

早孕期甲状腺功能状态与妊娠期糖尿病的相关性

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摘要:【目的】探讨早孕期甲状腺功能状态与妊娠期糖尿病(GDM)的相关性。【方法】选取2016年6月至2017年6月在我院产检的单胎孕妇2 112例。于妊娠9~13⁺6周测定游离甲状腺素(FT4)、促甲状腺素(TSH)及甲状腺过氧化物酶抗体(TPOAb);于24~28周行口服糖耐量试验(OGTT),结果异常者为GDM组(224例),正常者为非GDM组(1 888例),分析两组孕妇甲状腺激素水平的差异及利用Spearman秩相关分析甲状腺激素水平与OGTT各时相血糖的相关性。【结果】GDM孕妇与非GDM孕妇早孕期TSH[1.04(0.61~1.61) vs 1.11(0.59~1.77) μ U/mL, $P=0.292$]、FT4[16.22(14.22~18.31) vs 16.62(14.54~18.79) pmol/L, $P=0.087$]及各甲状腺功能异常的发病率比较差异均无统计学意义($P>0.05$);校正了孕妇年龄、产次及孕前体质量指数后,早孕期TSH和FT4与OGTT各时相血糖无明显的相关性。【结论】早孕期甲状腺功能状态与GDM无明显相关性。

关键词:甲状腺功能;妊娠期糖尿病;早孕期;相关性

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Correlation between Thyroid Function in the First Trimester and Gestational Diabetes Mellitus

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Abstract:【Objective】The present study aimed to evaluate the correlation between thyroid function in the first trimester and gestational diabetes mellitus (GDM).【Methods】A total of 2 112 singleton pregnant women had been recruited from the Third Affiliated Hospital of Sun Yat-Sen University during June 2016 to June 2017. Levels of free thyroxine (FT4), thyroid stimulating hormone (TSH) and thyroid peroxidase antibody (TPOAb) were measured at 9-13⁺6 gestational weeks. Oral glucose tolerance test (OGTT) was performed at 24-28 gestational weeks and the women were divided into GDM group ($n=224$) and non-GDM group ($n=1 888$). The differences of thyroid functions were compared between the two groups. Spearman was used to analyse the correlations between the thyroid hormone levels and the blood glucose levels of OGTT.【Results】There were no statistical differences in TSH [1.04(0.61-1.61) vs 1.11(0.59-1.77) μ U/mL, $P=0.292$] and FT4 [16.22(14.22-18.31) vs 16.62(14.54-18.79) pmol/L, $P=0.087$] between the two groups. The incidences of thyroid dysfunctions were also not different between the two groups ($P>0.05$). No correlations were found between TSH, FT4 and the blood glucoses of OGTT after adjusting the maternal age, parity and pregestational body mass index.【Conclusion】There was no significant correlation between thyroid function in the first trimester and GDM.

Key words: thyroid function; gestational diabetes mellitus; first trimester; correlation

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妊娠期甲状腺功能异常和妊娠期糖尿病(gestational diabetes mellitus, GDM)是产科常见的妊娠期内分泌疾病,对母儿均有较大危害,增加孕期并发症和不良妊娠结局的发生^[1-2]。早在1979年就有文献报道甲状腺疾病与糖尿病之间存在关联^[3]。研究发现,糖尿病患者存在胰岛素以外的多种激素分泌功能异常,且可能参与糖尿病的发病过程,在诸多的内分泌功能异常中,甲状腺功能异常占重要地位^[4]。因此,甲状腺疾病与妊娠期糖尿病的相关性也逐渐引起了关注^[5-7]。孕期甲状腺激素受多种因素影响而发生改变,尤其在早孕期^[8-10],此改变与妊娠期糖尿病是否相关,文献报道结论不一致且结论存在争议。本研究拟对早孕期单胎孕妇的甲状腺激素水平进行检测,了解早孕期甲状腺功能状态与妊娠期糖尿病之间的相关性,探讨甲状腺功能与孕期糖代谢之间的关系。

1 材料与方法

1.1 研究对象

选取2016年6月至2017年6月在我院产检的单胎孕妇,首次产检孕周均 $< 13^{+6}$ 周,排除年龄 > 40 岁、肥胖(体质量指数 $> 30 \text{ kg/m}^2$)、辅助生殖技术后妊娠者、甲状腺疾病或糖尿病家族史者及服用可能影响甲状腺功能或血糖水平药物者(雌激素类除外)等,共纳入孕妇2 112例。

