

doi: 10.13241/j.cnki.pmb.2018.21.030

干预治疗对 TPOAb 阴性亚甲减孕妇妊娠结局的影响 *

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摘要 目的:探讨干预治疗对不同 TSH 水平的妊娠期亚临床甲减合并甲状腺过氧化物酶(TPOAb)阴性孕妇妊娠结局的影响。**方法:**回顾性分析 2016 年 1 月 1 日至 2016 年 12 月 31 日在青岛大学附属医院产科分娩孕妇诊断为亚临床甲减且 TPOAb 阴性的孕妇不良妊娠结局的发生率,根据 2011 年(S1 标准)及 2017 年(S2 标准)美国甲状腺协会(ATA)指南对妊娠合并亚临床甲减推荐诊断的 TSH 水平不同分组,A 组($4 \text{ mIU/L} < \text{TSH} < 10.0 \text{ mIU/L}$)131 例,B 组($\text{TSH} < 4 \text{ mIU/L}$,在 T1 期 $\text{TSH} > 2.5 \text{ mIU/L}$,T2、T3 期 $\text{TSH} > 3.0 \text{ mIU/L}$)326 例,根据是否接受左甲状腺素钠片(商品名:优甲乐)治疗,分为治疗组(295 例)、未治疗组(194 例),同时选取 TPOAb 阴性且甲状腺功能正常的孕妇(306 例)作为对照组。**结果:**(1)依据 S1、S2 诊断标准,妊娠合并亚临床甲减的发生率分别为 13.57%、3.6%,治疗率分别为 39.67%、51.34%,不同诊断标准间比较差异具有统计学意义($P < 0.05$)。(2)A 组孕妇中,未治疗组妊娠期高血压疾病、妊娠期糖尿病、妊娠期贫血、流产、早产、胎儿窘迫的发生率均高于治疗组及对照组,差异具有统计学意义($P < 0.05$),而治疗组与对照组比较差异无统计学意义($P > 0.05$)。未治疗组胎盘早剥、胎膜早破、胎儿畸形、低体重儿的发生率虽高于治疗组及对照组,但两两比较差异均无统计学意义($P > 0.05$)。(3)B 组孕妇未治疗组妊娠期高血压疾病、妊娠期糖尿病、妊娠期贫血、流产、早产、胎儿窘迫、胎盘早剥、胎膜早破、胎儿畸形、低体重儿的发生率虽高于治疗组及对照组,三组及两两比较差异无统计学意义($P > 0.05$)。**结论:**对于青岛地区 TPOAb 阴性的妊娠期亚临床甲减孕妇, $4.0 \text{ mIU/L} < \text{TSH} < 10.0 \text{ mIU/L}$ 时,左甲状腺素钠片治疗能明显改善其不良妊娠结局。

关键词:妊娠期亚临床甲减;TPO 阴性;妊娠结局

中图分类号:R714.256 **文献标识码:**A **文章编号:**1673-6273(2018)21-4133-04

Effect of Intervention Therapy on the Pregnancy Outcome of Pregnant Women with TPOAb-negative Hypothyroidism*

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ABSTRACT Objective: To investigate the effect of intervention therapy on the pregnancy outcome of pregnant women with thyroid gland peroxidase antibody(TPOAb)-negative subclinical hypothyroidism(SCH). **Methods:** The incidence of adverse pregnancy outcomes in pregnant women who delivered and diagnosed as SCH and TPOAb negative in the Affiliated Hospital of Qingdao University from January 1, 2016 to December 31, 2016 was retrospectively analyzed. According to the different TSH standard of American Thyroid Association(ATA) published in 2011(S2) and 2017 (S2), the subjects were divided into the group A($4 \text{ mIU/L} < \text{TSH} < 10.0 \text{ mIU/L}$, 131 cases) and group B($\text{TSH} < 4 \text{ mIU/L}$, first-trimester $\text{TSH} > 2.5 \text{ mIU/L}$, second-trimester and third-trimester and $\text{TSH} > 3.0 \text{ mIU/L}$, 326 case). The subjects were divided into the treatment group (295 cases) and the untreated group (194 cases) according to acceptance of Levothyroxine sodium tablets (trade name: Euthyrox), the pregnant women with TPOAb negative and normal thyroid function were selected as the control group (306 cases) at the same time. **Results:** (1) According to S1 and S2 diagnostic criteria, the incidence of SCH in pregnancy was 13.57% and 3.6%, and the treatment rates were 39.67% and 51.34%, respectively. The difference was statistically significant between different diagnostic criteria($P < 0.05$). (2) In group A, the incidence of gestational hypertension, gestational diabetes mellitus (GDM), anemia, abortion, premature delivery, fetal distress in untreated group were higher than those in the treated group and the control group($P < 0.05$). No significant difference was found between treatment group and control group in the incidence of placental abruption, premature rupture of membranes, fetal malformation and low birth weight infants ($P > 0.05$). The incidence of was higher in the untreated group than that in the treatment group and the control group, but the difference showed no significant difference ($P > 0.05$). (3) In group B, the incidence of adverse pregnancy outcomes in the untreated group were higher than those in the treated group and the control group, but there was no significant difference between the three groups($P > 0.05$). **Conclusion:** For pregnant women with TPOAb-negative gestational subclinical hypothyroidism in Qingdao, when $4.0 \text{ mIU/L} < \text{TSH} < 10.0 \text{ mIU/L}$, levothyroxine sodium tablets can significantly improve the ad-

