论著·循证医学

调整左旋甲状腺素治疗剂量对甲状腺功能减退孕妇母婴结局影响的meta分析

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［摘要］**目的·**采用meta分析评价根据促甲状腺激素（thyroid stimulating hormone，TSH）水平调整左旋甲状腺素（levothyroxine，L-T4）治疗剂量对甲状腺功能减退孕妇母婴结局的影响。**方法·**检索中国知网、维普中文科技期刊数据库、万方数据知识服务平台、PubMed、Cochrane Library、Embase数据库，收集建库至2022年4月9日所有关于根据TSH水平调整L-T4剂量治疗甲状腺功能减退孕妇的对照研究文献，并追溯参考文献。2名研究人员独立对所获取的文献进行筛选、数据提取及质量评价，其中质量评价采用Cochrane评价表。结局评价指标包括妊娠高血压、妊娠糖尿病、产后出血、分娩方式、早产、胎儿死亡、新生儿窒息、低出生体质量儿，采用RevMan 5.3软件进行meta分析。**结果·**在6个数据库共检索到1 268篇文献，最终纳入8篇，其中中文文献4篇、英文文献4篇，整体研究偏倚风险处于中等水平。相对于对照组，根据甲状腺功能减退孕妇TSH水平调整L-T4剂量的试验组孕妇发生妊娠糖尿病风险*OR*值为0.61（95%*CI* 0.44~0.86，*P*=0.004），发生胎儿死亡风险*OR*值为0.38（95%*CI* 0.18~0.81，*P*=0.010），均具有统计学意义。而调整L-T4剂量的治疗方式在阴道分娩［*OR*=1.82（95%*CI* 0.75~4.40，*P*=0.180）］、妊娠高血压［*OR*=0.77（95%*CI* 0.53~1.12，*P*=0.170）］、产后出血［*OR*=1.20（95%*CI* 0.50~2.92，*P*=0.680）］、早产［*OR*=0.72（95%*CI* 0.48~1.06，*P*=0.100）］、低出生体质量儿［*OR*=1.00（95%*CI* 0.65~1.54，*P*=0.999）］和新生儿窒息［*OR*=0.50（95%*CI* 0.20~1.27，*P*=0.150）］发生风险方面与对照组差异无统计学意义。**结论·**根据TSH水平调整L-T4治疗剂量，可能有助于降低甲状腺功能减退孕妇的妊娠糖尿病和胎儿死亡风险。

［关键词］甲状腺功能减退；孕妇；左旋甲状腺素；剂量调整；母婴结局；meta分析
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A meta-analysis of the effects of levothyroxine dose adjustment on maternal and infant outcomes in pregnant women with hypothyroidism

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[Abstract] **Objective·**To evaluate the effects of levothyroxine (L-T4) dose adjustment according to the level of thyroid stimulating hormone (TSH) on maternal and infant outcomes in the pregnant women with hypothyroidism by meta-analysis. **Methods·**China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), Wanfang Data Knowledge Service Platform, PubMed, Cochrane Library and Embase were retrieved to collect all the controlled studies on the treatment of pregnant women with hypothyroidism by adjusting the dose of L-T4 according to TSH level from the establishment of the databases to April 9, 2022. The references were also traced. Literature screening, data extraction, and quality evaluation were performed independently by two researchers. Cochrane evaluation was used to evaluate the quality of the included literature. Outcome indicators included gestational hypertension, gestational diabetes, postpartum hemorrhage, delivery mode, preterm birth, fetal death, neonatal asphyxia, and low birth weight infants. RevMan 5.3 was used for meta-analysis. **Result·**A total of 1 268 articles were retrieved from 6 databases, and 8 were included in the study, including 4 Chinese articles and 4 English articles. The overall risk of study bias was at a moderate level. Compared with the control group, the *OR* of gestational diabetes risk was 0.61 (95%*CI* 0.44–0.86, *P*=0.004) and the *OR* of fetal death risk was 0.38 (95%*CI* 0.18–0.81, *P*=0.010) in the experimental group with L-T4 dose adjusted according to the TSH level of the pregnant women with hypothyroidism, which were both statistically significant. However, the treatment method of adjusting L-T4 dose did not affect the risks of vaginal delivery [*OR*=1.82 (95%*CI* 0.75–4.40, *P*=0.180)], gestational hypertension [*OR*=0.77 (95%*CI* 0.53–1.12, *P*=0.170)], postpartum hemorrhage [*OR*=1.20 (95%*CI* 0.50–2.92, *P*=0.680)], preterm birth [*OR*=0.72 (95%*CI* 0.48–1.06, *P*=0.100)], low birth weight infants [*OR*=1.00 (95%*CI* 0.65–1.54, *P*=

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0.999)], or neonatal asphyxia [*OR*=0.50 (95%*CI* 0.20－1.27, *P*=0.150)] significantly. **Conclusion·**Adjusting the L-T4 therapeutic dose according to the TSH level may help reduce the risks of gestational diabetes and fetal death in the pregnant women with hypothyroidism.

