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甲状腺功能减退孕妇糖代谢、肾功能指标的变化及临床意义*

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摘要 目的：探究妊娠期甲状腺功能减退患者糖代谢及肾功能变化及临床意义。**方法：**选择2015年6月至2019年8月来我院就诊的甲状腺功能减退孕妇60例作为甲减组及同期健康孕妇60例作为对照组。比较两组患者甲状腺功能[促甲状腺激素(TSH)、游离三碘甲状腺原氨酸(FT_3)及游离甲状腺素(FT_4)]、糖代谢指标[空腹血糖水平(FBG)、糖化血红蛋白(HbA1C)、餐后2 h抽取肘静脉血测定餐后2 h葡萄糖水平(2hPG)、胰岛素抵抗指标(HOMA-IR)]及肾功能[血清肌酐(Cr)、血清尿酸(UA)、血尿素氮(BUN)]，分析甲状腺功能与糖代谢及肾功能的关系，比较两组患者的妊娠结局。**结果：**甲减组孕妇的TSH、糖代谢、肾功能各指标水平较对照组显著升高，FT4较对照组明显降低($P<0.05$)。TSH与糖代谢各指标均呈正相关($P<0.05$)；FT4与糖代谢各指标均呈负相关($P<0.05$)，FT_3与Cr呈负相关($P<0.05$)，TSH、FT_4与Cr、UA、BUN均无明显相关性($P>0.05$)。甲减组的不良妊娠结局率为20.00%，显著高于对照组(6.67%，$P<0.05$)。**结论：**妊娠期甲状腺功能减退患者存在糖代谢紊乱、肾功能异常，可能导致不良妊娠结局。

关键词：妊娠期甲状腺功能减退；糖代谢；肾功能变化；妊娠结局

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Changes and Significances of Glucose Metabolism and Renal Function Index in Pregnant Women with Hypothyroidism*

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ABSTRACT Objective: To explore the changes of glucose metabolism and renal function in patients with gestational hypothyroidism and their clinical significance. **Methods:** A total of 60 pregnant women with hypothyroidism who visited our hospital from June 2015 to August 2019 were selected as the hypothyroidism group and 60 healthy pregnant women in the same period were selected as the control group. The thyroid function [thyroid-stimulating hormone (TSH), three free iodine thyroid former glycine (FT_3) and free thyroxine (FT4)], glucose metabolism index [(FBG), fasting blood glucose level, glycosylated hemoglobin (HbA1C), 2 h postprandial extract elbow venous blood determination of postprandial glucose level 2 h (2 HPG), insulin resistance index (HOMA IR)] and renal function (serum creatinine (Cr), serum uric acid (UA), blood urea nitrogen (BUN)] as well as the pregnancy outcome were compared between two groups of patients and the relationship between thyroid function and metabolism of glucose metabolism and renal function was analyzed. **Results:** The levels of TSH, glucose metabolism and renal function of pregnant women in the hypothyroidism group were significantly higher than those in the control group, and FT_4 was significantly lower than those in the control group ($P<0.05$). TSH was positively correlated with each index of glucose metabolism($P< 0.05$). FT_4 was negatively correlated with all indicators of glucose metabolism ($P< 0.05$), FT_3 was negatively correlated with Cr ($P<0.05$), and TSH, FT_4 were not significantly correlated with Cr, UA, and BUN ($P>0.05$). The adverse pregnancy outcome rate of hypothyroidism group was 20.00%, significantly higher than that of control group (6.67%, $P<0.05$). **Conclusion:** Patients with hypothyroidism during pregnancy have disorders of glucose metabolism and abnormal renal function, which may lead to adverse pregnancy outcomes.