* 基金项目:青岛市科技计划项目(2016-3-032-YY)

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(收稿日期:2018-05-20 接受日期:2018-06-17)

verse pregnancy outcomes.

Key words: Pregnancy subclinical hypothyroidism; TPO negative; Pregnancy outcome

Chinese Library Classification(CLC): R714.256 **Document code:** A

Article ID: 1673-6273(2018)21-4133-04

前言

妊娠期甲状腺疾病是内分泌学界与围产医学界共同关注的热点问题,大量研究表明,妊娠期间轻度 TSH 上升伴 TPOAb 阳性与妊娠不良结局相关。但 TPOAb 阴性是否与妊娠期亚临床甲减孕妇不良结局相关尚存在争议。2017 年,美国 ATA 指南^[1]调整了 TSH 参考值上限为 4 mIU/L,对于 TPOAb 阴性,2.5 mIU/L<TSH<4 mIU/L 的亚临床甲减孕妇是否需要治疗及 TSH>4.0 mIU/L 治疗效果尚需进一步的临床研究证明。本研究旨在观察青岛地区不同 TSH 水平对妊娠合并亚临床甲减孕妇妊娠结局的影响及左甲状腺素钠片干预治疗的效果。

1 材料与方法

1.1 资料来源

收集 2016 年 1 月 1 日至 2016 年 12 月 31 日在青岛大学附属医院住院分娩,包括流产、早产的产妇共 8966 人,符合妊娠合并亚临床甲减的孕妇 1217 人(依据 2011 年 ATA 诊断标准),其中 TPO 阴性孕妇 489 例,具体纳入及排除标准如下,纳入标准:(1)年龄 20-40 岁;(2)自然单胎妊娠;(3)既往无早产、流产、胎盘早剥、妊娠期糖尿病等不良妊娠史;(4)既往无甲状腺疾病、高血压、糖尿病、贫血、代谢性疾病、胰腺疾病及相关家族史;(5)在我院规律孕检,病例资料完整者;(6)所有入选孕妇在青岛居住至少 5 年,碘营养充足;(7)甲状腺过氧化物酶阴性。(8)符合 2011 年 ATA 指南关于妊娠合并亚临床甲减的诊断标准。排除标准:(1)双胎或多胎妊娠;(2)自身免疫性疾病史;(3)非甲状腺疾病造成的促甲状腺素(TSH)水平升高的情况,如非甲状腺疾病恢复期、早期肾上腺功能衰竭、慢性肾病;(4)服用影响甲状腺功能的药物,如甲状腺素、甲巯咪唑、胺碘酮;(5)血清转氨酶、肌酐升高(谷丙转氨酶 6-60 IU/L,谷丙转氨酶 0-55 IU/L,肌酐 40-106 μmmol/L);(6)通过辅助生殖技术妊娠;(7)子宫畸形或子宫纤维瘤;(8)BMI≥ 30 kg/m²。

