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孕早期亚临床甲状腺功能减退与流产发生的相关性*

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摘要 目的:探讨孕早期亚临床甲状腺功能减退与流产发生的相关性。**方法:**2017年2月至2019年选择在本院进行建档的孕早期孕妇120例,检测血清游离三碘甲状腺原氨酸(free triiodothyronine, FT3)、游离甲状腺素(free thyroxine, FT4)、促甲状腺激素(thyroid stimulating hormone, TSH)含量,判断亚甲减发生情况。调查所有孕妇的流产等妊娠结局情况并分析相关性。**结果:**在120例孕妇中,发生亚甲减18例(亚甲减组),发生率为15.0%。亚甲减组的年龄、孕周、孕次、产次、心率、收缩压、舒张压等指标与非亚甲减组对比差异无统计学意义($P>0.05$)。亚甲减组的血清TSH含量高于非亚甲减组,FT3值低于非亚甲减组($P<0.05$),两组FT4值对比差异无统计学意义($P>0.05$)。亚甲减组的流产发生率为38.9%,显著高于非亚甲减组的2.9%($P<0.05$)。亚甲减组的早产、前置胎盘、胎膜早破、产后出血、巨大儿、低体重儿、新生儿窒息等发生率也显著高于非亚甲减组($P<0.05$)。在120例孕妇中,Pearson相关分析法显示流产与亚甲减、血清TSH、FT3值都存在相关性($P<0.05$)。**结论:**孕早期亚甲减在临床上比较常见,可导致流产发生率增加,也可增加妊娠不良结局的发生几率,亚甲减与流产存在正向相关性。

关键词:孕早期;亚临床甲状腺功能减退;流产;早产;新生儿窒息

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Correlation between Subclinical Hypothyroidism in Early Pregnancy and Abortion*

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ABSTRACT Objective: To explore the correlation between subclinical hypothyroidism and miscarriage in early pregnancy. **Methods:** From February 2017 to 2019, 120 cases of pregnant women in early pregnancy who chose to file in our hospital were selected as the research objects. The serum free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (thyroid stimulating hormone) (TSH) were detected, and were to determine the occurrence of hypothyroidism. And the pregnancy outcomes such as abortion in all pregnant women were record and were given correlation analysis. **Results:** There were 18 cases of hypoparathyroidism occurred (subparathyroidism group) in the 120 cases, and the incidence rates were 15.0%. There were no significant differences in age, gestational week, gestation period, parity, heart rate, systolic blood pressure, and diastolic blood pressure compared between the subparathyroidism group and the non-subparathyroidism group ($P>0.05$). The serum TSH levels in the subparathyroidism group were higher than that in the non-subparathyroidism group, and the FT3 value were lower than that in the non-subparathyroidism group that compared were statistically significant difference ($P<0.05$). There were no significant difference in the FT4 value compared between the two groups ($P>0.05$). The incidence rates of miscarriage in the hypomethylene group were 38.9%, which were significantly higher than that in the non-subparathyroidism group (2.9%) ($P<0.05$). The prevalence of preterm birth, placenta previa, premature rupture of membranes, postpartum hemorrhage, gigantic infants, low birth weight infants, neonatal asphyxia, etc. were also significantly higher in the hypomethylated group than in the non-subparathyroidism group ($P<0.05$). In the 120 pregnant women, Pearson correlation analysis showed that there were correlation between abortion and hypothyroidism, serum TSH, and FT3 values ($P<0.05$). **Conclusion:** Hypothyroidism in the early pregnancy are more common clinically, which can lead increase in the incidence of miscarriage and increase the incidence of adverse pregnancy outcomes. There are positive correlation between hypothyroidism and abortion.