1.2 研究方法

1.2.1 甲状腺功能检查及甲状腺功能异常的诊断标准 所有研究对象于妊娠9-13⁺周采集清晨空腹静脉血3 mL,静置2 h离心,按3 000 r/min离心($r=8 \text{ cm}$),分离血清后使用雅培 Architect i2000全自动化学发光仪检测游离甲状腺素(free thyroxine, FT4)、促甲状腺素(thyroid stimulating hormone, TSH)及甲状腺过氧化物酶抗体(thyroid peroxidase antibody, TPOAb)。按2012年中华医学会内分泌学会和中华医学会围产医学分会决定联合发布的《我国妊娠和产后甲状腺疾病诊治指南》中推荐早孕期TSH的正常参考范围为0.1~2.5 mU/L^[11]。FT4尚无推荐的正常参考范围,本研究采取我院早孕期特异性参考值范围11.90~24.19 pmol/L。超生产厂家提供的TPOAb参考值60 mU/L诊断为抗体阳性。临床甲状腺功能减退

(甲减)诊断标准为血清TSH大于参考值上限,而FT4小于参考值下限;亚临床甲减诊断标准为血清TSH大于参考值上限,而FT4在参考值范围内;临床甲状腺功能亢进(甲亢)诊断标准为血清TSH小于参考值下限,而FT4大于参考值上限;亚临床甲亢诊断标准为血清TSH小于参考值下限,而FT4在参考值范围内。

1.2.2 口服葡萄糖耐量试验及GDM诊断标准 所有研究对象于妊娠24~28周行75 g口服葡萄糖耐量试验(oral glucose tolerance test, OGTT),检查前空腹至少8 h,检查时,5 min内口服含75 g葡萄糖的液体300 mL,分别抽取服糖前、服糖后1 h和2 h的肘静脉血测定血糖。GDM的诊断标准:按2010年国际糖尿病与妊娠研究组(The International Association of Diabetes and Pregnancy Study Groups, IADPSG)公布的GDM诊断标准,空腹、服糖后1 h和2 h血糖正常值分别为小于5.1、10.0和8.5 mmol/L,任意一项异常即可诊断为GDM^[12]。

1.3 统计学分析

应用SPSS 19.0软件进行统计分析。符合非正态分布的计量资料以中位数(四分位间距)表示,组间比较应用Mann-Whitney检验;符合正态分布的计量数据用表示;计数资料以率(%)表示,率的比较用 χ^2 检验。TSH、FT4与空腹血糖及OGTT各时相血糖之间的相关性分析使用Spearman秩相关分析,同时采用偏相关分析校正影响因素(孕妇年龄、产次及孕前体质量指数等), $P < 0.05$ 表示差异具有统计学意义。

2 结果

2.1 一般资料

本研究中诊断GDM孕妇共224例,发病率为10.6%,GDM组孕妇年龄较非GDM孕妇大($P < 0.001$),经产妇较正常孕妇多($P = 0.001$),差异均有统计学意义($P < 0.05$,表1)。GDM组孕妇早孕期空腹血糖(fasting plasma glucose, FPG)及OGTT各时相血糖均高于非GDM组孕妇,差异均有统计学意义(P 值均 < 0.001),但两组孕妇早孕期TSH、FT4及TPOAb的比较,差异无统计学意义($P = 0.292$, $P = 0.087$ 及 $P = 0.612$)。

表1 妊娠期糖尿病孕妇与非妊娠期糖尿病孕妇一般资料比较

Table 1 Characteristics of the study participants in GDM and Non-GDM

 $P_{30}(P_{25}, P_{75})$

Characteristics	Total ($n = 2\ 112$)	Non-GDM ¹⁾ ($n = 1\ 888$)	GDM ($n = 224$)	Z/ χ^2	P
Maternal age/years	30(27-34)	30(27-33)	33(29-36)	-7.766	< 0.001
Parity					
Nullipara/%	51.6	52.9	40.6	12.098 ³⁾	0.001
Multipara/%	48.4	47.1	59.4		
Pregestation BMI/(kg/m ²)	20.0(18.8-21.6)	20.0(18.8-21.5)	20.7(2.5)	-1.408	0.159
TSH ²⁾ /(μ U/mL)	1.10(0.59-1.74)	1.11(0.59-1.77)	1.04(0.61-1.61)	-1.053	0.292
FT4 ²⁾ /(pmol/L)	16.57(14.51-18.76)	16.62(14.54-18.79)	16.22(14.22-18.31)	-1.712	0.087
TPOAb/(U/mL)	28.0(28.0-32.9)	28.0(28.0-33.0)	28.0(28.0-32.7)	-0.507	0.612
FPG ²⁾ /(mmol/L)	4.43(4.19-4.67)	4.41(4.18-4.65)	4.60(4.30-4.86)	-6.235	0.000
75 g OGTT/(mmol/L)					
0 h	4.13(3.94-4.35)	4.11(3.93-4.32)	4.43(4.16-4.77)	-11.785	< 0.001
1 h	7.24(6.19-8.39)	7.04(6.05-8.06)	10.07(9.24-10.70)	-21.629	< 0.001
2 h	6.45(5.64-7.35)	6.30(5.56-7.03)	8.94(8.51-9.64)	-22.358	< 0.001

