Supplemental Information

Supplemental Figure 1(S1): Full Search Strategy – MEDLINE (Ovid)

- 1. Hypothyroidism/
- 2. "hypothyroid*".ab,ti,kf.
- 3. "hypothyroxinemia".ab,ti,kf.
- 4. (("thyroid-stimulating hormone*" or "thyroid stimulating hormone*" or TSH*) adj2 deficien*).ab,ti,kf.
- 5. (thyroid* adj3 (autoimmun* or "auto-immun*" or antibod*)).ab,ti,kf.
- 6. Thyroxine/
- 7. "levothyro*".ab,ti,kf.
- 8. "thyrox*".ab,ti,kf.
- 9. synthroid.ab,ti,kf.
- 10. lt4.ab,ti,kf.
- 11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
- 12. exp Pregnancy/
- 13. "pregnan*".ab,ti,kf.
- 14. "gestat*".ab,ti,kf.
- 15. Pregnant Women/
- 16. "maternal*".ab,ti,kf.
- 17. "prenatal*".ab,ti,kf.
- 18. 12 or 13 or 14 or 15 or 16 or 17
- 19. 11 and 18
- 20. randomized controlled trial.pt.
- 21. controlled clinical trial.pt.
- 22. random*.ab.
- 23. placebo.ab.
- 24. drug therapy.fs.
- 25. trial.ab.
- 26. groups.ab.
- 27. 20 or 21 or 22 or 23 or 24 or 25 or 26
- 28. exp animals/ not humans.sh.
- 29. 27 not 28
- 30. 19 and 29
- 31. limit 30 to yr="1980 -Current"

Supplemental Table (S2). Baseline patient characteristics

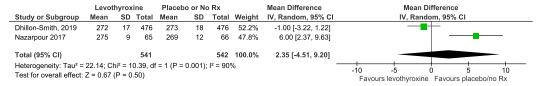
				_			Duration of	LT4 dosing and	Funding source
	Maternal Age (years)		Body Mass Index (kg/m ²)		Baseline FT4 (pmol/L)		Treatment	titration	
Study Author (year) Dhillon-Smith et al. (2019)	Intervention Arm (LT4)	Control Arm	Intervention Arm (LT4)	Control Arm 26.5± 5.5	Intervention Arm (LT4)	Control Arm 14.5±2	From before conception until the end of pregnancy	LT4 was d/c if TFT were outside assay specific limits at 6-8 wks, 1-18wks and 28 wks	UK national institute for health research
Nazarpour et al. (2017)	26.6 ± 5.8	27 ± 4.7	24.9± 5.1	24.6 ± 3.6	N/A	N/A	From the first trimester until the end of pregnancy	If TSH < 1.0 mcIU/mL: 0.5mcg/kg/d; If TSH 1.0-2.0, 0.75mcg/kg/d; If TSH > 2.0 or TPOAb > 1500IU/mL then 1mcg/kg/day	Did not receive any specific grant from any funding agency
Negro <i>et al.</i> (2005)	29.2 ± 4	30.1 ± 5	N/A	N/A	11.2 ± 1.8	11.7 ± 0.7	1 month before assisted reproductive technology until the end of pregnancy	1mg/kg/day	Unclear
Negro <i>et al.</i> (2006)	30 ± 5	30 ± 6	N/A	N/A	14.8 ± 4.2	14.6 ± 4.3	From the first trimester until the end of pregnancy	If TSH < 1.0 mcIU/mL: 0.5mcg/kg/d; If TSH 1.0-2.0, 0.75mcg/kg/d; If TSH > 2.0 or TPOAb > 1500IU/mL then 1mcg/kg/day	Unclear
Negro <i>et al.</i> (2016)	28.9 ± 5.2	29.9 ± 5.1	N/A	N/A	N/A	N/A	From the first trimester	If TSH 0.5-1.5, LT4 0.5mcg/kg/d; TSH 1.5-2.5, LT4	Unclear

							until the end of pregnancy	1mcg/kg/d. Titration: If TSH > 3.0 in 2nd or 3rd trimester, LT4 dose increased by 12.5mcg/d; If TSH <0.5 in 2nd or 3rd trimester, then decrease by 12.5mcg/d STARTING Dose: TSH >/= 2.5mIU/L:	National Key Technology R
Wang <i>et al</i> . (2017)	31.3 ± 3.9	31.7 ± 3.8	22.7 ± 3.3	22.8 ± 3.2	N/A	N/A	2-4 weks before controlled ovarian hyperstimula -tion until the end of pregnancy	starting dose is 50mcg/d; TSH <2.5mIU/L, starting dose is 25mcg/d. If body weight <50kg, then starting dosing decreased by 50% Titration: TSH in first trimester 0.1- 2.5mIU/L, 0.2- 3.0mIU/L in second trimester, 0.3- 3.0mIU/L in third trimester	and D program and Chinese National 973 program (Both form the Ministry of Science and Technology of China)

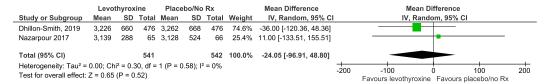
Table S2: N/A specifies that information was not available. FT4 denotes free thyroxine. LT4 denotes levothyroxine.