[Key words] hypothyroidism; pregnant woman; levothyroxine (L-T4); dose adjustment; maternal and infant outcome; meta-analysis

妊娠甲状腺功能减退（甲减）是育龄期女性常见的疾病，是由各种原因导致的甲状腺激素合成、分泌或生物效应不足，从而引发的全身低代谢综合征。由于诊断标准、地区碘摄入量和妊娠年龄的不同，各文献报道的妊娠甲减发病率差异较大。一项关于妊娠期甲状腺疾病真实患病率的系统综述[1]指出，临床甲减发病率约为0.50%，亚临床甲减发病率约为3.47%。ABALOVICH等[2]研究发现，如果妊娠甲减未进行有效治疗，胎儿流产风险为60%。多项研究[3-5]也一致认为母体甲减会增加不良妊娠结局发生的风险，且对胎儿神经认知发育有不利影响，包括早产风险增加、出生低体质量、妊娠流产和子代智商降低等。目前左旋甲状腺素（levothyroxine，L-T4）是公认治疗甲减的首选药物，但是关于L-T4在改善母婴结局和长期子代结局方面的有效性仍未完全阐明，且治疗剂量及方法尚未形成统一标准[6-7]。本研究通过文献检索及meta分析探究根据促甲状腺激素（thyroid stimulating hormone，TSH）水平调整L-T4治疗剂量对甲减孕妇母婴结局的影响，以期为临床实践提供参考。

1　资料与方法

1.1　文献纳入和排除标准

纳入标准：① 随机对照研究或非随机对照研究。② 妊娠临床或亚临床甲减孕妇，符合妊娠诊断标准且符合临床或亚临床甲减诊断标准。③ 干预方法为根据TSH水平调整L-T4治疗剂量，对照组为使用固定剂量，或未用L-T4，或使用安慰剂等。④ 评价指标包括甲减孕妇的TSH水平、妊娠结局及新生儿结局等。⑤ 文献语言为中文或英文。排除标准：① 资料来源不清、文献不完整且索取无果。② 数据缺失或存在问题，无法提取。③ 重复发表或者数据类似文献。

1.2　文献检索策略

检索中国知网（CNKI）、维普中文科技期刊数据库（维普，VIP）、万方数据知识服务平台（万方，Wanfang）、Embase、Cochrane Library、PubMed数据库，检索语种限制为中文和英文，检索时间为建库至2022年4月9日。通过PubMed数据库MeSH词表和Embase数据库Emtree词表检索主题词，根据检索结果调整并确定检索关键词。中文检索策略：① “孕妇”OR“妊娠”OR“怀孕”OR“孕期”OR“产妇”。② “甲状腺功能减退”OR“甲减”。③ “左旋甲状腺素”OR“优甲乐”OR“激素”OR“L-T4”。④ “剂量”。⑤ “①AND②AND③AND④”。英文检索策略：① “pregnant” OR “pregnancy” OR “expectant mother” OR “maternity” OR “maternal” OR “gestation” OR “gravidity” OR “parturient” OR “puerpera” OR “fetation”。② “hypothyroidism” OR “hypothyroid” OR “hypothyrea” OR “thyroid hypofunction”。③ “levothyroxine” OR “L-thyroine” OR “L-T4” OR “levoid” OR “euthyrox” OR “hormone”。④ “dosage” OR “dose”。⑤ “①AND②AND③AND ④”。

1.3　文献筛选与数据提取

将检索到的文献导入Endnote软件，首先由2名研究者独立进行重复文献的筛除。去重标准：① 文献的题目、作者、发表的杂志及时间都相同视为重复文献。② 同一作者在不同时间或不同杂志上发表，但文献内容相同者视为重复文献，保留发表内容较完整者。然后由2名研究者独立对文献的题目和摘要进行初筛。初筛标准：① 排除研究对象、干预措施、评价指标明显不符合要求的文献。② 排除非试验性研究。将初筛结果分为纳入、排除和不确定3组。对于纳入和不确定的文献，阅读全文，根据文献纳入和排除标准进行筛选。对于双方筛选结果不一致或均不确定的文献，通过讨论决定或交由第3位研究者决定。

对于最终纳入的文献进行数据提取。本研究具体摘录按照事先设计好的信息摘录表，采用Excel软件进行资料摘录。内容包括文献的一般信息、研究对象

的基线资料、研究设计方案和实施方案、试验组和对照组的干预措施、主要评价指标的结果等。

1.4 文献质量评价

由2位研究者应用Cochrane评价表，先独立评价文献质量，再根据评价标准对每篇文献质量进行讨论形成共识。评价项目：随机序列产生（选择性偏倚）、分配结果隐藏（选择性偏倚）、研究者盲法（实施偏倚）、结果评估者盲法（测量偏倚）、不完整结果数据处理（失访偏倚）、选择性结果报道（报道偏倚）和其他偏倚。各条目评估程度为低风险、高风险、不清楚。

1.5 评价指标

妊娠高血压、妊娠糖尿病、产后出血、分娩方式、早产、胎儿死亡（包括流产和死胎）、新生儿窒息、低出生体质量儿。

1.6 统计学分析

采用Revman 5.3软件进行meta分析。连续性资料采用加权均数差（weighted mean difference，WMD）和95%*CI*；定性资料采用优势比（*OR*）和95%*CI*。采用χ^2检验评估各研究间的异质性，检验水准α=0.1。若I^2≤50%，P≥0.01，提示各研究间具有同质性，采用固定效应模型；若I^2>50%，P<0.01，提示各研究间具有异质性，采用随机效应模型，并进行敏感性分析或亚组分析寻找异质性来源。

2 结果

2.1 文献筛选流程及结果

在中国知网、维普、万方、Embase、Cochrane Library、PubMed数据库共检索到1 268篇文献，导入Endnote软件删除重复文献467篇，根据题名和摘要删除不符合标准的文献629篇，剩余172篇。通过通读全文，删除164篇，最终纳入研究文献8篇[8-15]。文献筛选流程及结果见图1，纳入研究的基本特征见表1。

