doi: 10.13241/j.cnki.pmb.2019.07.027

不同剂量左旋甲状腺素对妊娠合并甲减患者胎儿发育的影响 *

李金鸽 贺译平 徐叶红 冯卫红 王艳霞

（西北妇女儿童医院产科 陕西 西安 710061）

摘要 目的:探讨不同剂量左旋甲状腺素对妊娠合并甲减患者胎儿发育的影响。**方法:**选择 2012 年 5 月至 2016 年 6 月在我院诊治的妊娠合并甲减孕妇 72 例作为研究对象,根据随机数字表法抽签分为观察组与对照组各 36 例,两组都给予左旋甲状腺素治疗,对照组应用剂量为低剂量,观察组应用剂量为高剂量,两组均治疗观察 3 个月,对比两组的临床疗效、治疗前后游离三碘甲状腺原氨酸(FT3)、游离甲状腺激素(FT4)、血清促甲状腺激素(TSH)水平的变化及并发症的发生情况。**结果:**治疗后,观察组的总有效率[97.2%(35/36)]显著高于对照组[83.3%(30/36)](P<0.05),两组 TSH 值显著低于治疗前(P<0.05),FT3 与 FT4 值均显著高于治疗前(P<0.05),且观察组的 FT3、FT4 值均明显高于对照组(P<0.05),而血清 TSH 值显著低于对照组(P<0.05)。治疗期间,观察组的早产、产后出血、宫内窘迫、妊娠高血压等并发症发生率为 11.1%,对照组为 30.6%,观察组显著低于对照组(P<0.05)。所有孕妇都顺利分娩,新生儿都存活,观察组新生儿的智力发育与精神运动发育评分都显著高于对照组(P<0.05)。**结论:**高剂量左旋甲状腺素治疗妊娠合并甲减患者的临床效果明显高于低剂量左旋甲状腺素,其可有效促进甲状腺激素分泌平衡,减少妊娠并发症的发生,促进新生儿的发育。

关键词:左旋甲状腺素;甲减;剂量;妊娠;胎儿

中图分类号:R714.256;R714.51 **文献标识码:**A **文章编号:**1673-6273(2019)07-1321-04

Effects of Different Doses of Levothyroxine on the Fetal Development in Patients with Pregnancy Combined with Hypothyroidism*

LI Jin-ge, HE Yi-ping, XU Ye-hong, FENG Wei-hong, WANG Yan-xia

(Obstetrics Department, Northwest Women and Children Hospital, Xi'an, Shaanxi, 710061, China)

ABSTRACT Objective: To investigate the effects of different doses of levothyroxine on the fetal development in patients with pregnancy combined with hypothyroidism. **Methods:** From May 2012 to June 2016, 72 cases of gravida combined with hypothyroidism were treated as research subjects. According to the random number table method, they were divided into the observation group and control group with 36 cases in each group. Both groups were treated with levothyroxine. The control group was given a low dose, while the observation group was given a high dose. The treatment lasted for 3 months. The clinical efficacy, changes of free triiodothyronine (FT3), free thyroid hormone (FT4), serum thyroid stimulating hormone (TSH) levels before and after treatment and incidence of complications were compared between the two groups. **Results:** After treatment, the total effective rate of observation group [97.2% (35/36)] was significantly higher than that in the control group [83.3% (30/36)] (P<0.05). The serum TSH level of both groups were significantly lower than those before treatment (P<0.05), the FT3 and FT4 levels were significantly higher than those before treatment (P<0.05), and the FT3 and FT4 levels in observation group were significantly higher than those in the control group(P<0.05). The serum TSH level was significantly lower than that of the control group (P<0.05). During the treatment period, the incidence of complications such as preterm delivery, postpartum hemorrhage, intrauterine distress and pregnancy-induced hypertension was 11.1% in the observation group and 30.6% in the control group. It was significantly lower in the observation group than that of the control group (P<0.05). All pregnant women delivered well and newborns were alive. The intelligence development and mental development scores of newborns in the observation group were significantly higher than those in the control group (P<0.05). **Conclusion:** The clinical effect of high-dose levothyroxine was significantly higher than that of low-dose levothyroxine in the treatment of patients with pregnancies with hypothyroidism, which can effectively promote the balance of thyroid hormone secretion, reduce the occurrence of pregnancy complications, and promote the development of newborns.

