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二甲双胍联合津力达颗粒治疗妊娠期糖尿病的临床效果及对患者血清VEGF、APN、Hcy水平的影响*

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摘要 目的：探讨二甲双胍联合津力达颗粒治疗妊娠期糖尿病的临床效果及对患者血清血管内皮生长因子(VEGF)、脂联素(APN)、同型半胱氨酸(Hcy)水平的影响。**方法：**选择2014年7月至2016年7月我院接诊的94例妊娠期糖尿病患者并通过随机数表法分为观察组(n=47)和对照组(n=47)。对照组使用二甲双胍治疗，观察组在对照组的基础上联合津力达颗粒治疗，均治疗至胎儿娩出。比较两组治疗前后血糖、血脂及血清VEGF、APN和Hcy水平的变化及产妇并发症和新生儿不良结局的发生情况。**结果：**与治疗前比较，两组治疗后血糖、血脂指标均显著改善(P＜0.05)，观察组空腹血糖(FBG)、餐后2 h血糖(2hPG)、糖化血红蛋白(HbA1c)、总胆固醇(TC)、三酰甘油(TG)、低密度脂蛋白胆固醇(LDL-C)水平均明显低于对照组，血清高密度脂蛋白胆固醇(HDL-C)水平明显高于对照组(P＜0.05)。两组治疗后血清VEGF、APN、Hcy水平较治疗前均显著改善(P＜0.05)，且观察组血清VEGF、Hcy均明显低于对照组，血清APN水平明显高于对照组(P＜0.05)。观察组妊娠期高血压、羊水过多、剖宫产、早产、巨大儿、新生儿黄疸、新生儿呼吸窘迫的发生率均明显低于对照组(P＜0.05)。**结论：**二甲双胍联合津力达颗粒治疗妊娠期糖尿病的临床效果显著，可有效控制血糖、血脂水平，降低不良母婴结局的发生率，可能与其有效调节血清VEGF、APN、Hcy水平有关。

关键词：妊娠期糖尿病；二甲双胍；津力达颗粒；血管内皮生长因子；脂联素；同型半胱氨酸
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Curative Efficacy of Metformin Combined with Jinlida Granules in Treatment of Gestational Diabetes Mellitus and Its Effects on Serum VEGF, APN and Hcy Levels*

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ABSTRACT Objective: To study the curative efficacy of metformin combined with Jinlida granules in the treatment of gestational diabetes mellitus and its effects on the serum vascular endothelial growth factor (VEGF), adiponectin (APN) and homocysteine(Hcy) levels. **Methods:** 94 patients of gestational diabetes mellitus who were treated from July 2014 to July 2016 in our hospital were selected. According to random number table, those patients were divided into the observation group (n=47) and the control group (n=47). On the basis of routine treatment, such as control diet, reasonable exercise and healthy diet, etc, the control group was treated with metformin, while the observation group was combined with Jinlida granules on the basis of the control group. The changes of blood glucose, blood lipid and serum VEGF, APN and Hcy before and after treatment were compared between the two groups, the incidence of maternal complications and neonatal adverse outcomes were compared. **Results:** Compared with before treatment, the blood glucose, blood lipid of both groups after treatment were significantly improved (P＜0.05), the fasting plasma glucose (FBG), postprandial 2h blood glucose (2hPG), glycosylated hemoglobin (HbA1c), total cholesterol (TC), triacylglycerol (TG), low density lipoprotein cholesterol(LDL-C) of observation group were significantly lower than those of the control group, the serum high density lipoprotein cholesterol (HDL-C) level was significantly higher than that of the control group(P＜0.05); after treatment, the serum VEGF, APN and Hcy levels were significantly improved than those before treatment in both groups (P＜0.05), and the serum VEGF, and Hcy levels of observation group were lower than those of the control group, the serum APN level was higher than that of the control group (P＜0.05); the incidence of gestational hypertension, hydramnios, cesarean section and premature delivery of observation group was significantly lower than that of the control group (P＜0.05); the incidence of giant child, neonatal Jaundice and neonatal respiratory distress in the observation group was significantly lower than that of the control group (P＜0.05). **Conclusion**: Metformin combined with Jinlida granules was effective for the

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gestational diabetes mellitus, which could effectively control the blood glucose, blood lipid levels and might be related to the regulation of serum VEGF, APN and Hcy levels.