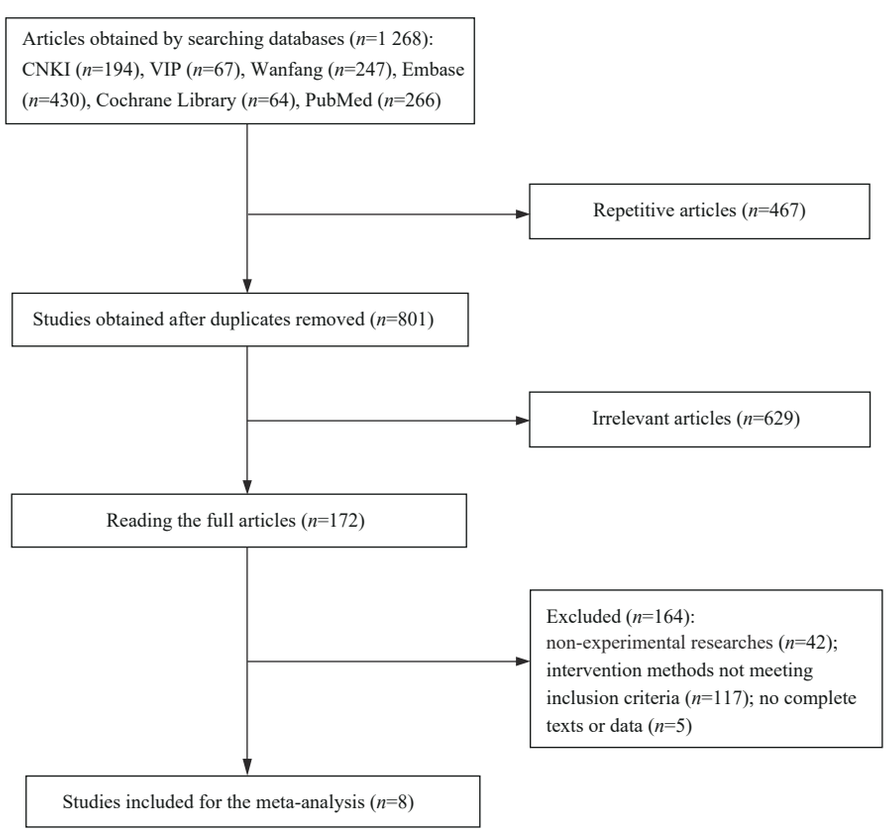

图1 文献筛选流程图

Fig 1 Flow diagram of the selection process of the included articles

表1　纳入研究基本特征

Tab 1　Basic characteristics of the studies

First author	Year of publication	Nation	Number of cases/*n*		Age/year		Intervention		Primary outcome index
			Exp	Con	Exp	Con	Exp	Con	
GAO[8]	2021	China	46	34	25.3±3.4	24.8±3.1	Guidance on routine maternal care was given. The initial dose of L-T4 was 50 μg/d. TSH level was re-examined 2 weeks later and the dose was adjusted	Guidance on routine maternal care was given. The iodized salt was increased and the fat was reduced in the diet	GH, PH, GDM, PD
YE[9]	2016	China	28	28	22−34	22−34	The fat was reduced, and the iodized salt and the protein were increased in the diet. Routine medication and nursing interventions were given. TSH was checked every 4–6 weeks and the L-T4 dose was adjusted	The fat was reduced, and the iodized salt and the protein were increased in the diet. Routine medication and nursing interventions were given	GDM, GH, DM, LBW, FD, NA
MA[10]	2020	China	42	42	28.74±4.08	28.25±4.15	The fat was reduced, and the iodized salt and the protein were increased in the diet. TSH level was checked once a month and the L-T4 dose was adjusted	The fat was reduced, and the iodized salt and the protein were increased in the diet. The dose of L-T4 was 50 μg/d	GH, GDM, FD, PD, NA, LBW, DM, abortion
LIU[11]	2021	China	49	49	26.9±4.6	26.8±4.7	The fat was reduced, and the iodized salt and the protein were increased in the diet. TSH level was checked termly and the L-T4 dose was adjusted	The fat was reduced, and the iodized salt and the protein were increased in the diet. The dose of L-T4 was 25 μg/d	DM, FD, abortion, PD, NA, LBW
CASEY[12]	2017	America	339	338	27.7±5.7	27.3±5.7	The initial dose of L-T4 was 100 μg/d. TSH level was checked once a month and the L-T4 dose was adjusted. TSH level was controlled in the range of 0.1–2.5 mIU/L	A placebo of 100 μg was given daily with a dummy adjustment	GDM, GH, LBW, PD, FD
BLUMENTHAL[13]	2017	Australia	92	933	33.47±1.41	35.00±5.20	The iodized salt was increased in the diet. The dose of L-T4 was 50 μg/d when TSH>2.5 mIU/L. TSH was checked every 4 weeks and the L-T4 dose was adjusted	The iodine was increased in diet and L-T4 was not given	DM, GH, GDM, PD, FD
WANG[14]	2012	China	28	168	Not mentioned	28.14±0.27	The initial dose of L-T4 depended on the pregnant woman′s TSH level. TSH 2.5–5 mIU/L: L-T4 50 μg/d; TSH >5–8 mIU/L: L-T4 75 μg/d; TSH>8 mIU/L: L-T4 100 μg/d. TSH level was checked every 4 weeks and the L-T4 dose was adjusted	L-T4 was not given	GH, PD, LBW, PH, abortion, NA
JU[15]	2016	China	184	273	29.31±3.36	28.88±3.53	The initial LT-4 dose was determined based on TSH level. Dose of LT-4 was adjusted according to the treatment objective of TSH	L-T4 was not given	GDM, GH, PH, PD, LBW

Note: Exp—experimental group; Con—control group; GH—gestational hypertension; PH—postpartum hemorrhage; GDM—gestational diabetes mellitus; PD—premature delivery; DM—delivery mode; LBW—low birth weight; FD—fetal death; NA—neonatal asphyxia.