Key words: Levothyroxine; Hypothyroidism; Dose; Pregnancy; Fetus

Chinese Library Classification(CLC): R714.51; R714.256 Document code: A

Article ID: 1673-6273(2019)07-1321-04

* 基金项目:陕西省社会发展科技攻关项目(2015SF135)

作者简介:李金鸽(1980-),女,硕士,主治医师,研究方向:产科,E-mail: Ljg_198001@163.com

(收稿日期:2018-07-12 接受日期:2018-08-08)

前言

甲状腺是控制人体代谢的重要器官,甲状腺素分泌不足会得甲减,反之则是甲亢[1]。流行病学调查显示当前甲减在我国的患病率显著增加,其中妊娠合并甲减的孕妇越来越多,文献报道其发生率为0.5‰-0.625‰,正日益成为威胁我国孕妇健康的重要疾病之一[2,3]。妊娠合并甲减患者常由于不排卵、月经迟发、不规则、量多等原因而导致妊娠并发症,比如并发胎盘早剥、子痫前期、糖尿病、贫血等[4,5]。同时,甲状腺激素对胎儿大脑的发育至关重要,大脑不可逆损伤可能与甲状腺激素所致孕妇叶酸水平下降有关,甲减可导致胎儿大脑神经不可逆损伤[6-8]。

左旋甲状腺素作为临床上常用的妊娠合并甲减药物,其可有效控制患者的血清甲状腺激素水平[9,10],但是左旋甲状腺素在临床上的使用剂量范围较宽,且孕妇的需求量比正常人大[11]。本研究主要探讨了不同剂量左旋甲状腺素对妊娠合并甲减患者胎儿发育的影响,旨在为临床用药提供参考,具体报道如下。

1 资料与方法

1.1 一般资料

选择2012年5月至2016年6月在我院诊治的妊娠合并甲减孕妇72例作为研究对象,纳入标准:符合妊娠合并甲减的诊断标准者;妊娠4-10周者;单胎妊娠;孕妇知情同意本研究;无遗传疾病个人史、家族史和生育史;无甲状腺疾病病史;研究得到医院伦理委员会的批准。排除标准:孕期额外补充碘剂者;有甲状腺疾病史者;精神病患者;伴有严重心、肝、肾等器质性病变者。随机将其分为观察组与对照组,每组各36例,两组基础资料比较差异均无统计学意义(P>0.05),具有可比性。见表1。

表1 两组一般临床资料的对比($\bar{x}\pm s$)

Table 1 Comparison of the general and clinical data between two groups($\bar{x}\pm s$)

Groups	n	Age(years)	Gestational weeks(weeks)	Parity(times)	Pregnancy(times)
Observation group	36	27.82± 3.14	6.33± 2.19	1.89± 1.33	3.10± 0.78
Control group	36	27.10± 4.49	6.82± 1.48	1.92± 0.92	3.02± 0.67

1.2 治疗方法

对照组给予左旋甲状腺素(常州康普药业有限公司,国药准字H20030502)25 μg,口服,1次/d。给予观察组左旋甲状腺素75 μg,口服,1次/d。两组都治疗观察3个月,在治疗期间限制脂肪摄入量,控制体重,加强营养,定期检查,注意休息。

1.3 观察指标

1.3.1 临床疗效 患者的临床症状和体征均消失,甲状腺激素水平恢复正常即为显效;患者的临床症状、体征、甲状腺激素水平有明显改善即为有效;无达到上述标准或加重即为无效。

1.3.2 甲状腺激素变化对比 治疗前后采用全自动生化仪检测患者血清中游离甲状腺激素(FT4)、游离三碘甲状腺原氨酸(FT3)、血清促甲状腺激素(TSH)等水平。

1.3.3 妊娠并发症观察 记录两组在妊娠期间出现的早产、产后出血、胎儿宫内窘迫、妊娠高血压等并发症情况。

1.3.4 新生儿发育评定 所有孕妇的新生儿在第14个月左右使用贝利婴幼儿发育量表进行神经智力发育情况的测评,包括智力发育评分与精神运动发育评分两方面。

1.4 统计方法

选择SPSS20.00软件进行数据分析,计量资料以($\bar{x}\pm s$)表示,组间比较经t检验;计数资料用(%)表示,组间比较经x^2检验等,以P<0.05为差异存在统计学意义。

2 结果

2.1 两组临床疗效的对比

治疗后,观察组的总有效率[97.2%(35/36)]高于对照组[83.3%(30/36)](P<0.05),见表2。

表2 两组临床疗效对比

Table 2 Comparison of the clinical efficacy between two groups

Groups	n	Excellent	Effectivity	Invalid	Total effective rate(%)
Observation group	36	30	5	1	97.2*
Control group	36	20	10	6	83.3

Note: compared with the Control group, *P<0.05.

