

doi: 10.13241/j.cnki.pmb.2017.23.025

二甲双胍联合门冬胰岛素对妊娠期糖尿病患者血清胆固醇、总胆红素、尿酸和尿微量蛋白水平及母婴结局的影响 *

包小燕¹ 李人立² 张丽芸³ 井秋芳⁴ 李洪涛⁵

(1 西宁市第一人民医院 内分泌科 青海 西宁 810000; 2 解放军第四医院 外二科 青海 西宁 810001; 3 西宁市第一人民医院 妇产科 青海 西宁 810000; 4 青海省疾病预防控制中心 检验科 青海 西宁 810007; 5 青海大学附属医院 外科 青海 西宁 810001)

摘要 目的:探讨二甲双胍联合门冬胰岛素对妊娠期糖尿病患者血清胆固醇(TC)、总胆红素(TBil)、尿酸(UA)、尿微量蛋白(mAlb)水平及母婴结局的影响。**方法:**选择2014年6月至2016年6月我院接诊的84例妊娠期糖尿病患者,通过随机数表法分为观察组(n=42)和对照组(n=42)。在常规治疗基础上,对照组使用门冬胰岛素治疗,观察组再联合盐酸二甲双胍。比较两组治疗前后血糖指标、TC、TBil、UA、mAlb的变化以及母婴结局。**结果:**治疗后,观察组空腹血糖(FBG)、餐后2h血糖(2hPG)、糖化血红蛋白(HbA1c)、TC、UA、mAlb水平均显著低于对照组($P<0.05$),TBil水平明显高于对照组($P<0.05$),妊娠期高血压、羊水过多、早产、剖宫产、巨大儿、新生儿黄疸的发生率均显著低于对照组($P<0.05$)。**结论:**二甲双胍联合门冬胰岛素对妊娠期糖尿病患者的疗效显著,可有效改善患者血糖指标以及TC、TBil、UA、mAlb水平,改善母婴结局。

关键词:妊娠期糖尿病;二甲双胍;门冬胰岛素;母婴结局

中图分类号:R714.256;R587.2 **文献标识码:**A **文章编号:**1673-6273(2017)23-4510-04

Effect of Metformin Combined with Insulin Aspart on Serum Cholesterol, Total Bilirubin, Uric Acid, Urinary Micro Protein Levels, Maternal and Infant Outcomes of Gravidia with Gestational Diabetes Mellitus*

BAO Xiao-yan¹, LI Ren-li², ZHANG Li-yun³, JING Qiu-fang⁴, LI Hong-tao⁵

(1 Department of Endocrinology, Xining First People's Hospital, Xining, Qinghai, 810000, China; 2 The second department of surgery, the fourth hospital of PLA, Xining, Qinghai, 810001, China; 3 Department of Obstetrics and Gynecology, Xining First People's Hospital, Xining, Qinghai, 810000, China; 4 Department of laboratory, Qinghai province disease prevention control center, Xining, Qinghai, 810007, China; 5 Department of surgery, Affiliated Hospital of Qinghai University, Xining, Qinghai, 810001, China)

ABSTRACT Objective: To study the effect of metformin combined with insulin aspart on the serum cholesterol(TC), total Bilirubin(TBil), uric Acid(UA), urinary Micro Protein(mAlb) levels and Maternal and Infant Outcomes of gravidia with Gestational Diabetes Mellitus. **Methods:** 84 patients of gestational diabetes mellitus who received therapy from June 2014 to June 2016 in our hospital were selected. According to random number table, those patients were divided into the observation group (n=42) and the control group (n=42), on the basis of routine treatment, The control group was treated with insulin aspart, while the observation group was combined with metformin hydrochloride. The blood glucose index and the levels of TC, TBil, UA, mAlb and maternal and infant outcomes were compared. **Results:** After treatment, the levels of fasting blood glucose (FBG), postprandial 2h blood glucose (2hPG), glycosylated hemoglobin (HbA1c), TC, TBil, UA and mAlb in the observation group were significantly lower than the control group, the levels of TBil was significantly higher than the control group ($P<0.05$); the incidence of gestational hypertension, hydramnios, premature birth, cesarean section, giant child and neonatal jaundice were significantly lower than the control group ($P<0.05$). **Conclusion:** Metformin combined with insulin aspart was well for gestational diabetes mellitus, which could effectively improve the blood glucose indicators and TC, TBil, UA, mAlb levels, maternal and infant outcomes.