Key words: Early pregnancy; Subclinical hypothyroidism; Abortion; Premature delivery; Neonatal asphyxia

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前言

当前随着社会环境的变化、人民生活行为的改变等多种因素的影响,导致孕早期的流产发生率逐渐增加^[1,2]。临床需要对早期自然流产的因素进行分析,以为早期指导优生优育提供帮助^[3]。妊娠期胎盘可分泌大量雌激素、孕激素等,机体处于特殊免疫状态,这些变化可影响妊娠结局^[4]。亚临床疾病是指没有或仅有非特异性的临床症状,亚临床甲状腺功能减退(简称亚甲减, Subclinical hyperthyroidism) 为临床上常见的亚临床甲状腺疾病,孕妇妊娠期发生亚甲减的几率为 1.0 %左右^[5,6]。特别是孕早期高水平人绒毛膜促性腺激素 (human chorionic gonadotropin, HCG) 可以和促甲状腺激素(thyroid stimulating hormone, TSH)受体结合,使得甲状腺激素分泌增多, TSH 水平降低,诱发亚甲减的发生^[7]。当前 TSH 依然是评价绝大多数孕早期孕妇甲状腺功能的金标准,不过由于其缺乏特异的临床症状和体征,在临床上容易被忽视^[8]。但是随着病情的进展,可能对妊娠结局造成影响,导致流产、死胎、新生儿认知能力障碍的发生率增加^[9,10]。并且妊娠对于甲状腺是一种应激试验,一些甲功正常而甲状腺储备功能下降的妇女在妊娠期容易发生亚临床甲减^[11,12]。本文具体探讨了孕早期亚甲减与流产发生的相关性,以明确亚甲减对母婴可能产生的影响。现总结报道如下。

1 资料与方法

1.1 研究对象

本研究为前瞻性队列研究,研究得到了医院伦理委员会的批准与所有孕妇的知情同意。2017 年 2 月至 2019 年选择在本院进行建档的孕早期孕妇 120 例,纳入标准:4~8 w 龄宫内妊娠;居住在本地地区≥ 3 年或为本地地区户籍;单胎妊娠;临床资料完整;年龄 18~35 岁。排除标准:临床资料不全、依从性较差孕

妇;甲状腺以外的自身免疫性疾病;既往早产史;正服用或者入院前 3 个月服用影响甲状腺功能的药物;合并遗传性疾病患者;采用辅助生殖技术的妊娠;宫外孕;患有先天性心脏病或心功能不全。

1.2 血液学检测

抽取所有孕妇的空腹静脉血 2~3 mL,不抗凝,静置 30 min 后 1500 rpm 离心 10 min,取上层血清, -20 ℃ 冰箱保存。采用酶联免疫法检测血清 FT3、FT4、TSH 含量,检测试剂盒都购自瑞士 Roche 公司。孕早期实验室特异 TSH 参考范围为 0.1~2.5 mIU /L。亚临床甲减诊断标准:孕早期 TSH 5.22~10.00 mIU/L, FT4 12.91~22.35 pmol/L; FT4 水平正常, TSH>10.00 mIU/L。同时记录所有孕妇的年龄、孕周、孕次、产次、心率、血压等指标。

1.3 妊娠结局

记录两组孕妇的流产发生情况,同时记录孕妇并发症发生情况,包括早产、前置胎盘、胎膜早破、产后出血。记录新生儿结局情况,包括巨大儿、低体重儿、新生儿窒息等。

1.4 统计方法

选择 SPSS 19.00,以 $\bar{x} \pm s$ 表示计量数据,对比方法为 t 检验;以 %、率等表示计数数据,对比方法为卡方 χ^2 分析,采用 Pearson 相关分析法分析相关性,以 logistic 回归分析影响因素, $P < 0.05$ 判定为具有显著性差异。

2 结果

2.1 亚甲减发生情况

在 120 例孕妇中,发生亚甲减 18 例(亚甲减组),发生率为 15.0 %。亚甲减组的年龄、孕周、孕次、产次、心率、收缩压、舒张压等指标与非亚甲减组对比差异无统计学意义($P > 0.05$),见表 1。

表 1 两组一般资料对比($\bar{x} \pm s$)

Table 1 Comparison of two groups of general information ($\bar{x} \pm s$)

