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## 地特胰岛素联合二甲双胍治疗妊娠糖尿病的疗效 及对患者血清内脂素、抵抗素、血脂水平的影响\*

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**摘要 目的:**研究地特胰岛素联合二甲双胍治疗妊娠糖尿病的临床疗效及对患者血清内脂素、抵抗素、血脂水平的影响。**方法:**选择2016年10月至2017年10月在我院进行治疗的妊娠糖尿病患者120例,按照随机数表法分为观察组和对照组。对照组给予二甲双胍治疗,观察组以对照组为基础联合地特胰岛素治疗。治疗后,观察和两组的临床疗效及不良反应的发生情况,治疗前后血清内脂素、抵抗素水平以及血脂血糖水平的变化。**结果:**治疗后,观察组总有效率(96.67%)明显高于对照组(85.00%)( $P<0.05$ );观察组血清内脂素、抵抗素、总胆固醇(TC)、甘油三脂(TG)、低密度脂蛋白胆固醇(LDL-C)、空腹血糖及餐后2h血糖水平均显著低于对照组( $P<0.05$ ),HDL-C水平明显高于对照组( $P<0.05$ );两组不良反应发生率比较差异无统计学意义( $P>0.05$ )。**结论:**与单用二甲双胍相比,地特胰岛素联合二甲双胍治疗妊娠糖尿病可有效调节患者血脂血糖水平,降低血清内脂素与抵抗素水平,从而显著提高临床疗效,且安全性较好。

**关键词:**地特胰岛素;二甲双胍;妊娠糖尿病;内脂素;抵抗素

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## Efficacy of Insulin Detemir and Metformin in the Treatment of Gestational Diabetes Mellitus and Its Effects on the Serum Visfatin, Resistin and Blood Lipid Levels\*

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**ABSTRACT Objective:** To study the curative efficacy of insulin detemir and metformin in the treatment of gestational diabetes mellitus and their effects on the serum visfatin, resistin and blood lipid levels. **Methods:** 120 cases of patients with gestational diabetes mellitus who were treated in our hospital from October 2016 to October 2017 were selected as the research objects, they were divided into the observation group and the control group according to the random number table method, the control group was treated with metformin, the observation group was treated with insulin detemir on the basis of control group. After treatment, the clinical effects, incidence of adverse reactions, changes of serum visfatin, resistin, blood lipid, blood glucose levels were compared between two groups. **Results:** After treatment, the total effective rate of observation group (96.67%) was significantly higher than that of the control group (85.00%) ( $P<0.05$ ); the serum visfatin, resistin levels of observation group were lower than those of the control group ( $P<0.05$ ); the serum TC, TG, LDL-C levels of observation group were lower than those of the control group, the serum HDL-C level was higher than that of the control group, the FBG and 2hPG levels of observation group was lower than those of the control group ( $P<0.05$ ). There was no significant difference in the incidence of adverse reactions between the two groups ( $P>0.05$ ). **Conclusion:** Insulin detemir and metformin can effectively adjust the blood lipid and glucose levels, reduce the fat grain and resistin levels in the serum, significantly improve the clinical curative effect with good security in the treatment of gestational diabetes mellitus.

**Key words:** Insulin detemir; Metformin; Gestational diabetes mellitus; Visfatin; Resistin

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妊娠糖尿病是指在妊娠期首次发生糖代谢异常,于妊娠中晚期较为常见,严重者会发生血尿症状,若不进行及时有效的治疗,极有可能导致流产,对母婴的生命健康造成极为严重的威胁<sup>[1-3]</sup>。临床普遍使用降糖药物对其血糖进行控制,以二甲双胍最为常见,具有一定的治疗效果。但长时间使用二甲双胍会

使机体产生耐药性,从而无法达到令人满意的临床疗效。血糖增高的病理生理机制是由胰岛素分泌缺陷或(及)胰岛素作用缺陷,导致患者摄入的糖类无法被机体吸收,最终引发血糖的升高<sup>[4]</sup>。因此,临床认为在糖尿病的治疗上不仅要有效控制患者血糖,同时还应提高其体内的胰岛素水平。

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地特胰岛素是近年来新研发的一种胰岛素类似物<sup>[1]</sup>,除了具有与胰岛素相同的药理作用外,还可控制患者体质量,已逐渐运用于临床。目前,临床已证实降糖药物联合地特胰岛素治疗糖尿病的疗效,但对于二者联用于妊娠糖尿病的效果尚不完全明确。因此,本研究采用地特胰岛素联合二甲双胍治疗妊娠糖尿病,探讨其临床疗效,同时分析患者血清内脂素、抵抗素与血脂水平的变化。