2.2　文献质量评价结果

共纳入8篇文献，其中中文4篇[8-11]、英文4篇[12-15]，整体研究偏倚风险处于中等水平。2篇[10-11]采用随机数字表进行分组，1篇[12]采用计算机进行分组，2篇[9,15]未具体指出随机分组的方法，1篇[8]根据患者意愿进行分组，1篇[14]根据患者的治疗方式进行分组，1篇[13]根据患者TSH水平进行分组。1篇[12]研究采用密封不透明的信封进行分配隐藏。所有研究

在研究者和受试者的盲法方面未明确交代。虽然所有研究均未提及对评估者是否实施了盲法，但是因为结果判断和测量主要是客观指标，基本不受评估者的主观影响，本文评价其为低偏倚风险（图2）。

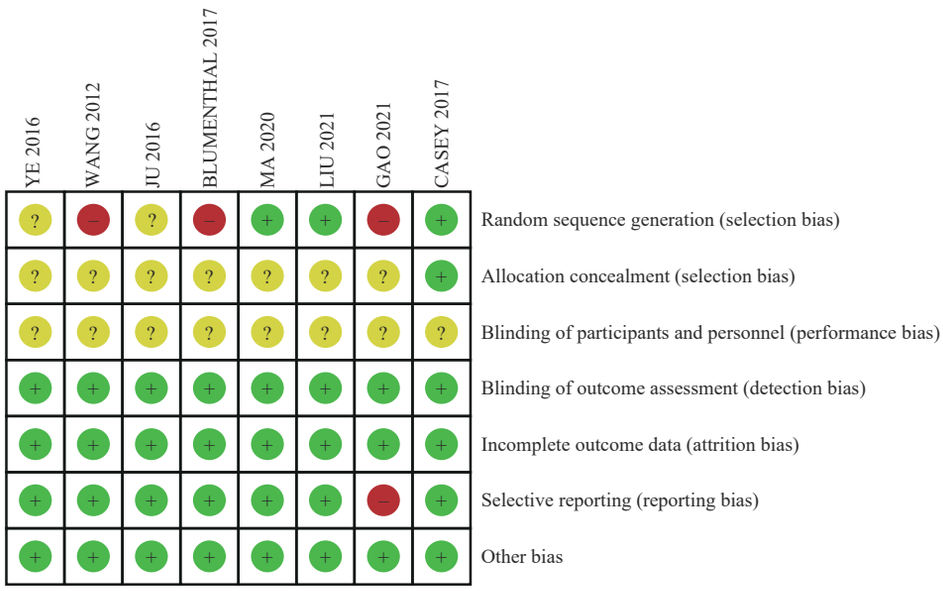

图2 纳入文献的风险偏倚评估

Fig 2 Risk bias assessment of the included articles

2.3 妊娠并发症和分娩方式

2.3.1 妊娠糖尿病 关于干预后2组甲减孕妇发生妊娠糖尿病风险的比较，共纳入6篇文献。异质性检验显示，各研究间具有同质性（P=0.180，I^2=34%），采用固定效应模型合并效应量。试验组共计731例，最终并发妊娠糖尿病60例，占8.21%；对照组共计1 648例，最终并发妊娠糖尿病144例，占8.74%。合并后OR=0.61（95%CI 0.44~0.86，P=0.004），差异有统计学意义。详见图3。

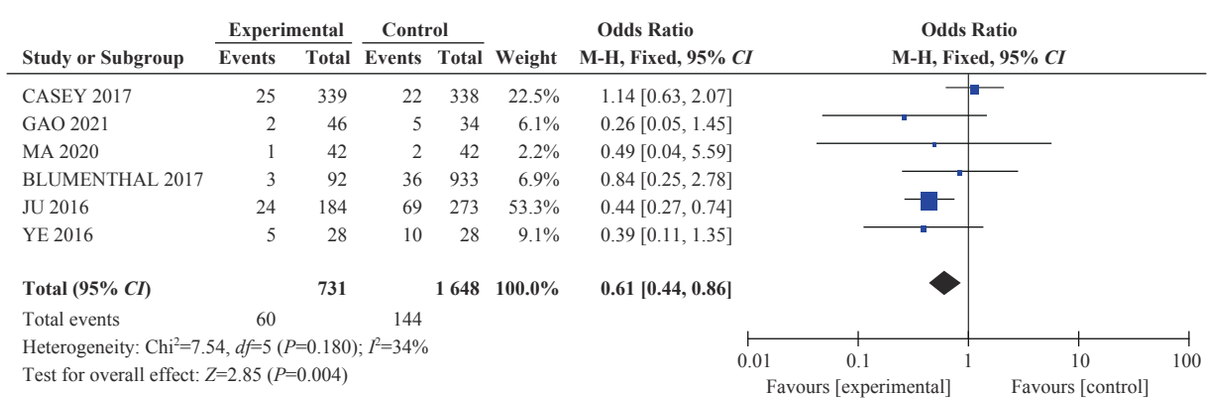

图3 2组甲减孕妇发生妊娠糖尿病风险的比较

Fig 3 Comparison of the risk of gestational diabetes in the pregnant women with hypothyroidism between the two groups

2.3.2 妊娠高血压 关于干预后2组甲减孕妇发生妊娠高血压风险的比较，共纳入7篇文献。异质性检验显示，各研究间具有同质性（P=0.460，I^2=0%），采用固定效应模型合并效应量。试验组共计759例，最终并发妊娠高血压50例，占6.59%；对照组共计1 816例，最终并发妊娠高血压89例，占4.90%。合并后OR=0.77（95%CI 0.53~1.12，P=0.170），差异无统计学意义。详见图4。

