Evaluation of the ovarian reserve in women and adolescent girls with Hashimoto's thyroiditis by serum anti-Müllerian hormone level: A systematic review and meta-analysis

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ABSTRACT

Objectives: Several researchers performed case-control studies to explore the relationship between Hashimoto's thyroiditis(HT) and ovarian reserve using anti-Müllerian hormone(AMH) in adolescent girls and women. But the results among these studies are inconsistent and the relationship between HT and ovarian reserve is still controversial. The study aimed to conduct the meta analysis of case-control studies to confirm the relationship between HT and ovarian reserve using AMH.

Methods: 6 electronic databases including PubMed, EMBASE, the Cochrane Library, China National Knowledge Internet(CNKI), SinoMed and Wanfang were searched from inception to December 2021. Endnote X7.0 software was applied to managing all the relevant records. Then data extraction and evaluation of methodological quality of included studies were conducted after two-step selection.Review manager 5.4 version software and Stata 12.0 version software were used to perform all statistical analyses.

Results: 10 case-control studies involving 1202 individuals were included in the present study. The preliminary results revealed AMH values were significantly higher in adolescent girls with euthyroid HT compared with healthy adolescent girls(MD = 1.97; 95%CI, 1.43–2.51; $P < 0.001$; $I^2 = 0\%$). The pooled results in the subgroup of female adults with euthyroid HT showed AMH values were not significantly different between patients with HT and healthy women(MD = -0.21; 95%CI, -0.51-0.09; $P = 0.18$; $I^2 = 38\%$). The pooled results in the two subgroups of female adults with subclinical hypothyroidism and overt hypothyroidism both showed AMH values were significantly lower in the HT group compared with healthy women [(MD = -0.60; 95%CI, -0.86 to -0.34; $P < 0.001$; $I^2 = 0\%$), (MD = -1.34; 95%CI, -1.94 to -0.74; $P < 0.001$; $I^2 = 65\%$)].

Conclusions: Ovarian reserve evaluated by serum AMH concentration is affected by female adults with subclinical hypothyroidism and overt hypothyroidism. The AMH level was significantly higher in euthyroid adolescent girls.

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1. Introduction Background

Hashimoto's thyroiditis (HT), also known as autoimmune or chronic lymphocytic thyroiditis, is one of the most frequent thyroid diseases in adolescent girls and women, which diagnosed by three aspects including antibodies specific to thyroid antigens, thyroid volume, and lymphocyte infiltration of parenchyma [1–3]. The incidence of HT has a rapid growth in the last 3 decades and is 0.3–1.5 persons per 1000 individuals [4,5]. HT could be divided into different types including euthyroid HT, subclinical hypothyroidism, overt hypothyroidism, or hyperthyroidism based on the thyroid function [6,7].

Secreted from granulose cells of preantral follicles (PAF) and early antral follicles (EAF), anti-Müllerian hormone(AMH) is a glycoprotein which could regulate the follicle growth and inhibit the accumulation of primordial follicle [8]. AMH has an initial increase during early adulthood and then has a slow decrease with age until it couldn't be detected when the primordial follicles is depleted [9]. It is well known that serum AMH concentration accurately reflects the reserve of antral follicles, and so it is the best available marker of functional ovarian reserve at present compared with follicle-stimulating hormone (FSH), antral follicle count(AFC) and inhibin B [10,11].

Because thyroid hormones(TH) are involved in regulating the menstrual cycle and oocytes possess triiodothyronine receptors and TH receptors on the cells' surface whichaffecting the secretion of follicle-stimulating hormone(FSH) and luteinizing hormone, the incidence of the disturbances of menstrual cycle and even the premature ovarian failure(POF) is increased in patients with HT [12,13]. Some published data indicated the disturbances of the menstrual cycle are increased as much as 3-fold in HT [14]. In order to further elucidate the impact of HT on ovarian reserve, several researchers performed case-control studies to explore the relationship between HT and ovarian reserve using AMH in adolescent girls and women. Some studies showed serum AMH values were affirmed to be significantly lower in the HT group [15–18]. In contrary, some studies showed AMH values were not significantly different between patients with HT and healthy women [19–22]. Two studies offered the evidence that AMH values were significantly higher in patients with HT [23,24]. The relationship between HT and ovarian reserve is still controversial, so we performed the first meta analysis of the published studies investigating the association between HT and ovarian reserve.