Key words: Gestational diabetes mellitus; Metformin; Insulin aspart; Maternal and infant outcomes

Chinese Library Classification(CLC): R714.256; R587.2 **Document code:** A

Article ID: 1673-6273(2017)23-4510-04

前言

妊娠期糖尿病主要指在妊娠前未存在糖尿病或糖耐量异

常,但在妊娠期首次发生糖尿病或者糖耐量异常,该病在产科的发病率为1%~15%^[1]。若孕妇血糖得不到良好的控制,则很可能会出现羊水过多、高血压、酮症酸中毒等并发症,同时也会使

* 基金项目:青海省自然科学基金项目(20154-Z-203)

作者简介:包小燕(1970-),女,本科,主治医师,研究方向:高原地区糖尿病及其并发症的治疗,电话:13369768332

(收稿日期:2016-12-27 接受日期:2017-01-21)

早产的机率增加,而且由于产妇子宫内代谢环境的变化,会增加围生儿并发症的发生率,对母婴的身心健康造成严重影响^[2]。目前,临床对该病的治疗主要采取胰岛素,但单独用药难以得到令人满意的效果,尤其是对于存在胰岛素抵抗的人群^[3]。二甲双胍是一种胰岛素增敏剂,近年来逐渐被应用于治疗妊娠期糖尿病患者^[4]。本研究旨在探讨二甲双胍联合门冬胰岛素治疗妊娠期糖尿病的疗效及对母婴结局的影响。

1 资料与方法

1.1 一般资料

选择我院接诊的 84 例妊娠期糖尿病患者。纳入标准:①符合妊娠期糖尿病诊断标准^[5];②经过常规控制饮食、运动、健康教育等方式血糖未得到明显控制,需采取药物治疗;③单胎;④同意参与此次研究。排除标准^[6]:①心、肝、肺、脑、肾等严重脏器疾病、遗传病、内分泌疾病;②不适用研究药物。通过随机数表法分为观察组和对照组,各 42 例。观察组年龄 23~41 岁,平均(29.84±2.05)岁;孕周 24~38 周,平均(31.37±1.75)周;初产妇 29 例,经产妇 13 例。对照组年龄 22~40 岁,平均(30.02±1.94)岁;孕周 24~39 周,平均(31.44±1.68)周;初产妇 25 例,经产妇 17 例。本次研究已获得我院伦理委员会批准,两组患者的一般临床资料比较差异无统计学意义($P>0.05$),具有可比性。

1.2 治疗方法

两组均给予常规健康教育、控制饮食、运动等方式。对照组使用门冬胰岛素 [规格 3 mL: 300 IU, 国药准字 J20050097, 厂

家:诺和诺德(中国)制药有限公司]治疗,在晚餐前,于皮下注射,最开始剂量为 0.2~0.3 IU(kg·d),之后根据血糖水平增减 2IU。观察组联合盐酸二甲双胍(规格 0.5 g, 国药准字 H20023370, 厂家:中美上海施贵宝制药有限公司),剂量 0.5g/次,2 次/d。两组均治疗至胎儿出生。

1.3 观察指标

①检测空腹血糖(FBG)、餐后 2 h 血糖(2hPG)、糖化血红蛋白(HbA1c);②抽取患者 5 mL 空腹静脉血,使用日立 7600-010 全自动生化分析仪,测定胆固醇(TC)、总胆红素(TBil)、尿酸(UA)浓度,并收集尿液,使用免疫比浊法测尿微量蛋白(mAlb)浓度;③记录两组产妇妊娠期高血压、低血糖、蛋白尿、羊水过多、早产、剖宫产等并发症;④记录两组巨大儿、新生儿黄疸、低血糖、呼吸窘迫等发生率。