2.3.3 产后出血 关于干预后2组甲减孕妇发生产后出血风险的比较，共纳入3篇文献。异质性检验显示，各研究间具有同质性（P=0.980，I^2=0%），采用固定效应模型合并效应量。试验组共计258例，最终

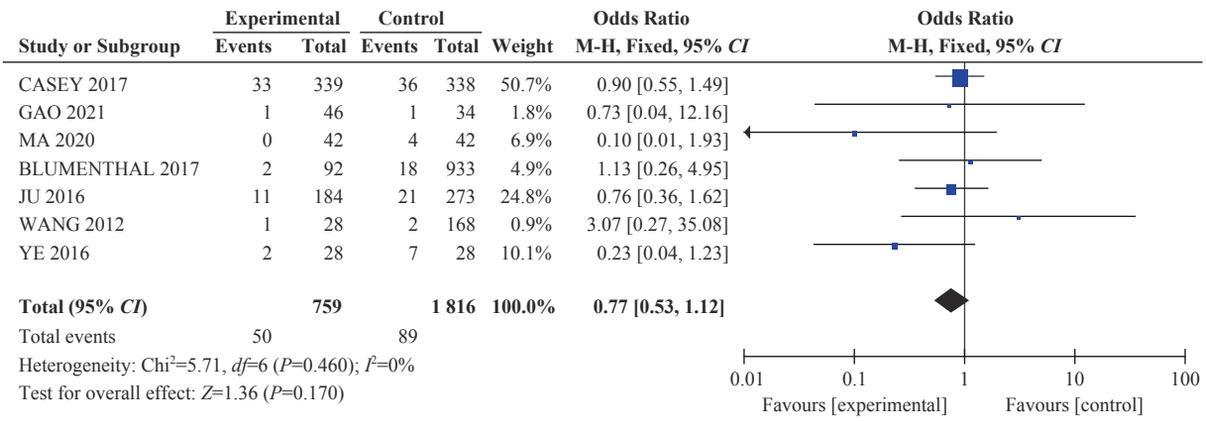

图4　2组甲减孕妇发生妊娠高血压风险的比较

Fig 4　Comparison of the risk of gestational hypertension in the pregnant women with hypothyroidism between the two groups

并发产后出血9例，占3.49%；对照组共计475例，最终并发产后出血12例，占2.53%。合并后*OR*=1.20（95%*CI* 0.50~2.92，*P*=0.680），差异无统计学意义。详见图5。

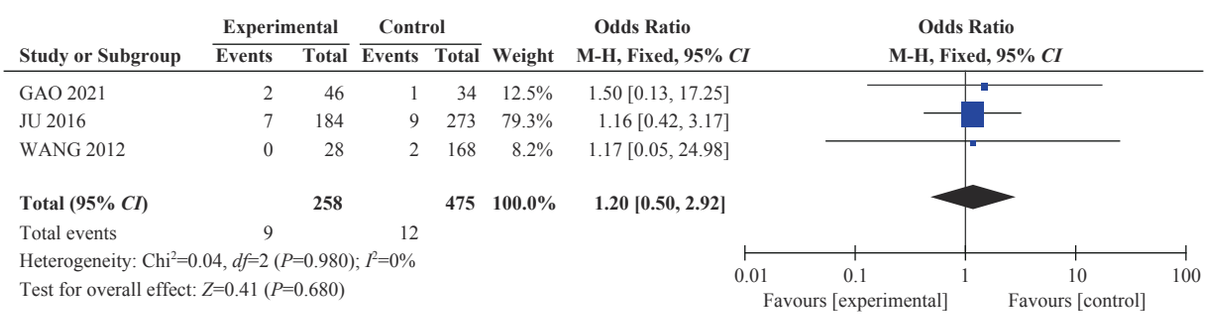

图5　2组甲减孕妇发生产后出血风险的比较

Fig 5　Comparison of the risk of postpartum hemorrhage in the pregnant women with hypothyroidism between the two groups

2.3.4　分娩方式　关于干预后2组甲减孕妇经阴道分娩的比较，共纳入4篇文献。异质性检验显示，各研究间具有异质性（*P*=0.009，I^2=74%），采用随机效应模型合并效应量。试验组共计211例，最终阴道分娩有159例，占75.36%；对照组共计1 052例，最终阴道分娩有731例，占69.49%。合并后*OR*=1.82（95%*CI* 0.75~4.40，*P*=0.180），差异无统计学意义。详见图6。

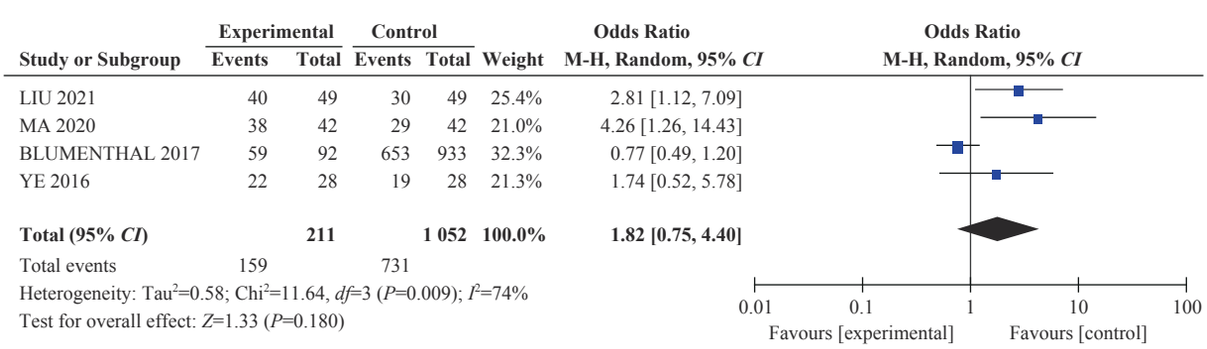

图6　2组甲减孕妇经阴道分娩的比较

Fig 6　Comparison of vaginal delivery in the pregnant women with hypothyroidism between the two groups