## 1 资料与方法

### 1.1 一般资料

选择 120 例 2016 年 10 月至 2017 年 10 月在我院接受治疗的妊娠糖尿病患者,纳入标准:(1)符合国际妊娠与糖尿病研究协会所指定的有关妊娠糖尿病的相关标准;(2)妊娠期两次或两次以上空腹血糖高于 6.8 mmol/L;(3)口服 50 gGCT 血糖高于 11.1 mmol/L,空腹血糖高于 5.8 mmol/L;(4)空腹血糖低于 5.8 mmol/L,口服 75 g 葡萄糖后 1h 血糖低于 10.3 mmol/L、2h 低于 8.6 mmol/L、3h 低于 6.7 mmol/L,OGTT 各点血糖水平两项或两项以上达到或超过上述标准。排除标准:(1)妊娠前糖尿病;(2)合并高血压、肝、肾疾病;(3)既往接受过胰岛素治疗;(4)患有炎症、内分泌疾病或慢性炎症等疾病;(5)依从性差,具有胰岛度耐受、二甲双胍耐受表现。将入选患者按照随机数表法分为两组,观察组 60 例,年龄 20~32 岁,平均年龄(25.43±4.15)岁;妊娠时间 23~37 周,平均孕周(30.32±3.21);病程 3~19 周,平均病程(17.85±4.12)。对照组 60 例,年龄 22~34 岁,平均年龄(26.43±3.53)岁;妊娠时间 21~38 周,平均孕周(31.52±2.56);病程 3~20 周,平均病程(18.34±3.71)。两组患者上述基线资料相比具有可比性。

### 1.2 治疗方法

所有患者均进行相同的糖尿病健康教育与饮食控制,并嘱咐其进行适当的运动。两组均口服二甲双胍(中美上海施贵宝

制药有限公司,0.5 g,20160912),初始剂量 0.5 g,根据患者血糖控制情况逐渐加量,最高 1 天不超过 2.5 g,1 天 2 次,于餐中服用。观察组加用地特胰岛素(丹麦诺和诺德公司,3 mL:300IU,20160926)0.1 U/kg,1 天 1 次,于睡前注射。两组患者均以 2 周为一个治疗疗程,共治疗 4 个疗程。

### 1.3 观察指标

观察两组临床疗效及不良反应的发生情况,检测治疗前后血清内脂素、抵抗素水平以及血脂血糖水平,血脂包括总胆固醇(TC)、甘油三酯(TG)、低密度脂蛋白胆固醇(LDL-C)、高密度脂蛋白胆固醇(HDL-C),血糖包括空腹血糖(FBG)与餐后 2h 血糖(2hPG)。

分别于治疗前后收集两组患者静脉血 5 mL,经离心处理后置于 -20℃ 环境中待检。血清内脂素与抵抗素水平均采用酶联免疫吸附法检测;使用全自动生物化学分析仪检测血脂水平;使用血糖监测仪检测器血糖水平。

疗效标准参照相关文献进行<sup>[2]</sup>:(1)显效:治疗后患者空腹、餐后 2h 血糖均降至正常水平;(2)有效:治疗后患者空腹血糖水平降至正常,但餐后 2h 血糖高于正常值;(3)无效:患者血糖水平无变化,空腹及餐后 2h 血糖均未达到正常水平。

### 1.4 统计学分析

本研究数据采用 spss19 软件包进行统计学处理,计量资料使用平均值±标准差表示,组间采用独立样本 t 检验进行比较,计数资料使用百分比表示,采用  $\chi^2$  检验进行比较,以  $P<0.05$  时表示其差异具有统计学意义。

## 2 结果

### 2.1 两组临床疗效的比较

治疗后,观察组总有效率为 96.00%,对照组为 85.00,组间比较差异具有统计学意义( $P<0.05$ ),详见表 1。

表 1 两组患者临床疗效比较[例(%)]

Table 1 Comparison of the clinical efficacy between two groups[n(%)]

| Groups        | n  | Excellent | Progress  | No change | Total effective        |
|---------------|----|-----------|-----------|-----------|------------------------|
| Observe group | 60 | 42(70.00) | 16(26.67) | 2(3.33)   | 58(96.67) <sup>a</sup> |
| Control group | 60 | 24(40.00) | 27(45.00) | 9(15.00)  | 51(85.00)              |

Note: Compared with the control group, <sup>a</sup>  $P<0.05$ .