2.2 两组治疗前后甲状腺激素水平的变化对比

治疗后,两组TSH值显著低于治疗前(P<0.05),FT3与FT4值均显著高于治疗前(P<0.05),且观察组的FT3、FT4值均明显高于对照组,而血清TSH值显著低于对照组,差异具有统计学意义(P<0.05),见表3。

2.3 两组妊娠并发症的发生情况对比

治疗期间,观察组的早产、产后出血、宫内窘迫、妊娠高血压等并发症发生率为11.1%,对照组为30.6%,观察组低于对照组(P<0.05),见表4。

2.4 两组新生儿发育情况对比

所有孕妇都顺利分娩,新生儿都成活,观察组的智力发育与精神运动发育评分都显著高于对照组(P<0.05),见表5。

3 讨论

甲状腺可通过分泌适量的甲状腺激素调节体内蛋白质、糖和脂肪的合成与代谢,影响人体新陈代谢和生长发育。甲减源于甲状腺激素合成及分泌减少,可导致患者出现精神不健全、抑郁、记忆力减退等临床表现,且影响患者的认知功能[12,13]。妊

表 3 两组治疗前后甲状腺激素的变化对比(n=36, $\bar{x}\pm s$)

Table 3 Comparison of the changes of thyroid hormone before and after treatment between the two groups (n=36, $\bar{x}\pm s$)

Groups	n	FT3(pmol/L)	FT4(pmol/L)	TSH(mU/L)
Observation group	Before treatment	2.67± 0.23	9.34± 2.89	8.81± 2.41
	After treatment	4.62± 0.44#*	12.78± 3.14#*	6.17± 1.99#*
Control group	Before treatment	2.68± 0.44	9.34± 2.98	8.79± 2.11
	After treatment	3.34± 0.52#	10.84± 3.11#	7.59± 1.99#

Note: compared with the Control group, *P<0.05; compared with the Before treatment, #P<0.05.

表 4 两组妊娠并发症的发生情况对比

Table 4 Comparison of the incidence of pregnancy complications between the two groups

Groups	n	Premature delivery	Postpartum hemorrhage	Intrauterine distress	Pregnancy hypertension	Total incidence rate (%)
Observation group	36	1	0	1	2	4(11.1)*
Control group	36	3	2	3	3	11(30.6)

Note: compared with the Control group, *P<0.05.

表 5 两组新生儿发育情况对比(分,$\bar{x}\pm s$)

Table 5 Comparison of the neonatal development between two groups (points, $\bar{x}\pm s$)

Groups	n	Mental development score	Mental development score
Observation group	36	123.94± 23.19*	120.98± 19.84*
Control group	36	112.29± 21.88	110.84± 20.64

Note: compared with the Control group, *P<0.05.

娠合并甲减的发生率既往很低,由于各种因素的影响,其在我国的发病率呈逐年升高的趋势。甲减可导致性腺及性器官发育障碍,也增加了孕期保健及治疗的难度,严重情况下可导致许多孕妇放弃妊娠[14]。左旋甲状腺素片作为一种人工合成的内分泌抑制剂,具有促进人体代谢、维持人体正常生长发育的疗效[15]。目前,国际上公认采用左旋甲状腺素治疗甲减,但对于剂量的选择还未明确规定[16]。本研究显示高剂量左旋甲状腺素治疗的甲减孕妇总有效率高于低剂量左旋甲状腺素治疗者,且患者FT3、FT4 值均明显高于左旋甲状腺素治疗者,而血清 TSH 值显著低于左旋甲状腺素治疗者,表明高剂量左旋甲状腺能提高妊娠合并甲减的治疗效果,促进甲状腺激素分泌平衡。

妊娠合并甲减患者易并发早产、流产、胎儿畸形,也易并发子痫前期、胎盘早剥、糖尿病等并发症[17-19]。妊娠合并甲减经左旋甲状腺素治疗的效果确切[20-22],但孕妇妊娠期间发生甲减后,应积极进行宫内治疗,以保证妊娠母体对胎儿甲状激素的供应[23-25]。本研究显示高剂量左旋甲状腺素治疗期间早产、产后出血、宫内窘迫、妊娠高血压等并发症发生率低于低剂量左旋甲状腺素治疗者,表明高剂量左旋甲状腺素的应用能减少妊娠并发症的发生。