2.4　新生儿并发症

2.4.1　胎儿死亡　关于干预后2组甲减孕妇的胎儿死亡风险的比较，共纳入6篇文献。异质性检验显示，各研究间具有同质性（*P*=0.890，I^2=0%），采用固定效应模型合并效应量。试验组共计578例，胎儿死亡7例，占1.21%；对照组共计1 558例，胎儿死亡59例，占3.79%。合并后*OR*=0.38（95%*CI* 0.18~0.81，*P*=0.010），差异具有统计学意义。详见图7。

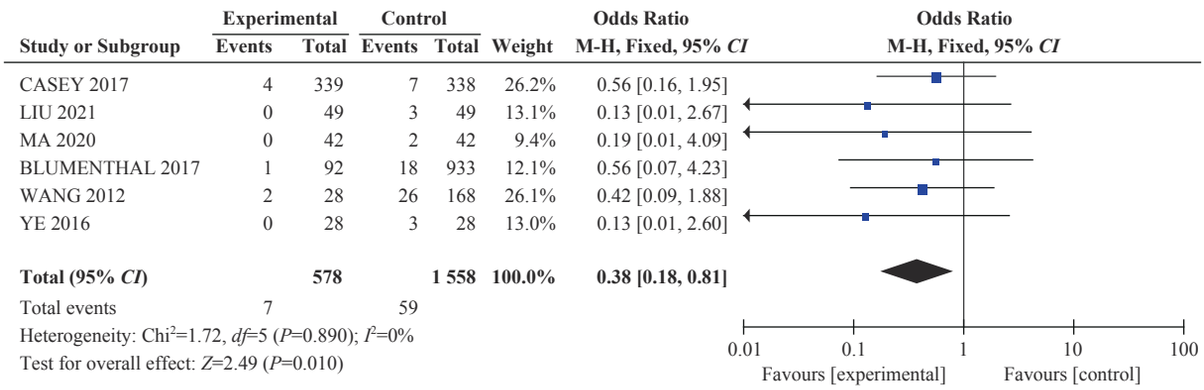

图7　2组甲减孕妇的胎儿死亡风险的比较

Fig 7　Comparison of the risk of fetal death in the pregnant women with hypothyroidism between the two groups

2.4.2　新生儿窒息　关于干预后2组甲减孕妇的新生儿窒息风险的比较，共纳入6篇文献。异质性检验显示，各研究间具有同质性（P=0.960，I^2=0%），采用固定效应模型合并效应量。试验组共计578例，最终发生新生儿窒息5例，占0.87%；对照组共计1 558例，最终发生新生儿窒息22例，占1.41%。合并后OR=0.50（95%CI 0.20~1.27，P=0.150），差异无统计学意义。详见图8。

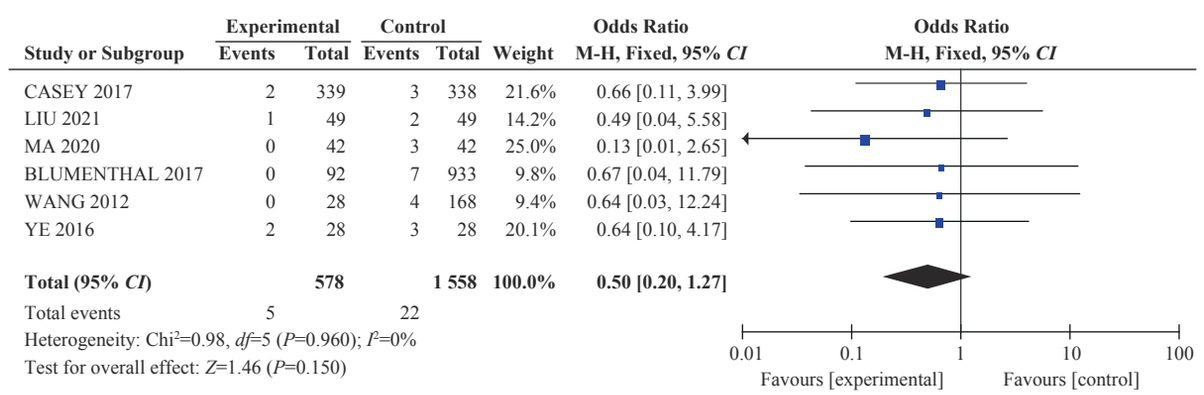

图8　2组甲减孕妇的新生儿窒息风险的比较

Fig 8　Comparison of the risk of neonatal asphyxia in the pregnant women with hypothyroidism between the two groups

2.4.3　早产　关于干预后2组甲减孕妇早产风险的比较，共纳入7篇文献。异质性检验显示，各研究间具有同质性（P=0.330，I^2=14%），采用固定效应模型合并效应量。试验组共计780例，最终早产有42例，占5.38%；对照组共计1 837例，最终早产有84例，占4.57%。合并后OR=0.72（95%CI 0.48~1.06，P=0.100），差异无统计学意义。详见图9。