2. Methods

2.1. Searching strategy

The present meta analysis was rigorously performed based on the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA), and the protocol of the present meta analysis was not prepared [25]. Using the combination between Medical Subject Headings(MeSH) and key words, the six electronic databases including PubMed, EMBASE, the Cochrane Library, China National Knowledge Internet(CNKI), SinoMed and Wanfang were independently searched by two investigators(CJS and TRS) from inception to December 2021. The key words were consisted of 'Hashimoto's thyroiditis' and 'anti-Müllerian hormone. Meanwhile, the manual searching was completed by finding the references of all the included studies and related-topic reviews. The language of published studies was restricted in Chinese and English. We used Endnote X7.0 software to manage all the literatures retrieved. The search strategy for PubMed was provided in Supplemental Table 1.

2.2. Selecting criteria

Firstly the selecting criteria were constructed according to the four aspects including patients, comparison, outcome measures and study design(PCOS) before performing the search. The inclusion criteria were shown as follow:

- (P) : All the patients were aged 12 and above, and the gender was female. The patients were clearly diagnosed with HT.
- (C) : Adolescent girls or women with normal levels of thyroidhormones and negative for anti-thyroperoxidase antibodies (anti-TPO) antibodies.
- (O) : Serum AMH values.
- (S) : Case-control studies or cohort studies.

The exclusion criteria were shown as follow:

- (P) : Patients with polycystic ovary syndrome(PCOS).
- (S) : Animal experiment or studies without sufficient information.

2.3. Study selection

After comprehensive searching, two investigators(CJS and XDZ) were independently assigned to review the title and abstract of all the relevant records to assess the eligibility. After that, full-text records were downloaded to further review to evaluate its eligibility.

2.4. Data extraction

After including the eligible studies, two investigators(CJS and TRS) independently extracted the basic materials including the first

author, publication year, country, age, inclusion criteria, sampling time of blood, assay method, the sensitivity of assay, and AMH values. If there was any inconsistent agreement between the two investigators, the third investigator(BW) would solve the discrepancy.

2.5. Evaluation of methodological quality of included studies

Two investigators(CJS and XDZ) independently assessed the methodological quality of case-control studies or cohort studies based on the Cochrane's Newcastle-Ottawa Scale(NOS).Three quality parameters of the NOS including selection, comparability, and outcome were evaluated from 8 items. Each item is scored from 1 point, except for comparability, which could be adapted to scoring up to 2 points.When the scores were 6 and above, themethodological quality of included studies was rated as high and the total scores was 9 [26,27].The third investigator(BW) would solve thediscrepancy.

2.6. Statistical analysis

The continuous data were described with mean difference(MD) with 95% confidence interval(CI). Owing tothe heterogeneity within and across trials, random-effect model was used to perform statistical analysis of AMH values in the present meta analysis [28]. The AMH values were analyzed through the inverse variance method, with MD effect measure with 95% CI in two groups.In order to express the heterogeneity, chi-square test was used to perform the qualitative description and I^2 statistic to perform the quantitative description. Whenthe value of I^2 was 25–50%, 50–75%, and$> 75\%$, it represents low, moderate, and significant heterogeneity [29]. Subgroupanalyses were conducted to assess between-group differences among the studies according to type of HT and age,andthe wald test was used for interaction for subgroup analyses.Sensitivity analysis was conducted by excluding studies one at a time in order to evaluate the robustness of pooled results about the direction and the size of adjusted effect estimates of the metaanalysis [30]. When a Pvalue is lower than0.05, it was considered statistically significant.Potential publication bias was evaluated by funnel plot, Egger's regression and Begg's rank tests ($P < 0.1$ was considered to be publication bias). Review manager 5.4 version softwareand Stata 12.0 version software were used to perform all statistical analyses.

3. Results

3.1. Results of searching and selecting

A total of 64 articles were captured from six electronic database. After two-step selection, 10 studies involving 1202 individuals were included in the present study [15–24]. The flow diagram of searching and selecting of records was presented in Fig. 1.

