverse maternal and infant outcomes greatly. The reason for this result was that metformin easily crossed the placenta through organic cation transporter and might reach the fetus, whose concentration was close to that of mothers [27]. Metformin can effectively reduce the production of anti-angiogenic factors and improve endothelial dysfunction [28]. Some studies have shown that metformin can clearly reduce the complications of pregnancy hypertension in patients with gestational diabetes mellitus, possibly by reducing the activation of endothelial cells and the inflammatory response of insulin resistance in mothers. Although metformin can cross the placenta, it is less likely to cause severe neonatal hypoglycemia than insulin because it neither stimulates pancreatic insulin release nor increases circulating insulin levels [29]. In conclusion, the use of metformin instead of insulin in treating gestational diabetes mellitus has a good effect on the safety and long-term benefits of mothers and children [30].

To summarize, metformin combined with insulin effectively improves the β-HCG and PAPP-A levels, reduces the occurrence of complications and the occurrence of adverse maternal and infant outcomes.

Disclosure of conflict of interest

None.

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