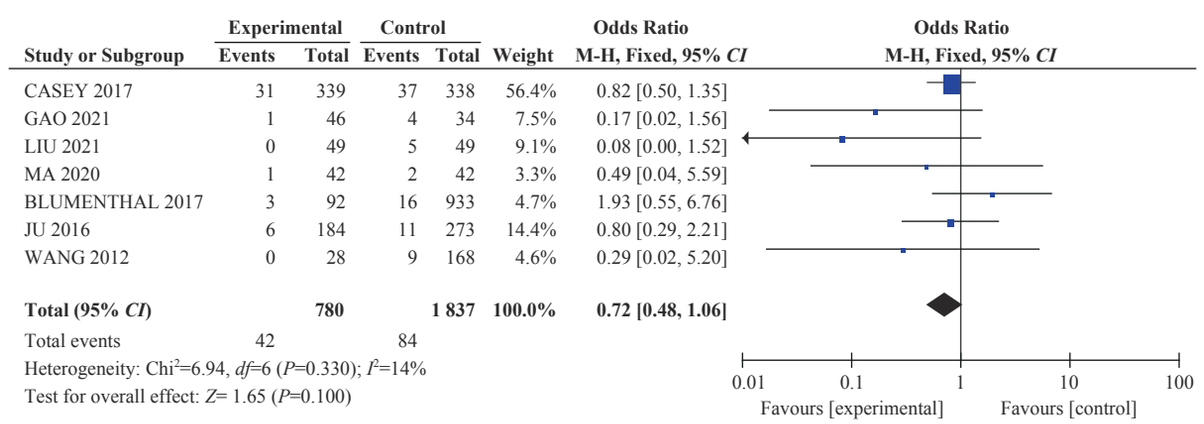

图9　2组甲减孕妇的早产风险的比较

Fig 9　Comparison of the risk of preterm birth in the pregnant women with hypothyroidism between the two groups

2.4.4　低出生体质量儿　关于干预后2组甲减孕妇出现低出生体质量儿风险的比较，共纳入6篇文献。异质性检验显示，各研究间具有同质性（P=0.460，I^2=0%），采用固定效应模型合并效应量。试验组共计670例，最终低出生体质量儿有42例，占6.27%；对照组共计898例，最终低出生体质量儿有48例，占5.35%。合并后OR=1.00（95%CI 0.65~1.54，P=0.999），差异无统计学意义。详见图10。

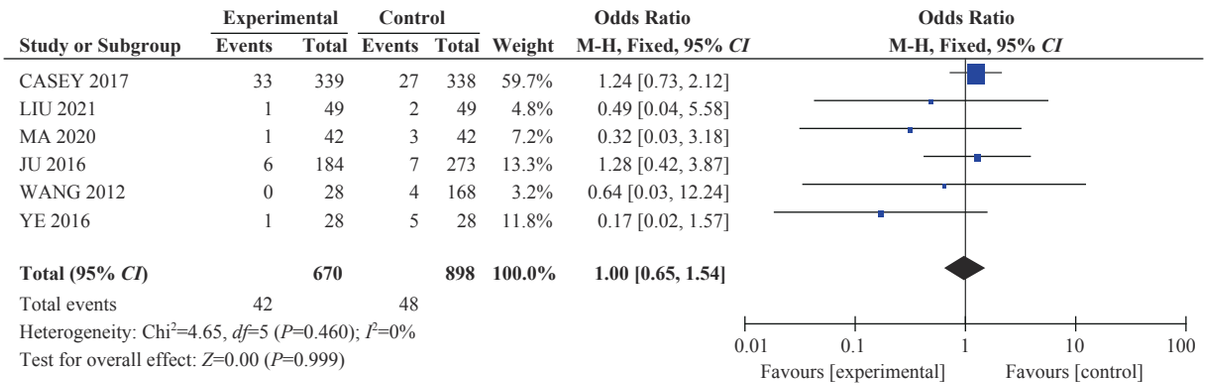

图10　2组甲减孕妇的低出生体质量儿风险的比较

Fig 10　Comparison of the risk of low birth weight infants in the pregnant women with hypothyroidism between the two groups

3　讨论

3.1　调整L-T4剂量能降低妊娠糖尿病和胎儿死亡风险

本研究共纳入6篇文献进行妊娠糖尿病发生率的meta分析，结果显示，与使用固定剂量或不使用L-T4相比，调整L-T4剂量有效降低了甲减孕妇发生妊娠糖尿病的风险。其中CASEY等[12]对试验组妊娠甲减孕妇进行TSH治疗，初始剂量为口服L-T4 100 μg/d，每月根据TSH结果调整用药剂量，控制TSH水平在0.1~2.5 mIU/L，对照组则使用安慰剂并进行虚假调整，结果试验组甲减孕妇妊娠糖尿病的发生率显著降低。研究[16]表明，孕期甲状腺功能障碍可能与妊娠糖尿病有关，妊娠早期亚临床甲减的患者妊娠糖尿病的发生率更高，但具体机制尚不清楚。