3.2. The basic characteristics of 10 included studies

As shown in Table 1, we concluded the basic characteristics of 10 included studies. For the 10 included studies in the meta analysis, the sample size of every study in HT group ranged from 21 to 108. The countries of publication of 10 studies were located in China, Turkey, Mexico and Poland. Three studies [19,20,24] only included the adolescent girls and the other studies enrolled female adults.
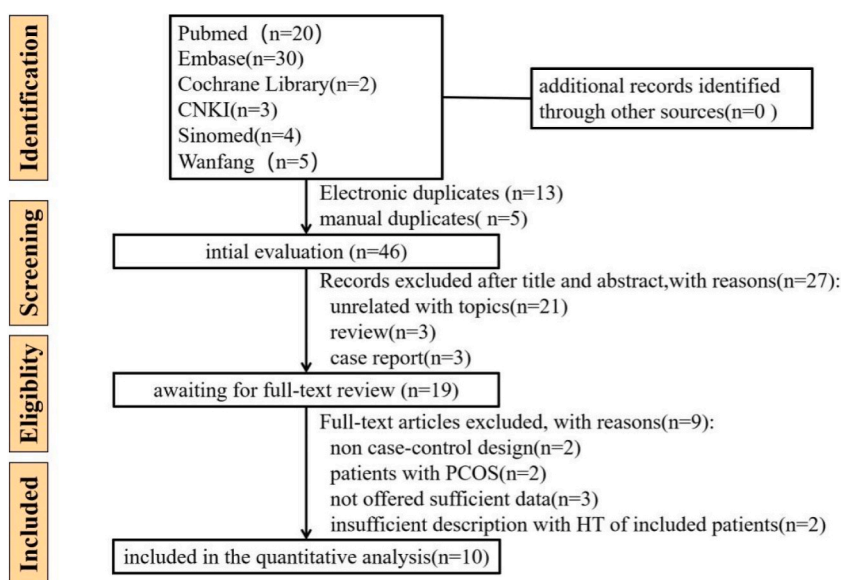

Fig. 1. The flow diagram of searching and selecting of records.

Table 1
The basic characteristics of all the included studies.

Study ID	Country	HT/C (N)	Age of Patients HT/C (years)	Inclusion criteria HT	C	sampling time of blood	Assay method	sensitivity of assay(ng/ml)	AMH HT/C (ng/mL)	NOS Scores
Shou 2021	China	63/48/45/53	29.71 ± 4.14/28.73 ± 3.62/28.62 ± 4.11/29.45 ± 3.84	3 groups: euthyroid; subclinical hypothyroidism; overt hypothyroidism	healthy fertile women	in the early follicular phase (days 2–4)	ECLIA	–	2.86 ± 1.05/2.40 ± 1.02/1.31 ± 1.27/3.01 ± 0.78	7
Shou (1) 2021	China	86/34/29/45	30.6(R:18–40)/—	3 groups from rural women: euthyroid; subclinical hypothyroidism; overthypothyroidism	healthy rural fertile women	–	ECLIA	–	2.81 ± 1.02/2.21 ± 1.04/1.29 ± 1.21/2.79 ± 1.01	6
Tuten 2014	Turkey	32/49	34.93 ± 8.87/34.16 ± 4.74	premenopausal women with HT under replacement therapy with thyroxine	healty women	in the early follicular phase	ELISA	0.006	4.54 ± 4.59/2.45 ± 1.27	8
Pirgon 2015	Turkey	30/30	15.1 ± 1.4/15.2 ± 1.4	non-obese HT, adolescents, euthyroid	healthy adolescents	in the early follicular phase	ELISA	0.09	10.6 ± 10.4/7.5 ± 7.3	9
Ünsal 2021	Turkey	108/172	32(IQR:27.3–38)/31(25–37)	euthyroid HT	healthy women	in the early follicular phase	ECLIA	–	1.99 ± 2.13/2.41 ± 2.02	7
Akin 2018	Turkey	30/30	14.4 ± 1.85/14.4 ± 1.85	adolescent HT, either euthyroid or subclinical hypothyroidism	euthyroid and auto-antibody negative adolescents	–	ELISA	0.08	1.96 ± 1.13/2.06 ± 1.28	8
Felipe 2021	Mexico	27/25	27.70 ± 4.71/26.2 ± 3.02	primary HT	normal levels of thyroid hormones and negative for anti-TPO antibodies	–	ELISA	0.35	2.42 ± 1.86/2.77 ± 2.50	8
Kucukler 2018	Turkey	21/21/32	35.4 ± 5.9/34.2 ± 4.7/32.0 ± 5.1	subclinical HT; overt HT	healthy women	in the early follicular phase (days 2–4)	ECLIA	–	1.5 ± 1.3/1.8 ± 2.2/2.1 ± 1.4	8
Erol 2016	Turkey	57/50	15.4 ± 1.4/15.1 ± 1.6	euthyroid adolescent HT	healthy adolescents	in the early follicular phase (days 3–5)	ELISA	0.028	4.68 ± 1.61/2.73 ± 1.25	8
Adamska 2021	Poland	39/46	26.8(IQR:24–29)/26(25–27)	euthyroid HT	healthy women	in the early follicular phase (days 3–5)	ELISA	0.08	5.09 ± 3.46/6.48 ± 3.14	8

Notes: '—': No report, HT: Hashimoto's thyroiditis, C:control group, AMH: anti-Müllerian hormone, R: range from minimum to maximum, IQR: interquartile range, ECLIA: electrochemiluminescence immunoassay, ELISA: enzyme-linked immunosorbent assay.