1.2 方法

1.2.1 诊断标准与分组 妊娠期亚临床甲减的诊断标准是血清 TSH> 妊娠期特异性参考值的上线(97.5th),血清 FT4 在血清参考值范围之内(2.5th-97.5th),TPOAb<34 U/L 为阴性。2011 年 ATA 推荐亚临床甲减的诊断^[2]为血清 TSH 在 2.5-10 mIU/L 之间,但 FT4 浓度正常(S1)。2017 年 ATA 指南推荐妊娠 TSH 参考值上线定为 4.0 mIU/L(S2)。依据两个指南中不同 TSH 诊断水平分组:A 组:4 mIU/L<TSH<10.0 mIU/L。B 组 TSH<4 mIU/L,在 T1 期 TSH>2.5 mIU/L,T2、T3 期 TSH>3.0 mIU/L,按 2011 年 ATA 推荐的标准(S1)诊断为亚临床甲减的孕妇 1217 人,其中 TPOAb 阴性孕妇 489 例,如按 2017 年 ATA 指南推荐标准(S2)诊断为亚临床甲减的孕妇 326 例,TPO 阴性孕妇 131 例。TPOAb 阴性孕妇根据患者是否接受左甲状腺素钠片治疗分为亚临床甲减治疗组(295 例)及亚临床甲减未治疗组(194

例),同时选取 TPOAb 阴性甲状腺功能正常(0.27 mIU/L<TSH<2.5 mIU/L,FT4 正常)的孕妇 306 名作为对照组。入选患者均规律在我院孕检,定期复查甲状腺功能,治疗组接受左甲状腺素钠片(优甲乐)治疗,根据甲功结果调整甲状腺素用量,使 TSH 水平尽快达标。治疗目标为 TSH 在 T1 期 0.1-2.5 mIU/L,T2 期 0.2-3.0 mIU/L,T3 期为 0.3-3.0 mIU/L。

1.2.2 妊娠不良结局观察指标 回顾性分析孕妇的临床资料,分别统计各组发生妊娠期高血压疾病、妊娠期糖尿病(GDM)、妊娠期贫血、流产、早产、胎膜早破、胎盘早剥、胎儿窘迫、低体重儿、胎儿畸形的例数,对各组不良妊娠结局的发生率进行比较分析。

1.3 统计学方法

统计学分析采用 SPSS22.0 软件进行,符合正态分布的计量资料数据用 $\bar{x} \pm s$ 表示,计数资料结果采用百分率表示,率的比较采用卡方检验、Fisher 确切概率法,以 P<0.05 为差异具有统计学意义。

2 结果

2.1 妊娠妇女亚临床甲状腺功能的患病率

依据 S1 诊断标准,妊娠合并亚临床甲减的发生率为 13.57%(1212/8966),TPOAb 阴性妊娠期亚临床甲减的发生率为 5.45%(489/1217),治疗率为 39.67%(194/489)。如根据 S2 体检诊断标准,妊娠合并亚临床甲减的发生率为 3.6%(326/8966),其中妊娠期亚临床甲减且 TPOAb 阴性的发生率 1.4%(131/8966),治疗率 51.34%(70/131)。与 S1 诊断标准相比较,S2 标准诊断的妊娠合并亚临床甲减的患病率、治疗率比较差异具有统计学意义(P=0.00)。

2.2 TPOAb 阴性的妊娠期亚临床甲减孕妇 4.0 mIU/L<TSH<10.0 mIU/L 时,三组孕妇不良妊娠结局的比较

治疗组、未治疗组、对照组妊娠期高血压疾病、GDM、妊娠期贫血、流产、早产、胎儿窘迫发生率比较差异具有统计学意义(P<0.05)。其中未治疗组妊娠期高血压疾病、GDM、妊娠期贫血、流产、早产及胎儿窘迫的发生率均高于治疗组、对照组,分别比较,差异具有统计学意义(P<0.0167),而治疗组与对照组比较差异无统计学意义(P>0.05)。未治疗组胎盘早剥、胎膜早破、胎儿畸形、低体重儿的发生率高于治疗组、对照组,但差异均无统计学意义(P>0.05)。见表 1。

2.3 TPOAb 阴性的妊娠期亚临床甲减孕妇 2.5 mIU/L<TSH<4.0 mIU/L 时,三组孕妇不良妊娠结局的比较

治疗组、未治疗组、对照组妊娠期高血压疾病、GDM、妊娠期贫血、流产、早产、胎儿窘迫、胎盘早剥、胎膜早破、胎儿畸形、低体重儿发生率比较差异无统计学意义(P>0.05),未治疗组不良妊娠结局发生率虽高于治疗组、对照组,但差异无统计学意义(P>0.05)。见表 1。

表 1 TPO 阴性亚临床甲减治疗组、未治疗组、对照组孕妇不良妊娠结局发生率比较[例(%)]

Table 1 Comparison of adverse pregnancy outcomes in women with TPO-negative subclinical hypothyroidism, treated, untreated and control groups[n(%)]

