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妊娠期糖尿病患者糖化血红蛋白水平与甲状腺激素水平 及不良妊娠结局的关系分析*

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摘要 目的:分析妊娠期糖尿病(GDM)患者糖化血红蛋白(HbA1c)水平与甲状腺激素水平及不良妊娠结局的关系。**方法:**选取2017年2月~2018年5月期间延安大学附属医院接收的GDM患者118例作为观察组,其中血清HbA1c水平 $\leq 6.5\%$ 55例, $>6.5\%$ 63例。另外选取同期来我院接受孕检的110例非GDM孕妇作为对照组,比较对照组、观察组血清HbA1c、甲状腺激素水平以及不良妊娠结局,比较观察组中不同HbA1c水平患者不良妊娠结局情况,采用Pearson相关性分析HbA1c水平与甲状腺激素水平的关系。**结果:**观察组初次测量、二次测量时的血清HbA1c水平均高于对照组($P<0.05$)。观察组血清三碘甲状腺原氨酸(T_3)、游离甲状腺原氨酸(FT_3)、总甲状腺素(T_4)、游离甲状腺素(FT_4)水平均低于对照组($P<0.05$)。观察组羊水过多、胎儿窘迫、新生儿低血糖、早产、巨大儿的发生率均高于对照组($P<0.05$)。HbA1c水平 $>6.5\%$ 的患者羊水过多、胎儿窘迫、新生儿低血糖、早产、巨大儿的发生率均高于HbA1c水平 $\leq 6.5\%$ 的患者($P<0.05$)。Pearson相关性分析结果可知,HbA1c与 T_3 、 T_4 、 FT_4 、促甲状腺素(TSH)无相关性($P>0.05$),而与 FT_3 呈负相关($P<0.05$)。**结论:**血清HbA1c水平可较好地预测GDM患者不良妊娠结局,GDM患者多处于甲状腺激素水平较低状态,且HbA1c与甲状腺功能指标 FT_3 密切相关。

关键词:妊娠期糖尿病;糖化血红蛋白;甲状腺激素;妊娠结局;相关性

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Analysis of the Relationship between Glycosylated Hemoglobin Level and Thyroid Hormone Level and Adverse Pregnancy Outcome in Patients with Gestational Diabetes Mellitus*

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ABSTRACT Objective: To analyze the relationship between glycosylated hemoglobin (HbA1c) level and thyroid hormone level and adverse pregnancy outcome in patients with gestational diabetes mellitus (GDM). **Methods:** 118 patients with GDM who were received in Yan'an University Affiliated Hospital from February 2017 to May 2018 were selected as observation group. Serum HbA1c level $\leq 6.5\%$ had 55 cases, and $>6.5\%$ had 63 cases. In addition, 110 non-GDM pregnant women who received pregnancy examination in our hospital during the same period were selected as the control group. Serum HbA1c, thyroid hormone levels and adverse pregnancy outcomes were compared between the control group and the observation group. The adverse pregnancy outcomes of patients with different HbA1c levels in the observation group were compared. Pearson correlation analysis was used to analyze the relationship between HbA1c level and thyroid hormone level. **Results:** The level of serum HbA1c in the observation group was higher than that in the control group at the first and second measurements ($P<0.05$). The serum levels of triiodothyronine (T_3), free thyronine (FT_3), total thyroxine (T_4) and free thyroxine (FT_4) in the observation group were lower than those in the control group ($P<0.05$). The incidence of excessive amniotic fluid, fetal distress, neonatal hypoglycemia, premature delivery and macrosomia in the observation group were higher than those in the control group ($P<0.05$). The incidence of excessive amniotic fluid, fetal distress, neonatal hypoglycemia, premature delivery and macrosomia in HbA1c level $>6.5\%$ were higher than those in HbA1c level $\leq 6.5\%$ group ($P<0.05$). Pearson correlation analysis showed that HbA1c were not correlated with T_3 , T_4 , FT_4 , thyrotropin (TSH) ($P>0.05$), but negatively correlated with FT_3 ($P<0.05$). **Conclusion:** Serum HbA1c level can better predict the adverse pregnancy outcomes of GDM patients, and most of GDM patients are in a low thyroid hormone level, HbA1c is closely related to thyroid function index FT_3 .

