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妊娠期甲状腺疾病诊断及治疗的研究进展

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摘要:妊娠期妇女体内激素水平会发生变化,使妊娠妇女甲状腺激素水平的测定和判断存在一定的困难,应选择适用于妊娠妇女的甲状腺激素水平特异值,进而正确评估甲状腺功能状态及对母体和胎儿的影响。孕前及妊娠期测定促甲状腺素和游离甲状腺激素有很大的必要性,因为甲状腺疾病以及单纯性甲状腺抗体阳性会导致多种妊娠不良结局,尤其是甲状腺功能减退对胎儿智力发育和认知功能具有非常大的影响。孕期甲状腺激素的监测对评估甲状腺功能状态及疾病预后具有非常大的作用,可以提示临床医师是否给予药物干预及如何调整药量。对于孕期甲状腺激素补充治疗后应达到的目标值以及甲状腺抗体阴性的亚临床甲状腺功能降低的妊娠患者是否给予干预,目前仍有异议。

关键词:甲状腺疾病;妊娠;甲状腺功能;甲状腺激素

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Research Progress of the Diagnosis and Treatment of Gestational Thyroid Disease

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ABSTRACT: During pregnancy, the levels of hormones change, which makes it difficult to determinate the thyroid hormone levela lot. We should determine the specific thyroid hormone level in pregnant women, thus we can correctly evaluate the status of thyroid function and the effect on the mother and the fetus. It is necessary to determinate thyrotropin and free thyroxine in prepregnancy and pregnancy, because the thyroid disease and thyroid antibodies alone can cause a variety of adverse pregnancy outcomes, especially hypothyroidism on fetal development and cognitive function is not very big effect. Monitoring of maternal thyroid hormone has great influence on the prognosis of disease status and thyroid function, which can prompt the clinician to give drug intervention and adjust the dosage. There remain objections as to which target should maternal thyroid hormone replacement therapy reach and whether intervene thyroid antibody negative patients with subclinical hypothyroidism.

Key words: Thyroid disease; Gestation; Thyroid function; Thyroid hormone

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前言

20 世纪 80 年代末荷兰学者 Vulsma 等[1]首次发现甲状腺合成障碍及无甲状腺新生儿的脐带血中存在甲状腺激素,这一发现推翻了母体甲状腺激素不能通过胎盘的传统观点。随后,西班牙学者 Escobar GM 通过实验研究系统地证实了母体甲状腺激素对胎儿脑发育具有重要作用,美国学者 Haddow 的研究也提示母体甲状腺激素缺乏对子代智力发育及认知能力有重要影响。这些研究结果使妊娠期甲状腺疾病在近十几年成为多个学科关注研究的焦点,本文将就妊娠期甲状腺疾病的诊断和治疗的研究进展进行综述。

1 妊娠期甲状腺疾病对母体及子代的影响

妊娠期妇女体内激素水平会发生较大改变,甲状腺激素也不例外,进而影响妊娠母体及胎儿生长发育[2]。研究发现,约 15%的妊娠妇女在孕期罹患各种甲状腺疾病,包括甲状腺机能亢进、亚临床甲状腺机能亢进,甲状腺机能减退、亚临床甲状腺机能减退、单纯性低甲状腺素血症以及单纯甲状腺抗体阳性(甲状腺功能检测正常)等[3]。多项临床前瞻性观察和动物实验研究均表明妊娠妇女体内甲状腺激素水平异常及单纯甲状腺抗体阳性都会对母体及胎儿带来不良后果[4],尤其是甲状腺机能减退及亚临床甲状腺机能减退,将会对胎儿的智力发育、认知能力带来非常严重的不良影响[5,6]。一项较新的研究显示孕期母体甲状腺激素缺乏会导致子代中枢神经系统炎症性疾病,因而正确评估孕妇甲状腺激素水平并给与合理干预可明显降低子代患中枢神经系统炎症性疾病的可能[7]。单纯性低甲状腺素血症对胎儿的发育的影响目前尚无明确定论,但据 Pop 等[8]的研究显示,FT4 水平第 10 个百分点以下的孕妇后代的智力评分减低。单纯性甲状腺抗体阳性对孕妇也有较大的影响,Glinoer 等进行了一项前瞻性研究,研究中的 87 名妇女甲状腺抗体阳性而甲状腺功能正常,其中约 20%的妇女在妊娠期间检测

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TSH＞4 mIU/L。Negro 等[9]的研究证实,随着妊娠进展 TSH 水平逐渐升高,妊娠第 12 周时,孕妇 TSH 水平平均升高 1.7-3.5 mIU/L,约 81%的患者在分娩时检测 TSH 发现异常。妊娠期间母体及胎儿对甲状腺激素的需求增加,甲状腺抗体阳性所提示的自身免疫对甲状腺的损伤可以导致甲状腺功能减退或亚临床甲状腺功能减退。妊娠期间甲状腺功能的改变与妊娠结局紧密相关,甲状腺毒症可导致流产、早产、死产以及胎儿宫内生长受限,低体重儿、孕妇充血性心衰等一系列不良后果[10]。