Groups	n	Age (years)	Gestational (week)	Pregnancy (times)	Parity (time)	Heart rate (times / minute)	Systolic pressure (mmHg)	Diastolic pressure (mmHg)
Methylene group	18	27.31± 1.48	6.59± 0.14	1.98± 0.13	0.98± 0.14	82.47± 1.44	128.09± 12.77	78.66± 5.15
Non-methylene group	102	27.98± 1.22	6.61± 0.22	1.99± 0.11	0.99± 0.17	82.78± 1.22	126.87± 13.65	78.87± 4.44

2.2 甲状腺功能指标对比

亚甲减组的血清 TSH 含量高于非亚甲减组, FT3 值低于

非亚甲减组,两组对比差异都有统计学意义 ($P < 0.05$), 两组 FT4 值对比差异无统计学意义($P > 0.05$),见表 2。

表 2 两组甲状腺功能指标对比($\bar{x} \pm s$)

Table 2 Comparison of thyroid function indicators between two groups ($\bar{x} \pm s$)

Groups	n	TSH(mIU/L)	FT3(pmol/L)	FT4(pmol/L)
Methylene group	18	4.52± 0.11*	4.02± 0.21*	13.29± 1.14
Non-methylene group	102	1.89± 0.09	4.33± 0.18	13.21± 0.98

Note: compare with the non-methylene group, * $P < 0.05$.

2.3 流产情况对比

亚甲减组的流产发生率为 38.9 %,显著高于非亚甲减组的 2.9 %,两组对比差异有统计学意义($P < 0.05$),见表 3。

2.4 妊娠并发症与新生儿情况对比

亚甲减组的早产、前置胎盘、胎膜早破、产后出血、巨大儿、

低体重儿、新生儿窒息等发生率也显著高于非亚甲减组($P < 0.05$),见表 4。

2.5 相关性分析

在 120 例孕妇中, Pearson 相关分析法显示流产与亚甲减、血清 TSH、FT3 值都存在相关性($P < 0.05$),见表 5。

表 3 两组流产情况对比(例,%)

Table 3 Comparison of abortion between the two groups (n,%)

Groups	n	Abortion
Methylene group	18	7(38.9)*
Non-methylene group	102	3(2.9)

表 4 两组妊娠并发症与新生儿情况对比(例,%)

Table 4 Comparison of pregnancy complications and neonatal conditions in two groups (n,%)

Groups	n	Premature birth	Placenta praevia	Premature rupture of membranes	Postpartum hemorrhage	Giant baby	Infant of low-birth weight	Asphyxia neonatorum
Methylene group	18	9 (50.0)*	4 (22.2)*	5 (27.8)*	6 (33.3)*	6 (33.3)*	6 (33.3)*	7 (38.9)*
Non-methylene group	102	12 (11.8)	3 (2.9)	2 (2.0)	4 (3.9)	6 (5.9)	9 (8.8)	2 (2.0)

表 5 孕早期亚临床甲状腺功能减退与流产发生的相关性

Table 5 Correlation between subclinical hypothyroidism and miscarriage in early pregnancy