Table 2
Results of sensitivity analysis of all the included studies.

Studies included		Random-effects summary MD(95% CI)	P	I^2 (%)
adolescent girls	**All studies**	1.19 [-0.66, 3.05]	0.21	92
	Without Akin et al.	**1.97 [1.43, 2.51]**	**<0.001**	**0**
	Without Erol et al.	0.67 [-2.01, 3.36]	0.62	46
	Without Pirgon et al.	0.93 [-1.08, 2.94]	0.36	96
Female adults	**All studies**	−0.56 [-0.96, −0.16]	0.006	84
	Without Adamska et al.	−0.52 [-0.93, −0.11]	0.01	85
	Without Felipe et al.	−0.58 [-0.99, −0.16]	0.007	85
	Without Kucukler1 et al.	−0.56 [-0.99, −0.13]	0.01	85
	Without Kucukler2 et al.	−0.58 [-1.00, −0.16]	0.007	85
	Without Shou(1)1 et al.	−0.63 [-1.05, −0.21]	0.003	82
	Without Shou(1)2 et al.	−0.56 [-1.00, −0.11]	0.01	85
	Without Shou(1)3 et al.	−0.47 [-0.87, −0.07]	0.02	82
	Without Shou1 et al.	−0.61 [-1.05, −0.17]	0.007	83
	Without Shou2 et al.	−0.55 [-1.01, −0.09]	0.02	85
	Without Shou3 et al.	−0.45 [-0.79, −0.11]	0.009	73
	Without Tuten et al.	−0.67 [-1.05, −0.29]	0.001	82
	Without Ünsal et al.	−0.57 [-1.02, −0.13]	0.01	85

Seven studies took the blood sample in the early follicular phase and three studies [15,20,21] didn't report the method of sampling. The scores of NOS of all the included studies were 6 and above, which indicating the overall methodological quality of included studies was rated as high (see Table 2).

3.3. The meta analysis of AMH level

Three studies were included in the subgroup of adolescent girls and the pooled results showed AMH values were not significantly different between patients with HT and healthy adolescent girls(MD = 1.19; 95%CI, −0.66-3.05; P = 0.21; I^2 = 92%) [19,20,24]. Seven studies were included in the subgroup of female adults and the pooled results revealed AMH values were significantly lower in the HT group compared with healthy women(MD = −0.56; 95%CI, −0.96 to −0.16; P = 0.006; I^2 = 84%) [15–18,21–23].There was no significant subgroup difference (P = 0.07) between them. The results were presented in Fig. 2.
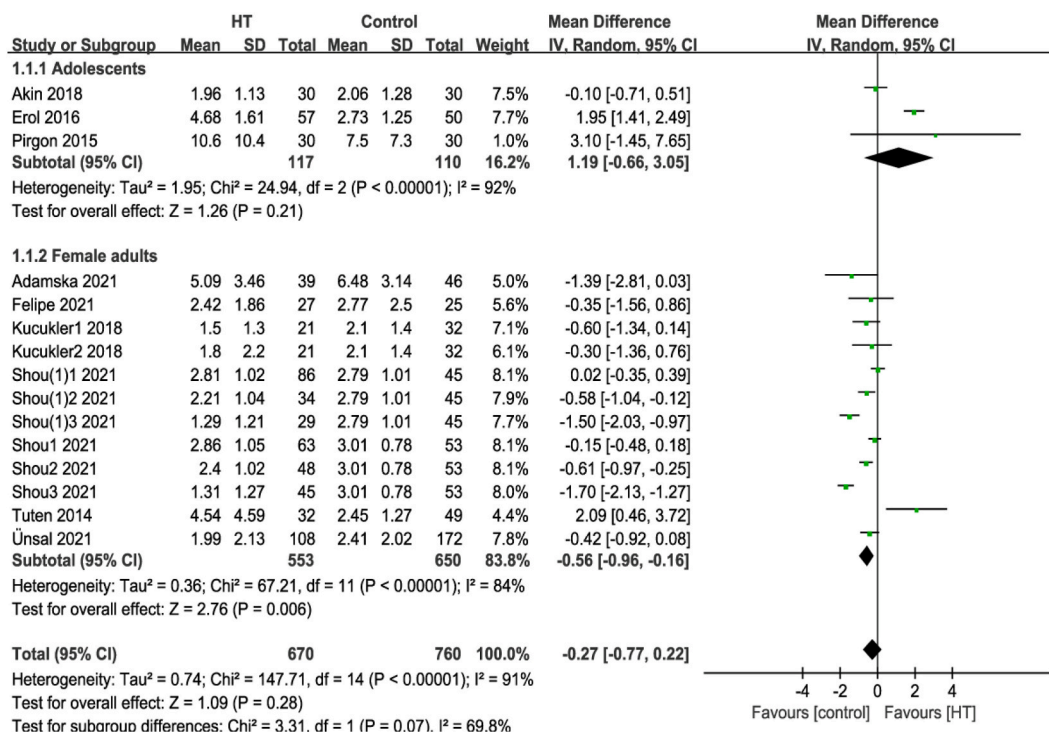