Key words: Gestational hypothyroidism; Glucose metabolism; Renal function change; Pregnancy outcome

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前言

甲状腺功能减低是以甲状腺激素抵抗或甲状腺激素血症为临床表现的全身性低代谢综合症[1]。妊娠期妇女由于基础代

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谢水平升高和胎儿生长发育需要，甲状腺激素需求增加易发生甲状腺功能减退[2,3]。甲状腺激素是身体的重要代谢类激素，与机体糖代谢及肾功能都有一定关系[4]。甲状腺功能减退孕妇可促使患者糖代谢紊乱，妊娠期患者若血糖水平升高，则能有效甲状腺功能代谢，加速降低甲状腺素水平，促使妊娠期甲状腺功能减退发生率增加；甲状腺激素在肾脏代谢和清除，其水平不足可影响肾脏的水和电解质代谢，而甲状腺激素不足通过降低心室收缩力导致心输出量减少而引起，肾血流量减少，导致肾功能异常。为探究甲状腺功能减退对孕妇糖代谢、肾功能、及妊娠结局影响，本文回顾性分析了妊娠甲减孕妇与健康孕妇的甲状腺、糖代谢、肾功能水平及其妊娠结局，以期为临床改善甲减孕妇妊娠结局提供一定的参考，结果报道如下。

1 资料与方法

1.1 一般资料

回顾性分析 2015 年 6 月至 2019 年 8 月来我院就诊的甲状腺功能减退[5]孕妇 60 例作为甲减组。排除标准：① 合并其他心、肝、肺重大疾病患者；② 伴有其他妊娠合并症；③ 妊娠前已有甲状腺功能异常或糖尿病、肾功能不全患者。年龄为 23~40 岁，平均(29.24± 3.12)岁；孕周 34~39 周，平均(35.43± 5.12)；初产妇 34 例，经产妇 26 例。另选同期体检甲状腺功能正常孕妇 60 例作为对照组，年龄为 24~42 岁，平均(30.11± 3.24)岁；孕周 33~40 周，平均(35.72± 5.31)；初产妇 35 例，经产妇 25 例。两组患者的一般资料比较差异均无统计学意义(P>0.05)。所有患者均知情并同意参与本研究，本研究经医学伦理委员会同意。

1.2 观察指标

(1)甲状腺功能指标：抽取清晨空腹肘静脉血，离心分离上层血清，采用基氮生物科技股份有限公司 MAGICL6800 自动化学发光免疫测定仪检测血清中促甲状腺激素(Thyroid stimulating hormone，TSH)、游离三碘甲状腺原氨酸(free three of the amino acid，FT_3) 及游离甲状腺素 (free thyroid hormone，FT_4)水平，TSH＞3.00 mIU/L 诊断为甲减，TSH 在 0.30~3.00 mIU/L 范围为正常[6]。(2)糖代谢指标：抽取孕妇清晨肘静脉血，测量空腹血糖水平 (Fasting blood glucose，FBG)、糖化血红蛋白(Hemoglobin A1c，HbA1C)、餐后 2 h 抽取肘静脉血测定餐后 2 h 葡萄糖水平(2-hour postprandial blood glucose，2hPG)、胰岛素抵抗指标 (Home ostasis model assessment insulin resistance，HOMA-IR)。(3)肾功能指标：抽取孕妇清晨肘静脉血，离心分离血清，采用贝克曼 AU5800 全自动生化分析仪检测血清肌酐(Creatinine，Cr)、血清尿酸(Uric acid，UA)、血尿素氮(Blood urea nitrogen，BUN)。

1.3 统计学方法

采用 SPSS 20.0 软件进行统计学分析，TSH、FT_3 等以 ($\bar{x}\pm s$) 表示，组间比较采用 t 检验；不良妊娠结局发生率采用 x^2 检验，以 P<0.05 为差异有统计学意义。甲状腺功能与糖代谢及肾功能相关性采用 Pearson 相关性分析

2 结果

2.1 两组甲状腺功能的比较

甲减组的 TSH 水平较对照组高，FT_4 较对照组低 (P<0.05)，两组 FT_3 水平比较无明显差异(P>0.05)，结果见表 1。

表 1 两组甲状腺功的比较($\bar{x}\pm s$)

Table 1 Comparison of the thyroid function between the two groups($\bar{x}\pm s$)

Groups	n	TSH(mIU/L)	FT3(pmol/L)	FT4(pmol/L)
Hypothyroidism group	60	5.26± 1.31	3.95± 0.64	11.36± 0.58
Control group	60	1.97± 0.83	4.02± 0.81	14.38± 2.12
t		16.433	0.525	10.643
P		0.000	0.600	0.000

2.2 两组糖代谢相关指标的比较

甲减组的 FBG、2hPG、HbA1c、HOMA-IR 均较对照组高(P<0.05)，结果见表 2。

表 2 两组糖代谢指标的比较($\bar{x}\pm s$)