1.4 统计学分析

数据用 spss18.0 软件包处理,计量资料以均数±标准差($\bar{x}\pm s$)表示,采用 t 检验,计数资料采用 χ^2 检验,以 $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组治疗前后血糖指标比较

两组患者治疗前 FBG、2hPG、HbA1c 水平比较差异均无统计学意义($P>0.05$);治疗后,两组 FBG、2hPG、HbA1c 水平均较治疗前显著降低($P<0.05$),且观察组 FBG、2hPG、HbA1c 水平均明显低于对照组($P<0.05$),见表 1。

表 1 两组治疗前后血糖指标比较($\bar{x}\pm s$)

Table 1 Comparison of the blood glucose indexes between two groups before and after treatment($\bar{x}\pm s$)

Groups		FBG(mmol/L)	2hPG(mmol/L)	HbA1c(%)
Observation group(n=42)	Before treatment	8.48±1.79	11.38±2.42	7.84±1.35
	After treatment	4.05±0.82* [#]	5.76±0.64* [#]	5.31±0.69* [#]
Control group(n=42)	Before treatment	8.53±1.75	11.41±2.35	7.79±1.39
	After treatment	5.61±1.03*	8.35±0.74*	6.26±1.05*

Note: Compared with before treatment, * $P<0.05$; compared with the control group, [#] $P<0.05$.

2.2 两组治疗前后 TC、TBil、UA、mAlb 水平比较

治疗前,两组 TC、TBil、UA、mAlb 水平比较差异均无统计学意义($P>0.05$);治疗后,两组 TC、TBil、UA、mAlb 水平均较

治疗前显著改善($P<0.05$),且观察组 TC、UA、mAlb 水平明显低于对照组, TBil 水平显著高于对照组($P<0.05$),见表 2。

表 2 两组治疗前后 TC、TBil、UA、mAlb 水平比较($\bar{x}\pm s$)

Table 2 Comparison of the levels of TC, TBil, UA and mAlb between two groups before and after treatment ($\bar{x}\pm s$)

Groups		TC(mmol/L)	TBil(μ mol/L)	UA(μ mol/L)	mAlb(mg/L)
Observation group (n=42)	Before treatment	4.58±0.61	8.58±0.49	278.45±15.68	18.49±1.87
	After treatment	2.58±0.43* [#]	12.46±0.63* [#]	211.31±12.35* [#]	9.37±1.35* [#]
Control group(n=42)	Before treatment	4.55±0.64	8.55±0.51	284.71±15.32	18.54±1.85
	After treatment	3.24±0.57*	10.32±0.54*	246.86±14.55*	13.46±1.79*

Note: Compared with before treatment, * $P<0.05$; compared with the control group, [#] $P<0.05$.

2.3 两组产妇并发症发生情况比较

两组产妇低血糖、蛋白尿的发生率比较差异均无统计学意义($P>0.05$),观察组妊娠期高血压、羊水过多、早产、剖宫产的发生率分别为 7.13%、7.13%、0.00%、9.52%,均比对照组显著降低($P<0.05$),见表 3。

2.4 两组新生儿情况比较

两组新生儿低血糖、呼吸窘迫的发生率比较差异均无统计学意义($P>0.05$),观察组巨大儿、新生儿黄疸的发生率分别为 7.13%、9.52%,均明显低于对照组($P<0.05$),见表 4。

表 3 两组产妇并发症发生情况比较(例,%)

Table 3 Comparison of the incidence of complication between two groups of maternal (n, %)

Groups	Gestational hypertension	Hypoglycemia	Proteinuria	Hydramnios	Premature birth	Cesarean section
Observation group(n=42)	3(7.13)*	2(4.76)	1(2.38)	3(7.13)*	0(0.00)*	4(9.52)*
Control group(n=42)	12(28.57)	4(9.52)	5(11.90)	15(35.71)	5(11.90)	14(33.33)

Note: Compared with the control group, *P<0.05.