	Group A				Group B			
	Treated group	Untreated group	Control group	P [▲]	Treated group	Untreated group	Control group	P [▲]
Number of samples	70	61	306		124	234	306	
Hypertension during pregnancy	2(2.9)	9(14.8)*	10(3.3)	0.002	6(4.8)	15(6.4)	10(3.3)	0.229
GDM	4(5.7)	12(19.7)*	25(8.2)	0.01	7(5.6)	16(6.8)	25(8.2)	0.631
Anemia in pregnancy	1(1.4)	8(13.1)*	7(2.3)	0.001	4(3.2)	10(4.3)	7(2.3)	0.393
Placental abruption	1(1.4)	1(1.6)	3(1.0)	0.425	1(0.8)	5(2.1)	3(1.0)	0.551
Premature Rupture	5(7.1)	9(4.8)	21(6.9)	0.114	12(9.7)	26(11.1)	21(6.9)	0.22
Miscarriage	1(1.4)	8(13.1)*	12(3.9)	0.003	6(4.8)	17(7.3)	12(3.9)	0.22
Premature delivery	1(1.4)	8(13.1)*	10(3.3)	0.004	2(1.6)	8(3.4)	10(3.3)	0.662
Fetal distress	1(1.4)	8(13.1)*	10(3.3)	0.004	8(6.5)	16(6.8)	10(3.3)	0.133
Fetal anomaly	0(0)	1(1.6)	4(1.3)	0.807	1(0.8)	4(1.7)	4(1.3)	0.826
Low birthweight infant	1(1.4)	3(4.9)	4(1.3)	0.127	3(2.4)	9(3.8)	4(1.3)	0.16

Note: [▲]Comparison of untreated group, treated group and control group; * There was a statistical difference between the untreated group and the treated group and the control group. GDM: Gestational diabetes.

3 讨论

妊娠期甲状腺疾病的发生受地理环境、生活方式、遗传等多因素的影响,甲状腺疾病的诊断一直是近年来国内外学者研究的热点问题。血清 TSH 为甲状腺功能减退及亚临床甲状腺功能减退诊断的一线指标,因此确定妊娠期 TSH 参考范围更是尤为重要。近些年,在没有建立妊娠期甲状腺特异参考范围的医院和地区,普遍采用 2011 年美国 ATA 指南推荐的标准(妊娠早期 TSH>2.5 mIU/L,中晚期 TSH>3.0 mIU/L),欧洲甲状腺学会指南也推荐使用 ATA 诊断标准,但 ATA 指南推荐的标准是否真的适合中国妊娠妇女?是否真的适用于世界各个国家和地区?单忠艳教授等的研究表明妊娠早期 TSH>2.5 mIU/L 诊断的亚临床甲减的孕妇随访至妊娠晚期,仅有 20.3%的孕妇仍然符合亚临床甲减的诊断标准^[9],而国内其他临床研究也表明我国妊娠早期 TSH 的参考值上限大于 2.5 mIU/L^[3,4]。美国、欧洲及亚洲的国外数据研究也表明妊娠早期 TSH 参考值上限>2.5 mIU/L,接近 4.0 mIU/L^[5-7]。2017 年 ATA 指南推荐对无法建立指南参考值范围的地区,建议将 TSH 参考值上限定为 4 mIU/L。妊娠合并亚临床甲减治疗方面,当 TSH 介于参考值范围上限和 10 mIU/L,TPOAb 阴性,是否需要 LT4 治疗临床证据不足,尚存在争议。青岛地区是一个碘营养充足的沿海城市,孕妇碘营养充足,碘缺乏孕妇主要为轻度碘缺乏,当孕妇碘营养缺乏合并 TPOAb 阳性较 TPOAb 阴性更容易发生亚临床甲减^[8]。本研究依据两个不同时期 ATA 指南的不同建议,以 2.5 mIU/L、4.0 mIU/L 为界限分组,回顾性分析青岛地区 TPOAb 阴性的亚临床甲减孕妇治疗与否对妊娠结局的影响,比较妊娠不

良结局的发生率,指导妊娠期亚临床甲减的治疗。

本研究结果显示根据 S1 诊断标准,TPOAb 阴性的妊娠期亚临床甲减的患病率为 13.57%,治疗率为 39.67%,明显高于 S2 诊断标准的患病率(3.6%)和治疗率(51.34%)。由此可见,不同诊断标准诊断妊娠期亚临床甲减患病率差异较大,研究合理的诊断标准尤其的重要。妊娠合并亚临床甲减的治疗率较低,分析原因可能与患者居住地、受教育程度及产次有关,刘彩霞和吴爱红的临床研究显示^[9]中专以下文化程度及居住在乡镇的孕妇对妊娠期甲状腺疾病的认识程度及接受治疗的比率低。因此,妊娠合并甲状腺疾病的教育尤其重要,提高治疗率对减少妊娠不良结局至关重要。