1) Compared with GDM group; 2) Sampling time at 9-13⁶ weeks; 3) χ^2 value; GDM: gestational diabetes mellitus; BMI: body mass index; FPG: fasting plasma glucose; OGTT: oral glucose tolerance test; TSH: thyroid stimulating hormone; FT4: free thyroxine; TPOAb: thyroid peroxidase antibody

2.2 GDM组孕妇与非GDM组孕妇早孕期甲状腺功能异常的差别

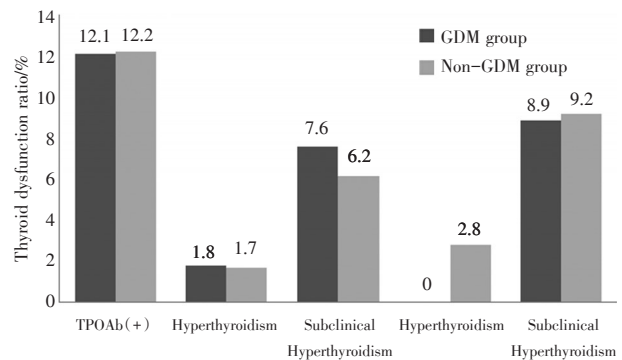
本研究中TPOAb阳性258例,发病率为12.2%;甲亢36例,发病率为1.7%;亚临床甲亢135例,发病率为6.4%;甲减18例,发病率为0.9%;亚临床甲减194例,发病率为9.2%。以是否存在GDM分组,测定两组间各甲状腺功能异常的发病率及TPOAb阳性率,结果显示两组间差异均无统计学意义($P > 0.05$, 图1)。

2.3 早孕期TSH、FT4与早孕期空腹血糖及OGTT各时相血糖的相关性分析

本研究中校正了孕妇年龄、产次及孕前BMI后,利用Spearman秩相关分析显示早孕期TSH、FT4与早孕期空腹血糖及OGTT各时相血糖无明显的相关性,检验偏相关系数的 P 值大于0.05(表2)。

3 讨论

孕期由于甲状腺素结合球蛋白合成增加、胎盘分泌人绒毛膜促性腺激素增多、血液稀释等原因,导致甲状腺功能状态有别于非孕期,尤其在早孕期更为明显^[8-10]。妊娠期甲状腺功能异常可引



No statistical differences were found between the two groups in the incidence of thyroid dysfunction (TPOAb(+): $\chi^2 = 0.01$, $P = 0.95$; Hyperthyroidism: $\chi^2 < 0.01$, $P = 0.92$; Subclinical hyperthyroidism: $\chi^2 = 0.61$, $P = 0.43$; Hypothyroidism: $\chi^2 = 1.17$, $P = 0.14$; Subclinical hypothyroidism: $\chi^2 = 0.02$, $P = 0.90$) (GDM group: $n = 224$; Non-GDM group: $n = 1\ 888$).

图1 妊娠期糖尿病孕妇与非妊娠期糖尿病孕妇早孕期甲状腺功能异常的差别图

Fig.1 Differences of thyroid function in the first trimester between women with GDM and without GDM

起流产、早产、胎盘早剥等不良妊娠结局,尤其是妊娠早期的甲状腺功能减退可影响胎儿神经系统

表2 早孕期TSH、FT4与早孕期空腹血糖及OGTT各时相血糖的相关性分析

Table 2 Correlation analysis between TSH, FT4 in the first trimester and blood glucoses in the first trimester and OGTT