Key words: Gestational diabetes mellitus; Metformin; Jinlida granules; Vascular endothelial growth factor; Adiponectin; Homocysteine

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前言

妊娠期糖尿病是一种产科常见的疾病，主要指在妊娠期无糖尿病或糖耐量异常，但在妊娠期首次出现此类现象，若患者未得到及时的治疗，极易引发高血压、羊水过多等并发症，还会增加早产的机率及巨大儿、呼吸窘迫等不良现象[1]。该病在世界中的发病率大约在 1~14%，在中国的的发病率大约在 1~5%，且逐渐呈明显升高趋势[2]。目前，临床上对于该病的治疗多以西药为主，但单一用药往往得不到令人满意的效果[3]。津力达颗粒属中药复方制剂，在临床上具有改善胰岛素敏感性的作用，并可保护胰岛素β 细胞，但其对妊娠期糖尿病的疗效尚不明确[4]。本研究旨在探讨二甲双胍联合津力达颗粒对妊娠期糖尿病的临床效果以及对患者血清血管内皮生长因子(VEGF)、脂联素(APN)、同型半胱氨酸(Hcy)水平的影响，现报道如下。

1 资料与方法

1.1 一般资料

选择我院接诊的妊娠期糖尿病患者 94 例。纳入标准[5]：① 符合妊娠期糖尿病诊断标准；② 经过控制饮食、合理运动、健康饮食的常规治疗措施后血糖控制效果不理想，需进行药物治疗；③ 均为单胎；④ 对此次研究知情同意。排除标准[6]：① 伴有心、肝、肾等严重脏器功能障碍；② 对研究药物过敏。通过随机数表法分为 2 组。观察组 47 例，年龄 23~42 岁，平均(32.23± 2.58)岁；孕周 25~39 周，平均(31.35± 1.78)周；初产妇 31 例，经产妇 16 例。对照组 47 例，年龄 22~41 岁，平均(32.26± 2.54)岁；孕周 25~38 周，平均(31.38± 1.75)周；初产妇 29 例，经产妇 18 例。两组一般资料无显著差异(P＞0.05)，具有可比性，且研究已获得伦理委员会批准实施。

1.2 治疗方法

两组均给予控制饮食、合理运动、健康饮食的常规治疗措施。对照组给予二甲双胍(规格 0.5 g，厂家：中美上海施贵宝制药有限公司，国药准字 H20023370)，剂量 0.5 g/ 次，2 次 /d。观察组联合津力达颗粒(规格 9 g/ 袋，厂家：石家庄以岭药业股份有限公司，国药准字 Z20050845)，1 袋 / 次，3 次 /d。均治疗至胎儿娩出。

1.3 观察指标

1.3.1 血糖 空腹血糖(FBG)、餐后 2 h 血糖(2hPG)、糖化血红蛋白(HbA1c)；

1.3.2 血脂 总胆固醇(TC)、三酰甘油(TG)、低密度脂蛋白胆固醇(LDL-C)、高密度脂蛋白胆固醇(HDL-C)；

1.3.3 实验室指标 治疗前后抽取 3 mL 空腹静脉血，检测 VEGF、APN、Hcy 的变化，血清 VEGF、Hcy 使用酶联免疫吸附法(深圳晶美生物技术有限公司试剂盒)，血清 APN 使用放射免疫吸附法(北方免疫试剂研究所)；

1.3.4 产妇并发症 妊娠期高血压、低血压、羊水过多、剖宫产、早产等；

1.3.5 新生儿不良结局 巨大儿、新生儿低血糖、黄疸、呼吸窘迫等。

1.4 统计学分析

采用 SPSS18.0 软件包处理，计量资料均数± 标准差($\bar{x}$± s)表示，采用 t 检验，计数资料以例(%)表示，采用 χ^2 检验，以 P<0.05 为差异具有统计学意义。

2 结果

2.1 两组治疗前后血糖水平的比较

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

表 1 两组治疗前后血糖水平的比较($\bar{x}$± s)