Index	Methylene	TSH	FT3
r	0.782	0.644	-0.485
P	0.000	0.000	0.006

3 讨论

孕早期亚甲减在临床上比较常见, 主要在于妊娠期因 HCG 升高正反馈促进了甲状腺激素的分泌, 后者又负反馈抑制了 TSH 的水平, 使血清 TSH 水平降低^[13,14]。特别是在孕早期, 母体和胎儿对甲状腺激素的需求量增加, 孕妇通过自身调节, 血清中雌二醇、甲状腺素结合球蛋白增加, 可增加内源性甲状腺激素的产生和分泌^[15]。并且此时孕妇碘经尿排泄增多, 肾血流量增加, 胎儿甲状腺对碘的需要量逐渐增加, 胎儿的下丘脑开始分泌促甲状腺激素释放激素, 从而促进分泌 TSH 能力^[16]。并且在妊娠 8~10 w 左右, HCG 与 TSH 具有相似的亚单位, 可刺激甲状腺靶器官分泌甲状腺素, 雌激素刺激肝脏合成甲状腺素结合球蛋白增多, 使血清中游离甲状腺素略有升高, 导致 TSH 分泌减少^[17,18]。本研究显示在 120 例孕妇中, 发生亚甲减 18 例, 发生率为 15.0%; 亚甲减组的年龄、孕周、孕次、产次、心率、收缩压、舒张压等指标与非亚甲减组对比差异无统计学意义; 亚甲减组的血清 TSH 含量高于非亚甲减组, FT3 值低于非亚甲减组, 两组 FT4 值对比差异无统计学意义。从机制上分析, 孕早期当发生亚临床甲减时, 为稳定血中 FT4 水平, 甲状腺释放 FT3, 这个可表现为 FT3 轻度增高的趋势。当前也有研究显示对于血清 TSH 水平异常的孕妇, 应追踪检查甲状腺球蛋白抗体(thyroid globulin antibody, TGAb)、甲状腺过氧化物酶抗体(thyroid peroxidase antibody, TPOAb), 同时应积极复查血清 TSH, 以排除 TSH 暂时性受抑制^[19,20]。不过随着孕周增加, 自身免疫系统识别的降低, 甲状腺自身抗体滴度逐渐下降, 母体对胎儿的免疫耐受增加, 也使得孕妇甲状腺功能指标分泌正常^[21,22]。

孕早期亚甲减的发生病因比较多, 包括精神压力、自身免疫、碘缺乏等, 特别是对孕妇及其子代的不利影响得到了广泛重视^[23]。有研究显示妊娠期合并亚临床甲减可能与、早产、自然流产、新生儿呼吸窘迫综合征、胎盘早剥、贫血、产后出血、畸形

儿、胎死宫内等显著相关^[24]。本研究显示亚甲减组的流产发生率为 38.9%, 显著高于非亚甲减组的 2.9%。从机制上分析, 孕早期亚甲减时心脏低动力、心输出量下降, 血管平滑肌收缩, 血浆胶体渗透压降低, 引起组织水肿, 外周阻力增加, 导致舒张压增高; 其也使得胆固醇降解减弱, 血脂水平增高; 同时 TSH 水平升高可使得黄体生成素反应迟滞, 形成黄体生成不足, 导致孕酮分泌减少, 诱发流产的出现^[25,26]。

孕早期亚甲减是多种原因引起的甲状腺激素不足所致的一组内分泌疾病, 多数孕妇无甲减症状或仅有轻微甲减症状。此时孕妇容易出现合并高血压疾病、贫血、新生儿低体重、糖代谢异常、胎儿宫内生长受限等并发症, 甚至会导致流产、早产等发生^[27]。本研究显示亚甲减组的流产发生率为 38.9%, 显著高于非亚甲减组的 2.9%; 亚甲减组的早产、前置胎盘、胎膜早破、产后出血、巨大儿、低体重儿、新生儿窒息等发生率也显著高于非亚甲减组。从机制上分析, 孕早期亚甲减可引起孕妇收缩压的升高, 也可影响心血管内皮细胞的活性, 这提示亚甲减与早产、前置胎盘、胎膜早破可能存在联系。同时甲状腺激素可影响胎儿的脑发育缺乏甲状腺激素, 将使神经细胞发育不良, 可以造成新生儿窒息发生率, 使得低出生体重儿发生率增高。当前也有研究显示合并亚甲减的孕妇与甲功正常的孕妇相比较, 低出生体重儿的发生率显著增加, 主要在于 TSH 有可能参与胎盘的发育、功能^[28,29]。

孕早期亚临床甲减对母胎的影响还在持续探讨中。本研究 Pearson 相关分析法孕早期孕妇的流产与亚甲减、血清 TSH、FT3 值都存在相关性。从机制上分析, 在妊娠期间, 母体本身处于一种免疫抑制状态, 亚临床甲减可对妊娠和胎儿结局产生不良影响^[30]。临床上要为孕早期亚甲减的防治提供依据, 并通过积极地干预来减少流产与妊娠不良结局的发生。本研究也存在一定的不足, 样本数量减少, 且相关性分析指标也比较少, 将在后续研究中深入探讨。