Characteristics	FPG	0 h PG	1 h PG	2 h PG
TSH	-0.009	0.020	0.037	0.009
<i>r</i>	-0.011	0.017	0.035	0.006
<i>r'</i>	0.613	0.427	0.110	0.780
<i>P'</i>				
FT4	-0.027	-0.049	-0.036	-0.028
<i>r</i>	-0.035	-0.058	-0.043	-0.037
<i>r'</i>	0.107	0.008	0.050	0.092
<i>P'</i>				

r: correlation coefficient; *r'*: partial correlation coefficient that were adjusted with maternal age, parity and pregestational body mass index; *P'*: *P* value for partial correlation coefficient; TSH: thyroid stimulating hormone; FT4: free thyroxine; FPG: fasting plasma glucose; OGTT: oral glucose tolerance test; PG: plasma glucose

发育,导致子代智力水平下降^[13]。孕期甲状腺激素改变是否引起糖代谢紊乱,甲状腺功能改变是否与妊娠期糖尿病存在相关性,目前文献报道结论不一致且存在争议。

本研究选取妊娠9~13⁺⁶周的早孕期妇女进行甲状腺功能分析,其优点在于该时期孕妇均未予药物干预,减少了后期部分孕妇因服用甲亢或甲减类药物而对结果产生干扰。在参考值的选择上,本研究选取的早孕期TSH参考值范围为目前国内外指南中推荐的标准0.1~2.5 mU/L;而FT4因临床上普遍采用电化学免疫方法间接测定,该方法受反应温度、缓冲液成分检测试剂不同等影响,因此参考值范围国内外目前尚无统一标准,需建立各机构妊娠期特异性参考值范围,我院采用雅培 Architect i2000全自动化学发光仪检测建立的早孕期特异性FT4参考值范围为11.90~24.19 pmol/L。本研究结果显示,GDM孕妇早孕期甲状腺功能状态与非GDM孕妇无明显差异,且甲状腺功能异常的发生率并未增加;在校正了孕妇年龄、产次及孕前BMI等因素影响后,早孕期TSH、FT4与早孕期空腹血糖及OGTT各时相血糖并无明显

相关性。杨帅等^[14]通过对妊娠9~13周的孕妇采用雅培 Architect i2000全自动化学发光仪检测方法进行甲状腺功能检测,其结果显示GDM孕妇早孕期FT4及TSH水平均低于非GDM孕妇,而两组孕妇TPOAb无明显差异。李春莉等^[15]对<12周的早孕期妇女采用与本研究相同的方法进行甲状腺功能检测,TSH及FT4参考范围选择分别为0.03~3.60 mU/L、11.49~18.84 pmol/L,其结果显示FT4与妊娠期糖尿病患病存在相关,FT4降低是妊娠期糖尿病患病风险增加的危险因素。应豪等^[7]选择德国西门子化学发光法检测甲状腺功能,TSH及FT4的参考范围选择分别为0.06~3.83 mU/L、12.35~19.89 pmol/L,发现早孕期(<13周)的甲状腺激素水平与后期妊娠期糖尿病发生的关系取决于TPOAb的状态,如为TPOAb阴性的孕妇,其妊娠期糖尿病发生的发生风险无明显增加。然而,Montaner等^[16]选择619名孕周<20周的妊娠妇女进行研究,甲状腺功能同样使用雅培化学发光仪检测,结果发现妊娠早期TPOAb阳性与后期妊娠期糖尿病的发生并不相关。王莉华等^[17]研究选择的孕周为14~28周,采用美国贝克曼库尔特有限公司 Beckman Coulter Inc DXI800全自动化学发光仪检测甲状腺功能,TSH参考范围为0.47~4.86 mU/L、FT4参考范围5.72~10.79 pmol/L,研究显示TSH水平与OGTT各时相血糖并无明显相关性,妊娠期甲状腺功能状态与妊娠期糖尿病之间存在相关性的证据不足。因此,不同研究中显示甲状腺功能与妊娠期糖尿病的关系不同,其原因可能与甲状腺功能的检测孕周、方法及TSH、FT4参考值范围等的选择不同有关。

在非孕人群中的研究发现,甲状腺功能会影响胰腺功能及碳水化合物的代谢,甲状腺激素可能通过免疫重叠、影响肠道对葡萄糖的吸收、增加儿茶酚胺受体表达及肝糖分解、增加胰岛素抵抗或损害胰岛β细胞功能等多种途径影响血糖水平^[18-21]。然而,有关孕期甲状腺功能对妊娠期糖尿病影响的机制目前仍未见报道。

综上所述,妊娠期甲状腺功能状态与妊娠期糖尿病的关系仍存在争议,仍需大样本量、多中心、选择统一的甲状腺功能检测方法和参考值范围的临床研究及设计周全的基础研究来进一步证实。

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