表 4 两组新生儿情况比较(例,%)

Table 4 Comparison of the complication between two groups of newborn (n, %)

Groups	Giant child	Neonatal hypoglycemia	Neonatal Jaundice	Neonatal respiratory distress
Observation group(n=42)	3(7.13)*	2(4.76)	4(9.52)*	2(4.76)
Control group(n=42)	13(30.95)	4(9.52)	15(35.71)	6(14.28)

Note: Compared with the control group, *P<0.05.

3 讨论

妊娠期糖尿病很大程度上会威胁母婴健康,不仅易致使孕妇发生多种并发症,还容易引发胎儿窘迫,严重甚至胎死宫内^[7]。研究表明高血糖是该病造成不良母婴结局的关键性因素,早期采取积极干预措施控制血糖可改善母婴结局^[8,9]。门冬胰岛素的活性和天然胰岛素相似,但具有更快的吸收效果,可更好的控制餐后血糖,降低低血糖的发生率^[10]。虽然该药物在妊娠期糖尿病患者中具有一定的效果,但由于部分患者存在胰岛素抵抗,往往需联合使用胰岛素增敏剂^[11]。盐酸二甲双胍是一种口服降糖药,主要是通过延缓葡萄糖的摄取使组织胰岛素敏感性及利用率增加发挥降糖作用^[12]。本研究结果显示联合用药的患者 FBG、2hPG、HbA1c 下降程度优于单独用药,可能由于二甲双胍具有增加胰岛素敏感性的作用,并与门冬胰岛素相互配合,从多个方面有效控制血糖。妊娠期糖尿病患者的母婴结局取决于血糖控制程度,较好的控制血糖可降低母婴并发症。本次研究也显示联合用药的患者在妊娠期高血压、羊水过多、早产、剖宫产发生率明显低于单独用药,且巨大儿、新生儿黄疸发生率也较低,也进一步说明联合用药在有效控制血糖后,可较好的改善母婴结局。这与 Zawiejska A^[13]等研究具有相似性。

在妊娠期糖尿病患者中,由于胰岛素缺乏或者胰岛素抵抗的情况,会出现脂代谢紊乱,降低脂蛋白酶活性,致使 TC 等水平的增加,通过检测患者的血脂水平对脂质代谢的变化进行了解^[14]。Krstevska B 等^[15]报道妊娠期糖尿病患者血脂水平和母婴结局存在着密切的关系。TBil 具有心血管保护效果,主要机制是对动脉粥样硬化产生抑制作用,有报道指出由于妊娠期糖尿病患者中糖代谢会对内皮细胞和肾脏功能造成损伤,TBil 浓度常呈下降趋势^[16]。血 UA 是机体内嘌呤类物质代谢产物,其水平的增加可提示肾脏能力的减弱,同时也可对氧自由基的水平间接反应^[17]。有研究指出在妊娠期糖尿病患者中,多存在血 UA 排泄障碍,肾小管排泄 UA 降低,致使血 UA 水平增加,而高浓度的 UA 会对糖尿病患者的微血管和大血管造成影响^[18]。正常人群中 mAlb 排泄量很低,若肾小球发生轻微损伤,尿 mAlb 会明显增加,可对肾小球的损伤程度进行早期反应^[19]。Kew S 等^[20]研究显示在妊娠期孕妇中,血容量水平增加,肾脏血流量、肾小球率过滤增加,会致使尿蛋白排泄量的增加,同时由于妊娠期

糖尿病患者处于高血糖状态,会对内皮细胞促进血管物质的释放造成影响,致使肾小球处于高滤过状态,损伤肾功能,对母婴结局也会造成一定影响。因此,为进一步评价治疗效果,本次研究还对产妇治疗前后 TC、TBil、UA、mAlb 的水平进行了检测,结果显示联合治疗的患者治疗后 TC、UA、mAlb 水平明显降低,TBil 水平增加,效果均优于单独用药,提示联合用药可积极改善 TC、TBil、UA、mAlb 水平,但其作用机制仍需进一步深入研究,这也可能是联合用药在改善母婴结局中的重要原因之一。