总之,孕早期亚甲减在临床上比较常见,可导致流产发生率增加,也可增加妊娠不良结局的发生几率,亚甲减与流产存在正向相关性。

参 考 文 献(References)

- [1] Khadilkar S. Thyroid-Stimulating Hormone Values in Pregnancy: Cut-off Controversy Continues?[J]. *J Endocr Soc*, 2019, 69(5): 389-394
- [2] Korevaar TIM, Derakhshan A, Taylor PN, et al. Association of Thyroid Function Test Abnormalities and Thyroid Autoimmunity With Preterm Birth: A Systematic Review and Meta-analysis [J]. *Jama*, 2019, 322(7): 632-641
- [3] Li J, Liu A, Liu H, et al. Maternal TSH levels at first trimester and subsequent spontaneous miscarriage: a nested case-control study [J]. *Endocr Connect*, 2019, 8(9): 1288-1293
- [4] Lopez-Munoz E, Mateos-Sanchez L, Mejia-Terrazas GE, et al. Hypothyroidism and isolated hypothyroxinemia in pregnancy, from physiology to the clinic [J]. *Taiwan J Obstet Gynecol*, 2019, 58(6): 757-763
- [5] Magri F, Chiovato L. Thyroid hormone therapy for subclinical hypothyroidism[J]. *Endocrine*, 2019, 66(1): 27-34
- [6] Nazarpour S, Ramezani Tehrani F. Levothyroxine treatment and pregnancy outcomes in women with subclinical hypothyroidism: a systematic review and meta-analysis[J]. *Arch Gynecol Obstet*, 2019, 300(4): 805-819
- [7] Nazarpour S, Ramezani Tehrani F, Amiri M, et al. Maternal Urinary Iodine Concentration and Pregnancy Outcomes: Tehran Thyroid and Pregnancy Study[J]. *Arch Gynecol Obstet*, 2020, 194(2): 348-359
- [8] Ocal N, Calis P, Inan MA, et al. Study on subclinical hypothyroidism in pregnancy: a bibliometric analysis via CiteSpace[J]. *Arch Gynecol Obstet*, 2020, 9(13): 1-12
- [9] Safarian GK, Gzgzyan AM, Dzhelelikhanova Lyailya K, et al. Does subclinical hypothyroidism and/or thyroid autoimmunity influence the IVF/ICSI outcome? Review of the literature [J]. *Gynecol Endocrinol*, 2019, 35(sup1): 56-59
- [10] Cecenarro L, Martinez-Barahona M, Palomera E, et al. Impact of positive thyroid autoimmunity on pregnant women with subclinical hypothyroidism[J]. *Clin Endocrinol (Oxf)*, 2018, 65(3): 150-155
- [11] Croce L, Rotondi M, Toloza FJK, et al. Practice Variation in the Care of Subclinical Hypothyroidism During Pregnancy: A National Survey of Physicians in the United States [J]. *Endocrine*, 2019, 3 (10): 1892-1906
- [12] Etemadi A, Amouzegar A, Mehran L, et al. Isolated Hypothyroxinemia in Iranian Pregnant Women, the Role of Iodine Deficiency: A Population-Based Cross-Sectional Study [J]. *Thyroid*, 2020, 30 (2): 262-269
- [13] Fan J, Zhang Y, Zhang C, et al. Persistency of Thyroid Dysfunction from Early to Late Pregnancy[J]. *Thyroid*, 2019, 29(10): 1475-1484
- [14] Karcaaltincaba D, Ozek MA. Prevalences of subclinical and overt hypothyroidism with universal screening in early pregnancy [J]. *Arch Gynecol Obstet*, 2020, 301(3): 681-686
- [15] Chen S, Zhou X, Zhu H, et al. Preconception TSH and pregnancy outcomes: a population-based cohort study in 184 611 women [J]. *PLoS One*, 2017, 86(6): 816-824
- [16] Cueva S, Burks C, Mcqueen D, et al. Maternal antithyroid antibodies and euploid miscarriage in women with recurrent early pregnancy loss [J]. *Fertil Steril*, 2018, 110(3): 452-458