### 2.2 两组治疗前后血清抵抗素与内脂素水平的比较

治疗前,两组血清抵抗素与内脂素水平比较差异无统计学意义( $P>0.05$ );治疗后,两组患者血清抵抗素与内脂素水平均较

治疗前显著降低( $P<0.05$ );且观察组血清抵抗素与内脂素水平均明显低于对照组( $P<0.05$ ),详见表 2。

表 2 两组治疗前后血清抵抗素与内脂素水平的比较( $\bar{x}\pm s$ )

Table 2 Comparison of the serum resistin and visfatin levels between the two groups before and after treatment( $\bar{x}\pm s$ )

| Group         | n  | Time             | Resistin( $\mu$ g/L)     | Visfatin(ng/mL)          |
|---------------|----|------------------|--------------------------|--------------------------|
| Observe group | 50 | Before treatment | 14.04±2.74               | 31.53±5.12               |
|               |    | After treatment  | 11.32±1.63 <sup>ab</sup> | 20.32±2.31 <sup>ab</sup> |
| Control group | 50 | Before treatment | 13.74±2.03               | 30.16±5.31               |
|               |    | After treatment  | 12.48±1.93 <sup>b</sup>  | 24.71±3.04 <sup>b</sup>  |

Note: Compared with the control group, <sup>a</sup>  $P<0.05$ ; compared with before treatment, <sup>b</sup>  $P<0.05$ .

### 2.3 两组治疗前后血脂水平的比较

治疗前, 两组患者 TC、TG、LDL-C 及 HDL-C 水平比较差异均无统计学意义( $P>0.05$ ); 经治疗, 两组血脂水平均较治疗前

有所改善, 与对照组相比, 观察组 TC、TG、LDL-C 水平均较低, HDL-C 较高( $P<0.05$ ), 详见表 3。

表 3 两组治疗前后血脂水平的比较( $\bar{x}\pm s$ , mmol/L)

Table 3 Comparison of the blood lipid levels between the two groups before and after treatment( $\bar{x}\pm s$ , mmol/L)

| Groups        | n  | Time             | TC                       | TG                       | LDL-C                    | HDL-C                    |
|---------------|----|------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Observe group | 50 | Before treatment | 5.34± 0.93               | 2.17± 0.43               | 3.45± 0.42               | 1.15± 0.24               |
|               |    | After treatment  | 4.57± 1.01 <sup>ab</sup> | 1.46± 0.35 <sup>ab</sup> | 2.62± 0.51 <sup>ab</sup> | 1.68± 0.79 <sup>ab</sup> |
| Control group | 50 | Before treatment | 5.29± 1.04               | 2.09± 0.51               | 3.41± 0.64               | 1.18± 0.41               |
|               |    | After treatment  | 4.93± 0.88 <sup>b</sup>  | 1.63± 0.45 <sup>b</sup>  | 2.84± 0.42 <sup>b</sup>  | 1.38± 0.62 <sup>b</sup>  |

Note: Compared with the control group, <sup>a</sup> $P<0.05$ ; Compared with before the operation, <sup>b</sup> $P<0.05$ .

### 2.4 两组治疗前后血糖水平的比较

治疗前, 两组空腹及餐后 2h 血糖水平比较差异均无统计学意义( $P>0.05$ ); 经治疗后, 两组空腹血糖与餐后 2h 血糖水平

均较治疗前显著降低, 且观察组明显低于对照组( $P<0.05$ ), 详见表 4。

表 4 两组治疗前后血糖水平的比较( $\bar{x}\pm s$ , mmol/L)

Table 4 Comparison of blood glucose levels between the two groups before and after treatment( $\bar{x}\pm s$ , mmol/L)

| Groups        | n  | Time             | FBG                      | 2hPG                     |
|---------------|----|------------------|--------------------------|--------------------------|
| Observe group | 50 | Before treatment | 10.42± 3.32              | 12.53± 3.75              |
|               |    | After treatment  | 4.67± 2.34 <sup>ab</sup> | 6.21± 2.42 <sup>ab</sup> |
| Control group | 50 | Before treatment | 10.31± 3.11              | 12.38± 3.62              |
|               |    | After treatment  | 5.92± 2.16 <sup>b</sup>  | 7.42± 2.94 <sup>b</sup>  |

Note: Compared with the control group, <sup>a</sup> $P<0.05$ ; Compared with before the operation, <sup>b</sup> $P<0.05$ .

### 2.5 两组不良反应发生情况的比较

治疗后, 观察组有 3 例患者出现低血糖, 对照组有 6 例患者出现低血糖, 两组不良反应发生率比较差异无统计学意义( $P>0.05$ )。

## 3 讨论

妊娠糖尿病是孕妇最为常见且危重的一种妊娠期并发症, 目前对于此疾病的发病机制尚未明确, 但国内外均有研究认为妊娠糖尿病的发病机制与潜在的胰岛β 细胞功能不足有关, 同时与胰岛素抵抗具有密切的关系<sup>[7-9]</sup>。胰岛素抵抗是指正常浓度的胰岛素的生理效应偏低, 主要表现为胰岛素抑制肝释放葡萄糖的能力以及周围组织利用葡萄糖的能力下降, 而机体为了调节其血糖水平, 会过多的分泌胰岛素, 而当β 细胞功能无法维持高胰岛素状态时则会出现明显的高血糖, 从而导致糖尿病的发生<sup>[10]</sup>。