妊娠合并甲减患者体内甲状腺激素水平出现异常,可直接影响胎儿的大脑智力和精神功能发育,还会损伤其空间记忆功能[26-28]。左旋甲状腺素可使妊娠合并甲减患者将外源性甲状腺素原转换为三碘甲状腺原氨酸,通过调节体内甲状腺内碘化物的含量,从而使甲状腺激素达到动态平衡,改善患者营养状况和妊娠结局[29-31]。本研究显示所有孕妇都顺利分娩,新生儿都成活,高剂量左旋甲状腺素治疗的产妇新生儿智力发育与精神运动发育评分都显著高于低剂量左旋甲状腺素治疗者,说明提高左旋甲状腺素剂量对胎儿的大脑发育起到积极作用,对改善甲减孕妇母儿结局具有一定的临床价值。但由于本次研究样本数还不够多,具体的作用机制还不深入,还有待更大样品数、多中心、长期随访来探讨。

综上所述,高剂量左旋甲状腺素可有效提高妊娠合并甲减患者的治疗效果,促进甲状腺激素分泌平衡,减少妊娠并发症的发生,促进新生儿的发育。

参考文献(References)

[1] Velasco I, Taylor P. Identifying and treating subclinical thyroid dysfunction in pregnancy: emerging controversies [J]. Eur J Endocrinol, 2018, 178(1): D1-D12

[2] Tingi E, Syed AA, Kyriacou A, et al. Benign thyroid disease in pregnancy: A state of the art review [J]. J Clin Transl Endocrino, 2016, 23 (6): 37-49

[3] Tuhan H, Abaci A, Cicek G, et al. Levothyroxine replacement in primary congenital hypothyroidism: the higher the initial dose the higher the rate of overtreatment [J]. Journal of Pediatric Endocrinology & Metabolism, 2016, 29(2): 133-138

[4] Chaudhary LN, Khatiwada S, Gelal B, et al. Iodine and Thyroid Function Status, and Anti-thyroid Peroxidase Antibody among Pregnant Women in Eastern Nepal [J]. J Nepal Health Res Counc, 2017, 15(2): 114-119

[5] Neelaveni K, Kumar KVSH, Sahay R, et al. Postpartum Follow-up in Women Diagnosed with Subclinical Hypothyroidism during Pregnancy[J]. Indian J Endocrinol Metab, 2017, 21(5): 699-702

[6] Kroopnick J M, Kim C S. Overview of Hypothyroidism in Pregnancy [J]. Seminars in Reproductive Medicine, 2016, 34(06): 323-330

[7] Akram FH, Johansson B, Möllerström G, et al. Incidence of Subclinical Hypothyroidism and Hypothyroidism in Early Pregnancy [J]. J Womens Health (Larchmt), 2017, 26(11): 1231-1235

[8] Alberiche M, Sánchez-Hernández R M, López M X, et al. Onset of Graves' disease during pregnancy in a woman with established hypothyroidism[J]. Gynecological Endocrinology, 2017, 33(1): 16-18

[9] Plowden TC, Schisterman EF, Sjaarda LA, et al. Thyroid-stimulating hormone, anti-thyroid antibodies, and pregnancy outcomes [J].Am J Obstet Gynecol, 2017, 217(6): 697.e1-697.e7

[10] Sullivan SD, Downs E, Popoveniuc G, et al. Randomized Trial Comparing Two Algorithms for Levothyroxine Dose Adjustment in Pregnant Women With Primary Hypothyroidism [J]. J Clin Endocrinol Metab, 2017, 102(9): 3499-3507

[11] Maheshwari A, Bhide P, Pundir J, et al. Routine serum thyroid-stimulating hormone testing-optimizing pre-conception health or generating toxic knowledge[J]. Hum Reprod, 2017, 32(9): 1779-1785

[12] Okuroglu N, Ozdemir A, Sertbas Y, et al. The relationship between thyroid antibody titer and levothyroxine dose in patients with overt primary hypothyroidism [J]. Annals of Saudi Medicine, 2017, 37(3): 189

[13] Casey BM, Thom EA. Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy[J]. N Engl J Med, 2017, 377(7): 701

[14] Hegedüs L, Brix TH. Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy[J]. N Engl J Med, 2017, 377(7): 700

[15] Nazarpour S, Ramezani T F, Simbar M, et al. Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease [J]. European Journal of Endocrinology, 2017, 176(2): 253

[16] Korevaar TIM, Medici M, Visser TJ, et al. Thyroid disease in pregnancy: new insights in diagnosis and clinical management[J]. Nat Rev Endocrinol, 2017, 13(10): 610-622

[17] Moog NK, Heim CM, Entringer S, et al. Childhood maltreatment is associated with increased risk of subclinical hypothyroidism in pregnancy[J]. Psychoneuroendocrinology, 2017, 10(84): 190-196