Key words: Gestational diabetes mellitus; Glycosylated hemoglobin; Thyroid hormone; Pregnancy outcomes; Correlation

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前言

妊娠期糖尿病(Gestational diabetes mellitus, GDM)是指既往无糖尿病史者,而在妊娠期才出现或确诊的糖尿病,属于高危妊娠的一种^[1]。GDM患者由于长期处于高血糖状态中,可导致孕妇高血压、肥胖、脂代谢异常等代谢相关并发症的发生,对母婴造成巨大伤害^[2,3],因此,早期的诊断并及时的干预具有重要的临床意义。糖化血红蛋白(Glycosylated hemoglobin, HbA1c)是临床上监测糖尿病病情严重程度的重要指标之一,可评价一定时间内人体糖代谢状况^[4,5]。近年来,不少研究发现,糖尿病除了与胰岛素分泌异常有关外,还与其他激素分泌异常有关^[6,7],尤其是甲状腺激素的分泌,若妊娠期孕妇甲状腺激素不受控制,可能造成孕妇流产、胎膜剥离等并发症。本研究随机选取GDM患者进行研究,定期检测其HbA1c水平,随访其妊娠结局,并设置非GDM对照,以探讨HbA1c与甲状腺激素水平及不良妊娠结局的关系。

1 资料与方法

1.1 一般资料

选取2017年2月~2018年5月期间延安大学附属医院接收的GDM患者,纳入标准:(1)均符合《2015年国际妇产科联盟(FIGO)妊娠期糖尿病诊疗指南解读》^[8]中的相关诊断标准;(2)均为单胎妊娠;(3)均经口服葡萄糖耐量试验确诊为GDM;(4)患者及其家属对本次研究知情同意,且签署同意书;(5)所有患者均追踪至终止妊娠,病历资料完整。排除标准:(1)合并恶性肿瘤、重要脏器功能损伤、认知功能障碍、免疫功能障碍者;(2)多胎、孕前糖尿病、合并妊娠其他并发症者;(3)既往有习惯性流产史者。符合上述标准的患者118例纳入观察组,年龄23~35岁,平均(31.34±1.48)岁;孕周23~28周,平均(26.42±0.93)周;初产妇61例,经产妇57例;血清HbA1c水平≤6.5% 55例,>6.5% 63例。另外选取同期来我院接受孕检的110例非GDM孕妇作为对照组,纳入标准:均在我院产检并生产,均为单胎、未合并妊娠其他并发症、无习惯性流产史等的健康孕妇;均经口服葡萄糖耐量试验确诊为非GDM,且HbA1c≤6.5%,且终止妊娠前维持HbA1c≤6.5%。其中年龄22~34岁,平均(29.16±1.71)岁;孕周22~30周,平均(27.06±1.25)周;初产妇63例,经产妇47例。两组研究对象年龄、孕周以及初产妇、经

产妇比例比较无统计学差异($P>0.05$),存在可比性。本次研究已获取我院伦理学委员会批准进行。

1.2 方法

1.2.1 GDM血糖控制 给予个体化饮食控制方案、指导孕妇进行适宜的运动训练等常规治疗,在此基础上治疗2周后,若其血糖仍处于不稳定状态者,则给予短效胰岛素治疗。

1.2.2 血清指标检测 抽取研究对象孕检当日清晨空腹静脉血5 mL,3200 r/min离心8 min,离心半径12 cm,取上清液,置于-30℃冰箱中待测。采用离子交换高效液相色谱法检测HbA1c水平;采用酶促化学发光免疫法检测三碘甲状腺原氨酸(Triiodothyronine, T_3)、游离甲状腺原氨酸(Free thyronine, FT_3)、总甲状腺素(Total thyroxine, T_4)、游离甲状腺素(Free thyroxine, FT_4)及促甲状腺素(Thyrotropin, TSH)水平,严格遵守试剂盒(上海信裕生物技术有限公司)说明书进行操作。所有研究对象均进行两次HbA1c水平的测定,第一次为孕检当天检测,第二次为终止妊娠后的第二日。

1.2.3 不良妊娠结局 观察母婴不良妊娠结局,包括:胎膜早破、羊水过多、早产、新生儿低血糖、胎儿窘迫、巨大儿。

1.3 不良妊娠结局诊断标准

羊水过多:分娩前超声检测孕妇腹部四象限最大羊水池深度>8 cm、四象限综合羊水池深度>18 cm或产后羊水量>2000 mL;早产:妊娠不满37周即分娩;巨大儿:新生儿体质量大于4 kg;胎膜早破:分娩前胎膜已破裂;胎儿窘迫:胎心率>180次/min或者胎心率<120/min持续10 min,胎心监测异常减速或持续减速;新生儿低血糖:新生儿全血血糖<2.2 mmol/L^[9]。