内脂素是一种新发现的脂肪细胞因子, 具有广泛的生理功能, 在妊娠过程中, 在胎膜表面大量表达可促进 IL-6 等炎性因子分泌, 在自然分娩以及感染性流产中发挥了重要的作用<sup>[11,12]</sup>。国外研究显示妊娠期糖尿病患者血清内脂素水平与胰岛素抵抗指数呈正比关系, 且其水平的高低会随着胰岛β 细胞功能的

衰退而增高<sup>[13,14]</sup>。而在高血糖状态下, 内脂素可通过激活胰岛素受体, 在一定程度上起到了降低血糖以及改善胰岛素抵抗的作用<sup>[15]</sup>。由此可见, 妊娠糖尿病患者胰岛素抵抗程度越重、血糖越高, 其血清内脂素水平也随之升高。反之, 高水平的内脂素也极有可能通过对胰岛素抵抗的影响而在整个疾病过程中发挥重要的作用。抵抗素是近几年所发现的脂肪细胞源性多肽类激素, 其主要功能为调空体重、能量消耗以及脂肪的分布, 同时还具有减弱胰岛素刺激细胞摄取葡萄糖的作用, 诱发产生胰岛抵抗, 可见抵抗素参与了胰岛素抵抗的形成, 极有可能是妊娠糖尿病发生发展中一个重要的细胞因子<sup>[16-18]</sup>。国内外研究表明妊娠期糖尿病孕妇血清抵抗素水平的增高可能与以下因素有关: (1) 孕期其体重的增加以及脂肪的过度累积, 增加的体脂导致更多的抵抗素合成; (2) 胰岛素可通过刺激脂肪细胞分泌抵抗素; (3) 妊娠期胎盘可分泌胰岛素<sup>[19,20]</sup>。

此外, 研究显示妊娠糖尿病孕妇的血脂水平存在异常<sup>[21,22]</sup>。对于正常妊娠的孕妇而言, 其肠道吸收脂肪的能力较强, 同时孕早期胰岛素水平与胰岛素敏感性均增强, 可通过抑制脂肪酶的活性促进脂肪酸与脂肪的合成。孕早期脂蛋白酶活性与脂肪合作的增加, 可间接导致 TG 水平增加, 而这种孕早期脂肪存储增多是为了满足胎儿生长发育的一种生理性适应措施。而对

于妊娠期糖尿病孕妇,其 TC、TG、LDL-C 水平显著升高, HDL-C 水平则更低<sup>[23]</sup>。据文献报道,胰岛素抵抗可随着孕周的增加而增加,而胰岛素抵抗的增加导致了 LDL-C 合成的增加,从而使脂蛋白活性下降,最终使 TC、LDL-C 水平显著升高,出现血脂代谢异常<sup>[24]</sup>。此外,随着妊娠周期的增加体内脂肪组织的降解能力加强,对肝脏合成 TC 具有一定的促进效果,从而导致患者体内血脂水平的升高。

在妊娠糖尿病治疗方面,降糖药物为首选的治疗方式,但临床发现其疗效具有一定的局限性。二甲双胍为临床常见的口服降糖药物,可阻碍胃肠道摄取葡萄糖,提高胰岛素的敏感性从而增加外周血糖利用葡萄糖<sup>[25,26]</sup>。而  $\beta$  细胞功能的降低可导致药物对血糖控制效果降低,限制了治疗的效果。本研究中,患者使用二甲双胍治疗后临床疗效为 85%,需联合相关的胰岛素抵抗的药物,以提高药物协同作用。

地特胰岛素是一种胰岛素类似物,是通过人胰岛素进行基因改变而形成,具有更优的临床控制能力与应用效果<sup>[27,28]</sup>。因其独特的分子结构可降低低血糖的发生率,同时对热量的防御性摄入具有一定的抑制作用,有效控制了患者体质量<sup>[29,30]</sup>。本结果显示患者在使用二甲双胍联合地特胰岛素治疗后总有效率提高至 96.67%,且患者血清内脂素与抵抗素均显著降低,且患者血脂血糖水平均得到显著改善,提示二者联合治疗妊娠糖尿病具有协同作用。一方面,通过降低血糖降低胰岛素抵抗,改善胰岛  $\beta$  细胞的分泌功能;另一方面,通过促进周围组织以及靶器官对糖的利用,抑制胰岛素拮抗激素清楚自由基,从而显著提高治疗效果。

综上所述,与单用二甲双胍相比,地特胰岛素联合二甲双胍治疗妊娠糖尿病可有效调节患者血脂血糖水平,降低血清内脂素与抵抗素水平,从而显著提高临床疗效,且安全性较好。

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