[18] Negro R, Schwartz A, Stagnaro-Green A. Impact of Levothyroxine in Miscarriage and Preterm Delivery Rates in First Trimester Thyroid Antibody-Positive Women with TSH Less Than 2.5 mIU/L[J]. Journal of Clinical Endocrinology & Metabolism, 2016, 101(10): jc20161803

[19] Baskoy K, Ay S A, Altundag A, et al. Is There Any Effect on Smell and Taste Functions with Levothyroxine Treatment in Subclinical Hypothyroidism[J]. Plos One, 2016, 11(2): e0149979

[20] Pop VJ, Broeren MA, Wiersinga WM, et al. Thyroid disease symptoms during early pregnancy do not identify women with thyroid hypofunction that should be treated[J]. Clin Endocrinol (Oxf), 2017, 87 (6): 838-843

[21] Fierabracci P, Martinelli S, Tamberi A, et al. Weight Loss and Variation of Levothyroxine Requirements in Hypothyroid Obese Patients After Bariatric Surgery[J]. Thyroid, 2016, 26(4): 499-503

[22] Stagnaro-Green A. Second trimester levothyroxine treatment for subclinical hypothyroidism or hypothyroxinaemia of pregnancy does not improve cognitive outcomes of children [J]. Evid Based Med, 2017, 22(4): 149

[23] Hennessey J V. The emergence of levothyroxine as a treatment for hypothyroidism[J]. Endocrine, 2017, 55(1): 6-18

[24] Maraka S, Ospina N M, O'Keeffe D T, et al. Subclinical Hypothyroidism in Pregnancy: A Systematic Review and Meta-Analysis [J]. Thyroid, 2016, 26(4): 580-590

[25] Hong K S, Jung-Woo S, Hyun R O, et al. Cardiac Effects of Thyrotropin Oversuppression with Levothyroxine in Young Women with Differentiated Thyroid Cancer[J]. International Journal of Endocrinology, 2016, 2016(3): 1-6

[26] Hillert W K, Per C, Torquil W, et al. Disease-Specific as Well as Generic Quality of Life Is Widely Impacted in Autoimmune Hypothyroidism and Improves during the First Six Months of Levothyroxine Therapy:[J]. Plos One, 2016, 11(6): e0156925

[27] Li X, Wang Y, Guan Q, et al. The lipid-lowering effect of levothyroxine in patients with subclinical hypothyroidism: A systematic review and meta-analysis of randomized controlled trials [J]. Clinical Endocrinology, 2017, 87(1): 1

[28] Kim H I, Kim T H, Kim H, et al. Effect of Rifampin on Thyroid Function Test in Patients on Levothyroxine Medication [J]. Plos One, 2017, 12(1): e0169775

[29] Rosario P W, Calsolari M R. Levothyroxine therapy in the subclinical hypothyroidism: a lifelong therapy? A long-term study [J]. Clinical Endocrinology, 2016, 85(5): 819

[30] Shah R. In older adults with subclinical hypothyroidism, levothyroxine did not improve symptoms or tiredness [J]. Annals of Internal Medicine, 2017, 167(4): JC14

[31] Uyttendaele M, Lambert S, Tenoutasse S, et al. Congenital Hypothyroidism: Long-Term Experience with Early and High Levothyroxine Dosage[J]. Hormone Research in Paediatrics, 2016, 85(3): 188-197

(上接第 1331 页)

[22] Peters CD, Mathiassen ON, Vase H, et al. The effect of renal denervation on arterial stiffness, central blood pressure and heart rate variability in treatment resistant essential hypertension: a substudy of a randomized sham-controlled double-blinded trial (the ReSET trial)[J]. Blood Press, 2017, 26(6): 366-380

[23] Yan S, Li M, Wang H, et al. Characteristics and risk factors of pulmonary arterial hypertension in patients with primary Sjögren's syndrome[J]. Int J Rheum Dis, 2018, 21(5): 1068-1075

[24] Schneider MP, Hilgers KF, Schmid M, et al. Blood pressure control in chronic kidney disease: A cross-sectional analysis from the German Chronic Kidney Disease (GCKD) study [J]. PLoS One, 2018, 13(8): e0202604

[25] Chin HJ, Kim DK, Park JH, et al. Effect of urine urea nitrogen and protein intake adjusted by using the estimated urine creatinine excretion rate on the antiproteinuric effect of angiotensin II type I receptor blockers[J]. Nutrition, 2015, 31(11-12): 1333-1338