甲状腺激素由甲状腺组织分泌,可通过胎盘进入到胎儿体内,促进胎儿大脑发育。随着孕周的增加,胎盘滋养细胞分泌的人绒毛膜促性腺激素、雌激素诱发的甲状腺结合球蛋白的升高以及基础代谢率变化,孕妇的 FT4、FT3 逐渐降低,TSH 水平反馈性增加,可引起亚临床甲状腺功能减退^[10]。多个临床研究结果显示亚临床甲减与不良妊娠结局密切相关^[11,12]。本研究结果显示 TSH>4.0 mIU/L 时,妊娠合并亚临床甲减孕妇未治疗组的妊娠期高血压疾病、GDM、妊娠期贫血、流产、早产及胎儿窘迫的发生率显著高于治疗组及正常对照组。由此可见,对于 TSH>4.0 mIU/L 的妊娠合并亚临床甲减孕妇,左甲状腺素钠片治疗是必要的,可明显改善不良妊娠结局。亚临床甲状腺功能减退孕妇体内甲状腺激素水平较低,可引机体内分泌紊乱,增加妊娠高血压的发病率^[13],而且亚临床甲状腺功能减退会给糖代谢、脂肪代谢造成影响,促使孕妇发生妊娠期糖尿病^[14,15]。妊娠期贫血是甲减患者常见的并发症,其发生可能是由于甲状腺

激素的缺乏抑制孕妇造血功能,胃酸缺乏又能使维生素 B12 和铁剂吸收障碍,多发生缺铁性贫血^[16]。国外许多临床研究表明妊娠合并亚临床甲减妇女流产率增加^[17]。国内研究发现妊娠合并亚临床甲减与流产发生率增加关系密切^[18,19]。TSH 水平每升高 1 倍,流产的风险可增加 60%^[20]。王少为等^[21]荟萃分析发现妊娠合并亚临床甲减孕妇发生早产的风险明显高于甲功正常组孕妇。Liu H 等^[22]开展针对 3315 名孕妇的前瞻性研究指出与甲功正常女性相比,亚临床甲减患者有较高的流产发生率(7.1% VS. 2.2%),TSH 越高,流产发生风险越高,且若合并有 TPOAb 阳性,这个风险将明显增加。伊朗学者对 366 名 TPOAb 阴性合并亚临床甲减孕妇进行的双盲前瞻性研究显示^[12] TSH>4 mIU/L 时,应用左甲状腺素钠片的治疗组早产的发生风险明显低于未治疗组,而 2.5 mIU/L<TSH<4 mIU/L 时,未治疗组与治疗组、正常对照组无统计学差异,与本研究结果相似。另有研究显示妊娠合并亚临床甲减妇女新生儿窘迫发生率较甲功正常孕妇明显增加^[23]。

此外,本研究结果显示当 2.5 mIU/L<TSH<4.0 mIU/L 时,未治疗组妇女不良妊娠结局的发生率虽高于治疗组及对照组,但差异无统计学意义,提示 TSH<4.0 mIU/L 时 TPO 阴性的妊娠期亚临床甲减药物治疗与否对妊娠不良结局无显著影响。国外学者的研究认为 TSH 上线值定为 2.5 mIU/L 可能使亚临床甲减的过度诊断,并无证据显示改善不良妊娠结局^[3,24,25]。根据本研究结果,将 TSH 参考上线定为 2.5 mIU/L,不适合中国青岛地区妊娠妇女,需提高 TSH 参考值,或采取妊娠特异性参考值,否则可能造成诊断过度。

综上所述,对于 TPO 阴性的妊娠期亚临床甲状腺功能减退妇女,TSH>4.0 mIU/L 孕妇需左甲状腺素钠片积极治疗,可减少妊娠并发症的发生,改善围产期结局。根据本研究结果,2.5 mIU/L<TSH<4.0 mIU/L 时,左甲状腺素钠片治疗 TPO 阴性的妊娠期亚临床甲减孕妇的围产期并发症无明显改善。本研究属于回顾性研究,由于 TPO 阴性的妊娠期亚临床甲减的发生率较低,本研究样本数偏少,不能排除结果出现偏差,故仍需进一步的大样本研究或前瞻性研究。

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