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

Groups		FBG(mmol/L)	2hPG(mmol/L)	HbA1c(%)
Observation group(n=47)	Before treatment	8.49± 1.65	11.47± 2.13	7.73± 1.26
	After treatment	4.01± 0.73*#	5.84± 0.72*#	4.54± 0.78*#
Control group(n=47)	Before treatment	8.53± 1.62	11.43± 2.15	7.77± 1.21
	After treatment	5.72± 1.02*	8.15± 1.16*	5.83± 1.06*

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

2.2 两组治疗前后血脂水平的比较

治疗前，两组血清 TC、TG、LDL-C、HDL-C 水平比较差异无统计学意义 (P＞0.05)；两组治疗后血清 TC、TG、LDL-C、HDL-C 水平均较治疗前显著改善 (P＜0.05)，且观察组血清 TC、TG、LDL-C 水平明显低于对照组，血清 HDL-C 水平明显高于对照组(P＜0.05)，见表 3。

2.3 两组血清 VEGF、APN、Hcy 水平的比较

治疗前，两组血清 VEGF、APN、Hcy 水平比较差异无统计学意义(P＞0.05)；两组治疗后血清 VEGF、APN、Hcy 水平均较治疗前显著改善(P＜0.05)，且观察组血清 VEGF、Hcy 水平明显低于对照组，血清 APN 水平明显高于对照组(P＜0.05)，见表 3。

表 2 两组治疗前后血脂水平的比较($\bar{x}\pm s$,mmol/L)

Table 2 Comparison of the serum lipids levels between two groups before and after treatment ($\bar{x}\pm s$, mmol/L)

Groups		TC	TG	LDL-C	HDL-C
Observation group(n=47)	Before treatment	5.34± 0.84	4.98± 0.87	4.87± 0.75	2.02± 0.32
	After treatment	2.98± 0.43*#	3.04± 0.38*#	3.04± 0.47*#	4.82± 0.74*#
Control group(n=47)	Before treatment	5.31± 0.85	4.95± 0.89	4.85± 0.76	2.05± 0.30
	After treatment	4.12± 0.57*	4.02± 0.46*	4.11± 0.53*	3.13± 0.47*

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

表 3 两组治疗前后血清 VEGF、APN、Hcy 水平的比较($\bar{x}\pm s$)

Table 3 Comparison of the serum VEGF, APN, Hcy levels between two groups before and after treatment ($\bar{x}\pm s$)

Groups		VEGF(pg/mL)	APN(mg/L)	Hcy(μmol/L)
Observation group(n=47)	Before treatment	178.43± 34.17	17.34± 2.29	23.19± 3.42
	After treatment	84.56± 14.53*#	29.54± 3.23*#	11.68± 1.56*#
Control group(n=47)	Before treatment	178.65± 34.02	17.37± 2.25	23.25± 3.38
	After treatment	123.47± 22.30*	21.76± 2.74*	16.82± 2.72*

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

2.4 两组产妇并发症发生情况的比较

两组产妇低血糖的发生率比较差异无统计学意义 (P＞0.05),观察组妊娠期高血压、羊水过多、剖宫产、早产发生率分别为 6.38%、8.51%、6.38%、0.00%,均明显低于对照组(23.40%、29.78%、27.66%、21.76%,P＜0.05),见表 4。

表 4 两组产妇并发症发生情况的比较(例,%)

Table 4 Comparison of the incidence of complications between two groups of maternal(n, %)

Groups	Gestational hypertension	Hypoglycemia	Hydramnios	Cesarean section	Premature delivery
Observation group(n=47)	3(6.38)*	2(4.26)	4(8.51)*	3(6.38)*	0(0.00)*
Control group(n=47)	11(23.40)	3(6.38)	14(29.78)	13(27.66)	6(21.76)

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

2.5 两组新生儿结局的比较

两组新生儿低血糖发生率比较差异无统计学意义 (P＞0.05),观察组巨大儿、新生儿黄疸、新生儿呼吸窘迫发生率分别为 8.51%、6.38%、2.13%,均明显低于对照组(27.66%、25.53%、14.89%,P＜0.05),见表 5。

表 5 两组新生儿结局的比较(例,%)

Table 5 Comparison of the incidence of complications between two groups of newborn (n, %)