1.4 统计学方法

采用SPSS22.0软件进行统计分析,计数资料以%表示,进行卡方检验,计量资料经检验均符合正态分布,以均值±标准差($\bar{x} \pm s$)表示,进行t检验,采用Pearson相关性分析HbA1c水平与甲状腺激素水平的关系,检验标准设置为 $\alpha=0.05$ 。

2 结果

2.1 观察组和对照组孕妇血清HbA1c水平比较

观察组和对照组二次测量时的血清HbA1c水平均低于初次测量($P<0.05$),观察组初次测量、二次测量时的血清HbA1c水平均高于对照组($P<0.05$),详见表1。

表1 观察组和对照组孕妇血清HbA1c水平比较($\bar{x} \pm s, \%$)

Table 1 Comparison of serum HbA1c levels between observation group and control group($\bar{x} \pm s, \%$)

Groups	n	First measurement	Second measurement
Control group	110	6.16±0.58	4.89±0.37*
Observation group	118	7.13±0.61	5.51±0.44*
t	-	12.286	11.473
P	-	0.000	0.000

Note: Compared with the first measurement, * $P<0.05$.

2.2 观察组和对照组孕妇血清甲状腺激素水平比较

观察组血清 T_3 、 FT_3 、 T_4 、 FT_4 水平均低于对照组($P<0.05$),但观察组和对照组血清TSH水平比较无统计学差异($P>$

0.05),详见表2。

2.3 观察组和对照组孕妇不良妊娠结局情况比较

观察组羊水过多、胎儿窘迫、新生儿低血糖、早产、巨大儿

的发生率均高于对照组($P<0.05$),观察组和对照组孕妇胎膜早破发生率比较差异无统计学意义($P>0.05$),详见表3。

表2 观察组和对照组孕妇甲状腺激素水平比较($\bar{x}\pm s$)Table 2 Comparison of thyroid hormone levels in pregnant women between observation group and control group($\bar{x}\pm s$)

Groups	T ₃ (nmol/L)	FT ₃ (pmol/L)	T ₄ (nmol/L)	FT ₄ (pmol/L)	TSH(mIU/L)
Control group(n=110)	2.87± 0.34	4.82± 0.35	178.13± 29.33	17.31± 1.39	1.69± 0.57
Observation group (n=118)	2.26± 0.46	4.37± 0.45	149.54± 31.52	14.25± 1.47	1.74± 0.63
t	11.320	8.386	7.077	16.123	0.627
P	0.000	0.000	0.000	0.000	0.531

表3 观察组和对照组孕妇不良妊娠结局情况比较【例(%)】

Table 3 Comparison of adverse pregnancy outcomes between observation group and control group[n(%)]

Groups	Premature rupture of membranes	Excessive amniotic fluid	Premature delivery	Neonatal hypoglycemia	Fetal distress	Macrosomia
Control group (n=110)	9(8.18)	4(3.64)	5(4.55)	3(2.73)	6(5.45)	7(6.36)
Observation group (n=118)	14(11.86)	13(11.02)	14(11.86)	11(9.32)	17(14.41)	18(15.25)
χ^2	0.851	4.494	3.992	4.296	5.030	4.609
P	0.356	0.000	0.000	0.000	0.000	0.000

2.4 观察组中不同 HbA1c 水平患者不良妊娠结局情况比较

($P<0.05$),不同 HbA1c 水平患者胎膜早破发生率比较差异无统计学意义($P>0.05$),详见表4。

HbA1c 水平 $>6.5\%$ 的患者羊水过多、胎儿窘迫、新生儿低血糖、早产、巨大儿的发生率均高于 HbA1c 水平 $\leq 6.5\%$ 的患者

表4 观察组中不同 HbA1c 水平患者不良妊娠结局情况比较【例(%)】

Table 4 Comparisons of adverse pregnancy outcomes among patients with different HbA1c levels in observation group[n(%)]

HbA1c level	Premature rupture of membranes	Excessive amniotic fluid	Premature delivery	Neonatal hypoglycemia	Fetal distress	Macrosomia
$\leq 6.5\%$ (n=55)	6(10.91)	2(3.64)	3(5.45)	2(3.64)	4(7.27)	4(7.27)
$>6.5\%$ (n=63)	8(12.70)	11(17.46)	11(17.46)	9(14.29)	13(20.63)	14(22.22)
χ^2	0.090	5.724	4.408	3.940	4.252	5.077
P	0.764	0.000	0.000	0.007	0.000	0.000