Table 2 Comparison of the glucose metabolism between the two groups($\bar{x}\pm s$)

Groups	n	FBG(mmol/L)	2hPG(mmol/L)	HbA1c(%)	HOMA-IR
Hypothyroidism group	60	5.48± 0.87	8.82± 0.78	6.62± 0.71	2.54± 0.62
Control group	60	4.52± 0.75	7.58± 0.63	3.54± 0.67	0.93± 0.22
t		6.474	9.580	24.439	18.956
P		0.000	0.000	0.000	0.000

2.3 两组肾功能的比较

甲减组的 Cr、UA、BUN 水平均较对照组高(P<0.05)，结果见表 3。

2.4 甲状腺功能与糖代谢指标的相关性

TSH 与 FBG、2hPG、HbA1c、HOMA-IR 均呈正相关 (P<0.05)；FT3 与 FBG、2hPG、HbA1c、HOMA-IR 无相关性 (P>0.05)；FT4 与 FBG、2hPG、HbA1c、HOMA-IR 均呈负相关 (P<0.05)，结果见表 4。

表 3 两组肾功能比较($\bar{x}\pm s$)

Table 3 Comparison of the renal function between the two groups($\bar{x}\pm s$)

Groups	n	Cr(μmol/L)	UA(μmol/L)	BUN(mmol/L)
Hypothyroidism group	60	74.13± 11.04	421.62± 56.47	5.93± 0.95
Control group	60	63.56± 7.35	354.14± 31.28	4.91± 0.72
t		6.173	8.097	6.628
P		0.000	0.000	0.000

表 4 甲状腺功能与糖代谢相关性

Table 4 Correlation between thyroid function and glucose metabolism

Index	FBG		2hPG		HbA1c		HOMA-IR	
	r	*P*	r	*P*	r	*P*	r	*P*
TSH	0.326	0.000	0.581	0.000	0.771	0.000	0.716	0.000
FT_3	0.040	0.661	0.100	0.275	-0.034	0.711	0.019	0.835
FT_4	-0.294	0.001	-0.458	0.000	-0.588	0.000	-0.534	0.000

2.5 甲状腺功能与肾功能的相关性

FT_3 与 Cr 呈负相关($P<0.05$),TSH、FT_4 与 Cr、UA、BUN 均无明显相关性($P>0.05$),结果见表 5。

表 5 甲状腺功能与肾功能相关性

Table 5 Correlation between thyroid function and renal function

Index	Cr		UA		BUN	
	r	*P*	r	*P*	r	*P*
TSH	0.277	0.246	0.646	0.315	0.447	0.483
FT_3	-0.531	0.031	-0.043	0.644	-0.137	0.135
FT_4	-0.230	0.724	-0.461	0.472	-0.345	0.354

3 讨论

妊娠时甲状腺处于应激状态,需分泌足量的甲状腺激素以满足机体正常的需要,否则易导致甲状腺功能减退,并增加孕妇糖代谢异常、肾功能异常等疾病风险,对妊娠结局有一定影响[7-9]。妊娠期血清人绒毛膜促性腺激素(HCG)水平升高,产生类促甲状腺激素(TSH)样作用,同时机体甲状腺素结合球蛋白的水平明显升高,对碘的需求量明显增加,肾脏清除碘明显提高,对 TSH 产生明显的反馈作用[10-12],这些生理变化最后导致血清 TSH 在妊娠中期和晚期逐渐升高[13],导致孕妇容易出现甲减。