Supplemental Figure (S3):

A. Weighted mean difference for gestational age at time of delivery (days)

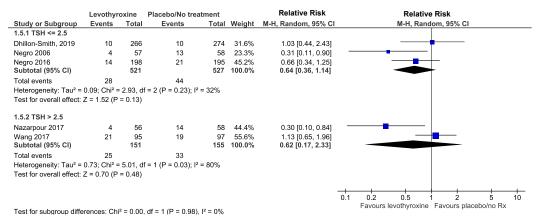


B. Weighted mean difference for birth weight (g)

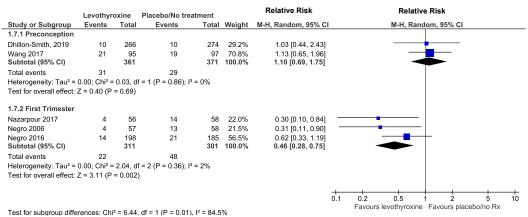


Supplemental Figure (S4): Stratified meta-analysis for preterm delivery subgroups.

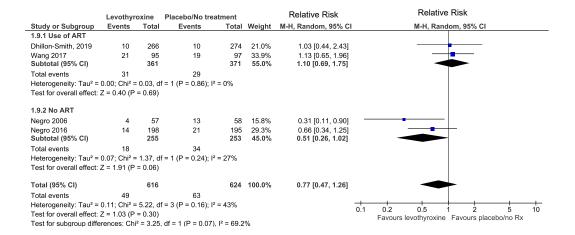
A. Stratified by TSH levels at baseline



B. Stratified by timing of levothyroxine initiation.



C. Stratified by use of assisted reproductive technologies

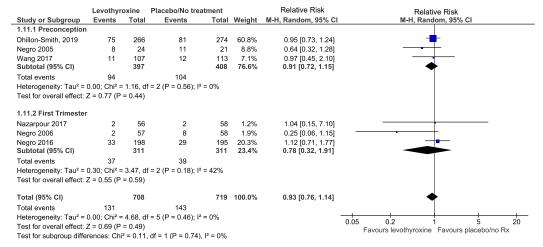


D. Stratified by study quality

	Levothyroxine		Placebo/No treatment		Relative Risk			Relative Risk
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C		M-H, Random, 95% CI
1.8.1 High								
Dhillon-Smith, 2019	10	266	10	274	100.0%	1.03 [0.44, 2.43]		- -
Subtotal (95% CI)		266		274	100.0%	1.03 [0.44, 2.43]		~
Total events	10		10					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 0.07 (P	= 0.95)						
1.8.2 Low								
Nazarpour 2017	4	56	14	58	19.5%	0.30 [0.10, 0.84]		
Negro 2006	4	57	13	58	19.3%	0.31 [0.11, 0.90]		
Negro 2016	14	198	21	195	29.2%	0.66 [0.34, 1.25]		
Wang 2017	21	95	19	97	31.9%	1.13 [0.65, 1.96]		
Subtotal (95% CI)		406		408	100.0%	0.58 [0.31, 1.09]		◆
Total events	43		67					
Heterogeneity: Tau ² =	0.25; Chi ² =	= 7.83, d	$f = 3 (P = 0.05); I^2$	2 = 62%				
Test for overall effect:	Z = 1.69 (P	= 0.09)						
							0.01	0.1 1 10 100
								Favours levothyroxine Favours placeho/no Rx

Supplemental Figure (S5): Stratified meta-analysis for miscarriage subgroups.

A. Stratified by timing of levothyroxine initiation.



B. Stratified by fixed levothyroxine versus adjusted levothyroxine dose.

	Levothyre	oxine	Placebo/No trea	atment		Relative Risk	Relative Risk
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.12.1 Fixed Dose							
Dhillon-Smith, 2019	75	266	81	274	56.8%	0.95 [0.73, 1.24]	- -
Negro 2005	8	24	11	21	8.2%	0.64 [0.32, 1.28]	
Subtotal (95% CI)		290		295	65.0%	0.89 [0.66, 1.20]	•
Total events	83		92				
Heterogeneity: Tau ² =	0.01; Chi ² =	1.13, d	f = 1 (P = 0.29); I ²	= 12%			
Test for overall effect:	Z = 0.76 (P	= 0.45)					
1.12.2 Adjusted Dose	e						
Nazarpour 2017	2	56	2	58	1.1%	1.04 [0.15, 7.10]	
Negro 2006	8	24	11	21	8.2%	0.64 [0.32, 1.28]	
Negro 2016	33	198	29	195	19.0%	1.12 [0.71, 1.77]	- • -
Wang 2017	11	107	12	113	6.7%	0.97 [0.45, 2.10]	
Subtotal (95% CI)		385		387	35.0%	0.95 [0.68, 1.33]	•
Total events	54		54				
Heterogeneity: Tau ² =	0.00; Chi ² =	1.81, d	$f = 3 (P = 0.61); I^2$	= 0%			
Test for overall effect:	Z = 0.29 (P	= 0.78)					
Total (95% CI)		675		682	100.0%	0.92 [0.76, 1.13]	•
Total events	137		146				
Heterogeneity: Tau ² =	0.00; Chi ² =	2.99, d	f = 5 (P = 0.70); I ²	= 0%			0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z = 0.80 (P	= 0.43)					0.1 0.2 0.5 1 2 5 10 Favours levothyroxine Favours placebo/no Rx
Test for subgroup diffe	erences: Chi	$^{2} = 0.08$, df = 1 (P = 0.77).	I ² = 0%			i avours levouryroxine Pavours placebo/ilo RX

Supplemental Figure (S6): Funnel plot for preterm delivery