2.5 HbA1c 水平与甲状腺激素水平的相关性分析

Pearson 相关性分析结果可知,HbA1c 与 T₃、T₄、FT₄、TSH 无相关性($P>0.05$),而与 FT₃ 呈负相关($P<0.05$),详见表5。

表5 HbA1c 水平与甲状腺激素水平的相关性分析

Table 5 Analysis of the correlation between HbA1c level and thyroid hormone level

Indexes	HbA1c	
	r	P
T ₃	-0.173	0.259
FT ₃	-0.498	0.019
T ₄	-0.136	0.294
FT ₄	-0.159	0.282
TSH	-0.127	0.325

3 讨论

妊娠作为特殊时期,可导致妇女身体出现一系列身体变化,正常情况下,妇女妊娠早期时,其空腹血糖会低于非妊娠期,妊娠中晚期空腹血糖会进一步下降,而此阶段也是 GDM 的高发期^[10,11]。妊娠期间血糖减少的主要原因为胎儿生长发育需消耗母体大量的血糖,加之妊娠时机体胰岛素可极大的促进葡萄糖进入血液,使其血糖明显下降^[12,13]。既往研究表明^[14],健康的妊娠期妇女其饭后血糖峰值较非妊娠妇女更高,且其恢复至正常血糖水平的时间也更长。由此可见,为了更好的维持机体糖代谢,妊娠期妇女需要分泌更多的胰岛素,然而对于胰岛素障碍的妊娠期妇女而言,该过程若是无法顺利进行则使得机

体糖代谢出现异常,致使血糖持续升高,形成 GDM^[15-17]。GDM 发病机制十分复杂,多在一定环境、遗传及背景下产生糖代谢异常为主要特征的相关综合征。随着对其发病机制的深入,

GDM 患者除存在胰岛素异常外,还存在相关激素分泌异常等情况,如甲状腺激素^[18-20]。HbA1c 作为评价一段时间内血糖控制水平的金指标,本研究通过研究 GDM 患者与非 GDM 孕妇的 HbA1c 水平、甲状腺激素水平及不良妊娠结局发生率,以探讨上述指标的关系。

本次研究结果显示,两组二次测量时 HbA1c 均低于初次测量,且观察组初次测量、二次测量时的 HbA1c 均高于对照组,可见 GDM 患者中均存在较高水平的 HbA1c,但经治疗控制血糖后,其水平可下降。HbA1c 作为人体血液内红细胞中血红蛋白游离氨基、葡萄糖游离基通过非酶促反应进行结合产生的产物,其生产过程缓慢,具有连续性及不可逆性,且不受有无应用胰岛素、患者抽血时间及是否处于空腹状态等相关因素影响,可良好地反映患者中长期血糖的控制效果^[21-23]。本研究结果还显示,观察组 T₃、FT₃、T₄、FT₄ 水平均低于对照组,但两组 TSH 水平比较无差异,可见 GDM 患者的甲状腺激素水平多处于较低状态,妊娠期间孕妇胎盘分泌大量激素,导致孕妇的下丘脑-垂体-甲状腺轴系统处于特殊应激状态,进而影响甲状腺激素的产生,引起甲状腺功能减退^[24,25]。而 Pearson 相关性分析结果可知,HbA1c 与 T₃、T₄、FT₄、TSH 无相关性,而与 FT₃ 呈负相关,可见机体持续的高血糖对孕妇甲状腺激素的释放存在一定影响,分析其原因,GDM 孕妇糖代谢紊乱时,致使外周组织 5-脱碘酶活性下降,进而减少了 FT₃ 表达^[26,27]。同时本次研究结果还显示,观察组羊水过多、早产、新生儿低血糖、胎儿窘迫、巨大儿的发生率均高于对照组,且随着血清 HbA1c 水平的升高,上述不良妊娠结局发生率亦呈升高状态,分析原因,机体长期的高血糖可引起胎儿血糖升高,产生巨大儿,同时还可引起尿液增多,而胎儿尿液是羊水的主要成分,最终导致羊水过多;母体高血糖还可导致胎盘毛细血管受损,致使胎盘血供不足,易发生胎儿窘迫;而新生儿低血糖则是由于 GDM 患者病情越重,越需要大量药物治疗降低血糖,从而引起新生儿低血糖^[28-30]。

综上所述,血清 HbA1c 水平可较好地预测 GDM 患者不良妊娠结局,GDM 患者多处于甲状腺激素水平较低状态,且 HbA1c 与甲状腺功能指标 FT₃ 密切相关,临床可通过检测 GDM 患者 HbA1c、甲状腺激素水平评估其妊娠结局,并做好防治工作,以减少 GDM 对母婴的损害。

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