2 妊娠期间甲状腺疾病的诊断标准

由于妊娠期间雌激素水平升高,TBG 水平随之升高,TT4 势必升高，因而在妊娠时 TT4 不能作为判断甲状腺功能的指标。妊娠初期 hCG 分泌增加,由于 hCG 的 α 亚单位与 TSH 具有相似的结构,可刺激甲状腺激素分泌。甲状腺激素分泌增多后通过负反馈作用,抑制 TSH 分泌,TSH 水平降低,其下限较之非孕妇女平均降低 0.4 mIU/L[3,11,12]。妊娠期临床甲状腺减低的诊断标准是:TSH＞妊娠期参考值上限，并且 FT4＜妊娠期参考值下限[13]。

2011 年版 ATA 指南提出,T1 期妊娠妇女若 TSH＞10 mIU/L,无论 FT4 是否降低,都可诊断为临床甲减,但对于这一标准,学术界尚有争议。备孕的甲状腺功能减低患者在怀孕前半期(1-20 周)应每四周检测一次甲状腺功能(包括 TSH 在内),可以检测到 92%的异常值,若检测频度降低到每六周一次,则可以检测到 73%的异常值[14],在怀孕的后半期(26-32 周),应每周检测一次甲状腺功能。低甲状腺素血症的诊断标准:孕妇血清 TSH 水平正常，而 FT4 水平低于参考值范围的第 5 或者第 10 个百分位点[15,16]。妊娠甲亢综合症应该与 Graves 病甲亢鉴别,发生于早期妊娠,多与 hCG 水平增高有关,可有心悸、焦虑多汗等高代谢症状,实验室检测为 FT3、FT4 水平升高,TSH 水平降低或正常,甲状腺自身抗体阴性[10]。

3 妊娠期甲状腺疾病的治疗

妊娠期甲状腺疾病对母体及胎儿均有不良影响,因此应该对其进行适当的干预,以确保母体及胎儿的安全和健康。妊娠期甲状腺机能减低可导致非常严重的后果,必须给予甲状腺激素补充治疗，其治疗目标是 TSH T1 期 0.1-0.2 mIU/L,T2 期 0.2-0.3 mIU/L,T3 期 0.3-3.0 mIU/L。药物首选 L-T4 治疗,治疗剂量 2.0-2.4 μg/kg/d，治疗过程中应观察临床表现，并逐渐加量,以尽早达标。亚临床甲减患者并甲状腺自身抗体阳性应给予甲状腺激素替代治疗[17],据一项 RCT 研究结果显示,L-T4 干预亚临床甲减合并自身抗体阳性患者，可改善妊娠不良结局;另外一项 RCT 研究表明，对于甲状腺功能正常并甲状腺自身抗体阳性的患者,T1 期给予 L-T4 补充,可减少妊娠不良结局。亚临床甲减的治疗药物,控制目标以及甲状腺功能和自身抗体的监测可参考临床甲减。激素初始补充剂量应根据 TSH 水平确定,TSH＞妊娠特异参考值上限,L-T4 起始剂量 50 μg/d,TSH＞8.0 mIU/L,L-T4 起始剂量 75 μg/d,TSH＞10.0 mIU/L,L-T4 起始剂量 100 μg/d。循证医学证据表明,妊娠期妇女亚临床甲减有增加不良妊娠和子代认知功能发育受损的风险[12]。尽管目前对于亚临床甲减治疗的积极意义尚无足够的证据支持,但临床医师对给予积极甲状腺激素补充的正面作用和不治疗或者甲状腺减量补充的负面作用已经达成了共识[18]。而对于甲状腺自身抗体阳性的亚临床甲减妊娠妇女,相关研究提示应补充甲状腺激素。Graves 病患者如选择药物治疗,应在怀孕前换用 PTU,MMI 有导致胎儿畸形的风险,妊娠 T1 期优选 PTU,后期可改用 MMI,以避免肝脏毒性的发生[11,19]。对于妊娠甲亢综合症应以对症治疗为主,如果有剧吐症状应控制呕吐,给予补液治疗,维持水电解质平衡,由于妊娠后期甲状腺激素水平自行可恢复正常,故不主张给予药物抗甲状腺治疗[3]。

4 展望及疑问

目前,对于妊娠期甲状腺疾病的诊断和治疗的研究已经取得了很大的进展,例如正确评估妊娠期甲状腺功能,亚临床甲减并甲状腺自身抗体阳性对子代智力认知能力的影响,妊娠期甲状腺功能检测的时间,妊娠期甲亢的药物治疗等[20]。但仍有一些问题存在争论,如由于 TSH 检测方法和试剂的不同,确定妊娠期特异参考值范围尚有难度,关于亚临床甲减(甲状腺自身抗体阴性)对妊娠结局的影响也存在着不同的看法,不同的研究得出了相反的结果,认为亚临床甲减对妊娠没有不良影响的研究的数据结果多来自有一些研究亚组的数据[6,21],这一点使其意义受到质疑,尚需要较大研究的完整数据来支撑这一结论。截至目前的大部分研究结果支持妊娠期亚临床甲减会增加妊娠不良结局的结论。

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