综上所述,二甲双胍联合门冬胰岛素对妊娠期糖尿病患者的疗效显著,可有效改善患者血糖指标以及 TC、TBil、UA、mAlb 水平,改善母婴结局。

参考文献(References)

- [1] Zhao M, Li GH. The value of fasting plasma glucose and lipid profiles between 7 and 15 gestational weeks in the prediction of gestational diabetes mellitus [J]. Chinese Journal of Obstetrics and Gynecology, 2016, 51(11): 835-839
- [2] Blackwell SC, Landon MB, Mele L, et al. Relationship Between Excessive Gestational Weight Gain and Neonatal Adiposity in Women With Mild Gestational Diabetes Mellitus [J]. Obstet Gynecol, 2016, 128(6): 1325-1332
- [3] Madhuvrata P, Govinden G, Bustani R, et al. Prevention of gestational diabetes in pregnant women with risk factors for gestational diabetes: a systematic review and meta-analysis of randomised trials [J]. Obstet Med, 2015, 8(2): 68-85
- [4] Tan MH, Alquraini H, Mizokami-Stout K, et al. Metformin: From Research to Clinical Practice [J]. Endocrinol Metab Clin North Am, 2016, 45(4): 819-843
- [5] Feig DS, Murphy K, Asztalos E, et al. Metformin in women with type 2 diabetes in pregnancy (MiTy): a multi-center randomized controlled trial[J]. BMC Pregnancy Childbirth, 2016, 16(1): 173
- [7] Farzan SF, Gossai A, Chen Y, et al. Maternal arsenic exposure and gestational diabetes and glucose intolerance in the New Hampshire birth cohort study[J]. Environ Health, 2016, 15(1): 106
- [8] Momeni Javid F, Simbar M, Dolatian M, et al. A Comparative Study on Dietary Style and Physical Activity of Women With and Without Gestational Diabetes[J]. Acta Med Iran, 2016, 54(10): 651-656

- [9] Colicchia LC, Parviainen K, Chang JC. Social Contributors to Glycemic Control in Gestational Diabetes Mellitus [J]. *Obstet Gynecol*, 2016, 128(6): 1333-1339
- [10] Zhu B, Zhang L, Fan YY, et al. Metformin versus insulin in gestational diabetes mellitus: a meta-analysis of randomized clinical trials [J]. *Ir J Med Sci*, 2016, 185(2): 371-381
- [11] Bergel R, Hadar E, Toledano Y, et al. Pharmacological Management of Gestational Diabetes Mellitus [J]. *Curr Diab Rep*, 2016, 16(11): 118
- [12] Ashoush S, El-Said M, Fathi H, et al. Identification of metformin poor responders, requiring supplemental insulin, during randomization of metformin versus insulin for the control of gestational diabetes mellitus [J]. *J Obstet Gynaecol Res*, 2016, 42(6): 640-647
- [13] Zawiejska A, Wender-Ozegowska E, Grewling-Szmit K, et al. Short-term antidiabetic treatment with insulin or metformin has a similar impact on the components of metabolic syndrome in women with gestational diabetes mellitus requiring antidiabetic agents: results of a prospective, randomised study [J]. *J Physiol Pharmacol*, 2016, 67(2): 227-233
- [14] Bhograj A, Suryanarayana KM, Nayak A, et al. Serum adiponectin levels in gestational diabetes mellitus [J]. *Indian J Endocrinol Metab*, 2016, 20(6): 752-755
- [15] Krstevska B, Jovanovska SM, Krstevska SS, et al. Maternal Lipids May Predict Fetal Growth in Type 2 Diabetes Mellitus and Gestational Diabetes Mellitus Pregnancies [J]. *Pril (Makedon Akad Nauk Umet Odd Med Nauki)*, 2016, 37(2-3): 99-105
- [16] Khosrowbeygi A, Shiamizadeh N, Taghizadeh N. Maternal circulating levels of some metabolic syndrome biomarkers in gestational diabetes mellitus [J]. *Endocrine*, 2016, 51(2): 245-255
- [17] Javadian P, Alimohamadi S, Gharedaghi MH, et al. Gestational diabetes mellitus and iron supplement; effects on pregnancy outcome [J]. *Acta Med Iran*, 2014, 52(5): 385-389
- [18] Roca-Rodríguez MM, López-Tinoco C. Postpartum development of endothelial dysfunction and oxidative stress markers in women with previous gestational diabetes mellitus [J]. *J Endocrinol Invest*, 2014, 37(6): 503-539
- [19] Roy S, Sherman A, Monari-Sparks MJ, et al. Association of Comorbid and Metabolic Factors with Optimal Control of Type 2 Diabetes Mellitus [J]. *N Am J Med Sci*, 2016, 8(1): 31-39
- [20] Kew S, Swaminathan B, Hanley AJ, et al. Postpartum microalbuminuria after gestational diabetes: the impact of current glucose tolerance status [J]. *J Clin Endocrinol Metab*, 2015, 100(3): 1130-1136