- [17] Du YJ, Xin X, Cui N, et al. Effects of controlled ovarian stimulation on thyroid stimulating hormone in infertile women [J]. *Eur J Obstet Gynecol Reprod Biol*, 2019, 234: 207-212
- [18] So S, Yamaguchi W, Murabayashi N, et al. Effect of moderately increased thyroid-stimulating hormone levels and presence of thyroid antibodies on pregnancy among infertile women[J]. *Reprod Med Biol*, 2020, 19(1): 82-88
- [19] Talat A, Khan AA, Nasreen S, et al. Thyroid Screening During Early Pregnancy and the Need for Trimester Specific Reference Ranges: A Cross-Sectional Study in Lahore, Pakistan [J]. *Cureus*, 2019, 11 (9): e5661
- [20] Wu MQ, Liu J, Wang YQ, et al. The Impact of Subclinical Hypothyroidism on Adverse Perinatal Outcomes and the Role of Thyroid Screening in Pregnancy[J]. *Front Endocrinol (Lausanne)*, 2019, 10(8): e522
- [21] Furukawa S, Miyakawa K, Shibata J, et al. Women with Subclinical Hypothyroidism Are at Low Risk of Poor Pregnancy Outcome in Japan[J]. *Tohoku J Exp Med*, 2017, 242(3): 167-172
- [22] Hernandez M, Lopez C, Soldevila B. Impact of TSH during the first trimester of pregnancy on obstetric and foetal complications: Usefulness of 2.5 mIU/L cut-off value [J]. *Clin Endocrinol (Oxf)*, 2018, 88(5): 728-734
- [23] Miko E, Meggyes M, Doba K, et al. Characteristics of peripheral blood NK and NKT-like cells in euthyroid and subclinical hypothyroid women with thyroid autoimmunity experiencing reproductive failure[J]. *J Reprod Immunol*, 2017, 124(11): 62-70
- [24] Rao M, Zeng Z, Zhou F, et al. Effect of levothyroxine supplementation on pregnancy loss and preterm birth in women with subclinical hypothyroidism and thyroid autoimmunity: a systematic review and meta-analysis[J]. *Hum Reprod Update*, 2019, 25(3): 344-361
- [25] Shan L, Zhou Y, Peng S, et al. Implantation failure in rats with subclinical hypothyroidism is associated with LIF/STAT3 signaling[J]. *Endocr Connect*, 2019, 8(6): 718-727
- [26] Uchida S, Maruyama T, Kagami M, et al. Impact of borderline-subclinical hypothyroidism on subsequent pregnancy outcome in women with unexplained recurrent pregnancy loss[J]. *J Obstet Gynaecol Res*, 2017, 43(6): 1014-1020
- [27] Velasco I, Taylor P. The role of levothyroxine in obstetric practice[J]. *Ann Med*, 2018, 50(1): 57-67
- [28] Zhang Y, Wang H, Pan X, et al. Patients with subclinical hypothyroidism before 20 weeks of pregnancy have a higher risk of miscarriage: A systematic review and meta-analysis[J]. *PLoS One*, 2017, 12 (4): e0175708
- [29] Zhou Y, Wang X, Zhang Y, et al. Circulating MicroRNA Profile as a Potential Predictive Biomarker for Early Diagnosis of Spontaneous Abortion in Patients With Subclinical Hypothyroidism [J]. *Front Endocrinol (Lausanne)*, 2018, 9(18): e128
- [30] Sitoris G, Veltri F, Kleynen P, et al. The Impact of Thyroid Disorders on Clinical Pregnancy Outcomes in a Real-World Study Setting [J]. *Thyroid*, 2020, 30(1): 106-115