本研究结果还发现，根据TSH调整L-T4剂量能降低甲减孕妇的胎儿死亡风险。发育中的胎儿在妊娠16周之前完全依赖于母体的甲状腺激素，充足的甲状腺激素是胎儿生长的关键因素之一，甲状腺激素可直接作用于早期胎盘发育、刺激血管生成并促进胚胎植入与分化，若母体发生甲减则会增加流产的风险[17-18]。一项Logistic回归分析[14]显示，血清TSH≥2.5 mIU/L是影响早孕自然流产的主要因素。2017年美国甲状腺协会制定的指南[19]指出，建立妊娠期参考值范围纳入的人群必须符合无甲状腺疾病史、碘摄入充足及甲状腺过氧化物酶抗体（TPOAb）阴性等特点；如果无法建立特异性参考值范围，建议将早期妊娠TSH上限定为4 mIU/L。DING等[20]根据2017年美国甲状腺协会指南的最新标准，纳入血清TSH>4 mIU/L的孕妇作为研究对象，meta分析结果显示，与未接受治疗的对象相比，接受L-T4治疗的甲减孕妇的流产发生率更低。另一项meta分析研究[21]结果也提示，L-T4可降低甲减孕妇流产的发生率，也与本研究的结果一致。但是目前对亚临床甲减孕妇是否使用L-T4治疗仍存在分歧。MAGRI等[22]研究表明，L-T4治疗亚临床甲减孕妇的证据仍然不足；PEARCE[23]建议TSH>10 mIU/L或TPOAb阳性的亚临床甲减孕妇使用L-T4治疗。不同的研究结果可能是因为使用了不同的TSH截断水平作为亚临床甲减的诊断标准。我国也越来越重视甲减孕妇TPOAb的状态，所有备孕妇女甲状腺筛查指标至少包括血清TSH、游离甲状腺素（free thyroxine，FT4）和TPOAb。2019年我国发布《妊娠和产后甲状腺疾病治疗指南》（第2版）[24]，根据TPOAb是否阳性进一步分层细化治疗方案：若TSH介于2.5~4.0 mIU/L，伴TPOAb阳性，推荐L-T4治疗；若TSH介于2.5~4.0 mIU/L，且TPOAb阴性，则不推荐L-T4治疗。2022年我国《孕产期甲状腺疾病防治管理指南》[25]建议所有备孕妇女甲状腺筛查必须包括TPOAb。波兰内分泌学会指南[26]建议甲状腺功能正常但是TPOAb阳性的孕妇和甲减孕妇一样，每4周检测1次TSH，并且在孕30周至少再检测1次。

3.2 调整L-T4剂量对分娩方式及妊娠高血压、产后出血、早产、新生儿窒息、低出生体质量儿的发生风险均无影响

甲减并不是剖宫产的指征，能否经阴道分娩主要依据产力、产道、胎儿及心理因素。本研究共纳入4篇文献进行阴道分娩率的meta分析，结果显示调整L-T4剂量对甲减产妇的阴道分娩率并无影响。而王文娟[27]对甲减孕妇使用L-T4治疗效果进行随机对照研究，结果发现试验组自然分娩率（100%）高于对照组（88.89%），P<0.05，差异有统计学意义；该研究结果与本研究的结果不同，可能是两者的研究对象诊断标准、干预措施不同所致。本研究meta分析结果显示，调整L-T4治疗剂量并未降低妊娠高血压的发生率。最新的一项关于妊娠期亚临床甲减与妊娠高血压关系的系统评价[28]指出，虽然妊娠期亚临床甲减与妊娠高血压发病风险增加相关，但是现有的证据仍不能支持这些接受L-T4干预的孕妇能从中受益。本研究发现调整L-T4剂量并未降低甲减孕妇产后出血的风险，因本研究仅纳入3篇文献，包括试验组258例、对照组475例，所以结论仍需要进行大样本试验进一步确认。另外，调整L-T4治疗剂量在早产、新生儿窒息和低出生体质量儿风险方面未见获益。但是，对于妊娠期糖尿病伴亚临床甲减孕妇，宋茜茜等[29]发现血糖、TSH等水平升高可影响骨钙素、25-羟基维生素D的表达，可引起孕妇骨质流失，骨密度降低，增加新生儿窒息和低出生体质量儿风险。目前，亚临床甲减对妊娠结局的影响以及是否应治疗亚临床甲减孕妇仍存在争议，但是考虑到亚临床甲减可能会对母体和婴儿造成的不良结局，因此大多数专家和指南仍建议治疗[19]。早期筛查、全程监测是管理妊娠甲状腺功能障碍的重要工作之一。西班牙内分泌和营养学会最新制定的《妊娠期甲状腺功能障碍管理共识》[30]指出，当孕前存在甲减的女性一旦确认怀孕即开始第1次TSH水平检测，以后每4周检测1次直到妊娠20周，调整L-T4剂量，保证达到治疗目标，即TSH<2.5 mIU/L，并至少在妊娠30周之前再做1次TSH检测（强烈建议，高级证据）。

3.3 研究的局限性

本研究存在一定局限性：① 各研究纳入的研究对象的诊断标准未统一，研究可能存在偏倚。② 纳入的部分研究未提及具体随机方法，也未说明分配隐藏及盲法的具体方法，存在临床偏倚。③ 只纳入中英文2种语言的文献，研究结论的推广还需更多的临床样本。本研究所纳入的文献大多在盲法方面不明确，希望后期相关研究在随机分配、分配隐藏和盲法上进一步符合标准。纳入研究的样本量相对较小且多为单中心研究，未来需要更高质量、更大样本的随机对照研究进一步论证本研究结果。

L-T4在人体内半衰期长、药效持久，是目前临床上用于妊娠期甲减治疗的首要药物。目前研究证据表明，对于甲减孕妇，根据TSH水平调整L-T4治疗剂量可能有助于有效降低其妊娠糖尿病、胎儿死亡的风险。

利益冲突声明/Conflict of Interests

所有作者声明不存在利益冲突。

All authors disclose no relevant conflict of interests.

作者贡献/Authors′Contributions

姚屹瑾负责研究的构思与设计，陈惠和朱唯一负责数据收集、整理，陈惠负责撰写文章，朱唯一负责统计分析和文章的修改与审校。所有作者均阅读并同意了最终稿件的提交。

The study was designed by YAO Yijin. The data were collected and processed by CHEN Hui and ZHU Weiyi. The manuscript was drafted by CHEN Hui. The statistics of data and the manuscript revision were completed by ZHU Weiyi. All the authors have read the last version of paper and consented for submission.

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