(上接第 4578 页)

- Zhang Long, Xu Xiao-hui, Geng Peng-bo, et al. Therapeutic effect evaluation of recombinant human brain natriuretic peptide combined with irbesartan in the treatment of congestive heart failure [J]. *Journal of Hunan Normal University (Medical Sciences)*, 2015, 12(6): 32-35
- [12] Nicholson C. Chronic heart failure: pathophysiology, diagnosis and treatment [J]. *Nursing Older People*, 2014, 26(7): 29-38
- [13] Hasin T, Kushwaha S S, Lesnick T G, et al. Early trends in N-terminal pro-brain natriuretic peptide values after left ventricular assist device implantation for chronic heart failure [J]. *American Journal of Cardiology*, 2014, 114(8): 1257-1263
- [14] Gür M, Uçar H, Kuloğlu O, et al. Estimated glomerular filtration rate is associated with both arterial stiffness and N-terminal pro-brain natriuretic peptide in newly diagnosed hypertensive patients [J]. *Clinical and Experimental Hypertension*, 2014, 62(6): 374-379
- [15] Mir T S, Marohn S, Lær S, et al. Plasma concentrations of N-terminal pro-brain natriuretic peptide in control children from the neonatal to adolescent period and in children with congestive heart failure [J]. *Pediatrics*, 2003, 110(6): 513-517
- [16] Richards A M. Brain natriuretic peptide-guided management of chronic heart failure: first do no harm [J]. *European Journal of Heart Failure*, 2013, 15(8): 832-834
- [17] Gong H, Wang X, Ling Y, et al. Prognostic value of brain natriuretic peptide in patients with heart failure and reserved left ventricular systolic function [J]. *Experimental & Therapeutic Medicine*, 2014, 7(6): 1506-1512
- [18] Du J B, Da C H, Zhao Y, et al. The role of brain natriuretic peptide and serum triiodothyronine in the diagnosis and prognosis of chronic heart failure [J]. *Acta Cardiologica*, 2012, 67(3): 291-296
- [19] Brouwers C, Spindler H, Larsen M L, et al. Association between psychological measures and brain natriuretic peptide in heart failure patients [J]. *Scandinavian Cardiovascular Journal*, 2012, 46(3): 154-162
- [20] Tachi M, Amano Y, Inui K, et al. Relationship of postcontrast myocardial T1 value and delayed enhancement to reduced cardiac function and serious arrhythmia in dilated cardiomyopathy with left ventricular ejection fraction less than 35 [J]. *Acta Radiologica*, 2015, 13(3): 312-319
- [21] Lubien E, Demaria A, Krishnaswamy P, et al. Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings [J]. *Acc Current Journal Review*, 2002, 105(5): 595-601