研究表明甲状腺激素的调控与分泌与糖代谢的调控与分泌均是通过下丘脑 - 垂体 - 靶腺轴 [14]。有研究显示妊娠早期 TSH、FT4 等甲状腺激素指导异常与糖代谢指标相关，认为妊娠早期甲状腺功能异常可能导致妊娠期糖尿病发生风险增加[15-18]。本研究比较了甲减组与对照组甲状腺激素与糖代谢相关指标,结果显示甲减组的 TSH 水平较对照组高,FT4 较对照组低,FBG、2hPG、HbA1c、HOMA-IR 均较对照组高，说明甲状腺功能减退会影响孕妇糖代谢。进一步对甲状腺功能与糖代谢相关指标行 Pearson 相关性分析，结果提示在甲状腺激素中与糖代谢紊乱相关的指标主要是 TSH 和 FT4。TSH、FT4 水平降低对经胎盘释放胰岛素抵抗类激素起诱导作用,诱导并加重胰岛素抵抗[19],且 FT4 水平越低,胰岛素抵抗越严重,胰岛素敏感性越低,出现糖代谢紊乱[20]。另有研究表明亚临床甲状腺功能减退和甲状腺功能减退患者发生妊娠糖尿病的风险是甲状腺功能正常风险的 1.56 和 1.78，由此证实甲状腺功能异常易造成糖代谢紊乱,从而引发妊娠糖尿病[21-24]。本研究结果也证明了这一点,提示孕妇在妊娠早期不仅要进行甲状腺激素相关指标的筛查,而且要进行糖代谢相关指标的筛查,做到妊娠糖尿病的早期防治。

血清肌酐是反映肾功能的重要指标。研究显示血清尿酸是早期妊娠期高血压肾损伤评估的敏感指标之一[25]。有研究显示 TSH＞10.0 mU/L 的甲状腺功能减低患者血清尿素、尿酸、肌酐水平均明显高于甲状腺功能正常者[26]。本研究结果显示甲减组的 Cr、UA、BUN 水平均高于对照组,与相关研究相符,说明甲状腺功能减退会影响孕妇肾功能。进一步对甲状腺激素与肾功能相关指标行 Pearson 相关性分析，结果显示 FT3 与 Cr 呈负相关,TSH、FT4 与 Cr、UA、BUN 均无明显相关性。其原因可能是甲减可引起肾脏功能下降,但肾功损害与 TSH 和 FT4 无关,FT3 是甲状腺激素在细胞发挥生理作用的活化形式,也是影响肾功能的主要的甲状腺激素[27,28]甲状腺激素缺乏导致心输出量减少致全身血循环不足,更易造成肾脏血流量减少、滤过率降

低，血清内 FT3 水平越低，肌酐水平则越高，进一步降低肾血流量和肾小球滤过率，加重肾功能损伤，导致肾结构和功能改变。同时，肾损伤越严重，尿蛋白的丢失也越多，如此形成一个恶性循环。

有研究表明妊娠期甲状腺功能减退可对妊娠结局和胎儿产生不利影响，可分别增加胎儿畸形、产后出血、妊娠期糖尿病、早产的发生率。本研究结果显示甲减组的不良妊娠结局包括早产、流产、剖宫产、极低体质儿等发生率为 20.00%，明显高于正常健康孕妇。研究表明甲状腺过氧化物酶抗体可作用于胚胎或胎盘，如过高的甲状腺过氧化物酶抗体水平会增加母体免疫系统对胎儿的免疫应急反应几率而增加流产率。而甲状腺功能减退会增加孕妇甲状腺过氧化物酶抗体的分泌，导致其水平升高，另外糖代谢紊乱可诱发微血管病变，使毛细血管壁内皮增厚、管腔变窄，增加血管内压，引起周围组织供血不足，增加妊娠期高血压的发生，并增加剖宫产率和产后出血的风险，所以甲减组早产、流产等不良结局发生率明显高于对照组。同时妊娠期甲减会降低孕妇的代谢水平，致能量的摄入少于健康对照组，而且妊娠期甲减会影响子宫胎盘供氧、供血，受此影响，胎儿在宫内生长发育不佳，所以甲减组低出生体质量儿、胎儿窘迫等不良结局发生率高于健康对照组。长期的高血糖状态还可增加胎尿排出量，使子宫内羊水过多，增加母体自发性早产几率。而肾血管病变是妊娠高血压疾病重要发病因素，进而导致多器官缺血缺氧损伤，并易引发多器官如肝、肾、子宫、胎盘功能障碍，进而影响妊娠结局。由此可知，甲减会导致孕妇糖代谢紊乱、肾功能异常，并易增加早产、流产、剖宫产等不良结局。因此，对于孕妇应积极进行甲功检查，并对甲减孕妇进行一定干预，可能改善其妊娠结局。

综上，妊娠期甲状腺功能减退患者其糖代谢紊乱、肾功能异常，并导致不良妊娠结局，孕妇应积极筛查甲功，对甲减孕妇应进行一定干预，以改善妊娠结局。

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