Groups	Giant child	Neonatal hypoglycemia	Neonatal Jaundice	Neonatal respiratory distress
Observation group(n=47)	4(8.51)*	2(4.26)	3(6.38)*	1(2.13)*
Control group(n=47)	13(27.66)	3(6.38)	12(25.53)	7(14.89)

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

3 讨论

临床研究表明对妊娠期糖尿病患者的治疗应以控制血糖为主,早期的干预措施可明显改善不良母婴结局[7,8]。二甲双胍是妊娠期糖尿病的常用药物,可使患者周围相关组织细胞对葡萄糖的吸收利用能力增加,且有效抑制肝糖原、肝糖输出[9,10]。

在中医中,妊娠期糖尿病属"消渴"范畴,病机为体弱阴虚、饮食不节、劳累过度等,以多饮、多尿、乏力、咽干口燥、便秘为主要表现,属气阴两虚之证,治疗应以清热除燥、养阴生津为主[11]。本研究所应用的津力达颗粒在临床上具有畅通脾络、滋补气血等功效,降糖效果显著,药方中人参、麦门冬为君药,具有益气养阴之效,臣药中,苍术、茯苓可健脾益气,知母、生地黄、葛根可养阴生津,黄连、苦参可清泻脾热,黄精具有补益肺脾肾之效,再加以淫羊藿温脾阳,丹参活血化瘀等,诸药联合,共奏养阴、运脾、生津之效。在现代药理学中证实,其中人参、黄连可达到降糖之效;葛根可增加胰岛素敏感性;麦门冬可对胰岛素抵抗进行改善,并增加葡萄糖利用能力;知母可减少肝糖原分解[12,13]。Zhang Y 等[14]在糖尿病和血脂异常患者中应用津力达颗粒后,可得到满意的降脂、降糖效果,并可改善胰岛素抵抗,促进治疗效率的提高。本次研究显示联合用药的患者治疗后血糖、血脂的改善程度明显优于单独应用二甲双胍的患者,提示联合用药可从多方面协同控制血糖。而妊娠期糖尿病患者的母婴结局取决于血糖的控制情况,良好的控制血糖也降低母婴并发症, 本研究也显示联合用药的患者在妊娠期高血压、羊

水过多、剖宫产、早产、巨大儿、新生儿黄疸、呼吸窘迫的发生率明显比单独用药的患者低，提示二甲双胍联合津力达颗粒对妊娠期糖尿病患者的血糖控制效果优异，有利于改善母婴预后。VEGF 是近年来发现的促血管生成因子，可增加血管通透性，并对巨噬细胞、单核细胞产生趋化作用，促使血管内皮细胞的生长[15]。有研究表明在妊娠期糖尿病患者中，由于其受到炎症刺激，且血糖水平的升高会对血管内皮细胞造成损伤，激发 VEGF 的升高，而持续高水平的 VEGF 会增加不良母婴结局的发生率[16]。APN 主要由脂肪细胞分泌，具有调节糖脂代谢、抗炎、保护血管等效果。相关报道表明在妊娠期糖尿病患者中，APN 水平呈明显下降趋势，且和胰岛素抵抗密切相关[17]。Hcy 作为蛋氨酸的代谢中间产物，由于妊娠期糖尿病患者的高血糖可引发患者出现过度排尿，过度排尿会致使水溶性 B 族维生素和叶酸的流失，而叶酸的流失则会增加 Hcy 的表达[18]。Gatford KL 等[19]报道显示 Hcy 表达的升高可促使血糖的升高，且可降低胰岛素敏感性，和妊娠期糖尿病的发生、发展、不良母婴结局存在着密切的关系。本研究结果显示联合用药的患者血清 VEGF、Hcy 下降程度更明显，APN 则显著升高，分析原因和津力达颗粒中有效成分所产生的改善胰岛素敏感、胰岛素抵抗等相关[20]，但具体机制有待进一步研究。

综上所述，二甲双胍联合津力达颗粒治疗妊娠期糖尿病的临床效果显著，可有效控制血糖、血脂水平，降低不良母婴结局的发生率，可能与其有效调节血清 VEGF、APN、Hcy 水平有关。

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