Fig. 2. Meta analysis of AMH level.

3.4. Subgroup analysis based on types of HT

In order to further explore the association between different types of HT and AMH level, subgroup analysis was conducted according to types of HT. The pooled results of two studies including adolescent girls with euthyroid HT suggested AMH values were significantly higher in patients with HT compared with healthy adolescent girls(MD = 1.97; 95%CI, 1.43–2.51; $P < 0.001$; $I^2 = 0$%; presented in Fig. 3) [19,24].

The pooled results in the subgroup of female adults with euthyroid HT showed AMH values were not significantly different between patients with HT and healthy women(MD = −0.21; 95%CI, −0.51-0.09; $P = 0.18$; $I^2 = 38$%) [15–18]. The pooled results in the two subgroups of female adults with subclinical hypothyroidism and overt hypothyroidism both showed AMH values were significantly lower in the HT group compared with healthy women [(MD = −0.60; 95%CI, −0.86 to −0.34; $P < 0.001$; $I^2 = 0$%), (MD = −1.34; 95% CI, −1.94 to −0.74; $P < 0.001$; $I^2 = 65$%)] [15,16,22]. There was significant subgroup difference ($P = 0.003$) between them and it indicated the type of HT may be one of the reasons for heterogeneity.The results were displayed in Fig. 4.

3.5. Sensitivity analysis

The results of sensitivity analysis showed the direction and size of adjusted summary MD changed meaningfully and I^2 was 0 when excluding one study performed by Akin et al. in the subgroup of adolescent girls [20]. Thus, only two studies were retained in the final meta-analysis of subgroup of adolescent girls [19,24].

The direction and magnitude of adjusted summary MD did not change meaningfully in the subgroup of female adults, which revealing the stability of the meta-analysis of subgroup of female adults.

3.6. Publication bias

Although the number of the included studies in each subgroup was less 10, we performed the assessment of publication bias of all the included studies by funnel plot. The funnel plot showed little evidence of asymmetry, which revealing little evidence of publication bias(seen in Fig. 5).The results of Begg's ($P = 0.488$) and Egger's($P = 0.594$) also didn't show evidence of publicationbias.

4. Discussion

Ovarian reserve plays an important role in pregnancy and keeping menstrual regularity and AMH is considered as the most sensitive marker to predict the ovarian reserve in clinical practice [31].In recent years, plenty of researchers explored the association between ovarian reserve and HT using AMH level. Some studies showed HT was associated with decreased AMH level [15–18]. However, some studies showed HT was not related with AMH level [19–22]. The relationship between HT and ovarian reserve is still controversial. No any previous meta-analysis addressing similar question was available for relative appraisal. The present study is the first meta analysis to confirm the relationship between HT and AMH level and the results of the present study could offer the evidence for clinical staffs to evaluate the ovarian reserve in women and adolescent girls with HT by serum AMH level.

In the meta analysis, the pooled analysis in subgroup of adolescent girls with HT revealed AMH values were not significantly different between patients with HT and healthy adolescent girls [19,20,24]. However, inthe subgroup of female adultsAMH values were significantly lower in the HT group compared with healthy women [15–18,21–23].

The results of sensitivity analysis in subgroup of adolescent girls showed the direction and size of adjusted summary MD changed meaningfully and I^2 was 0 when excluding one study performed by Akin et al. , which indicating the heterogeneity probably came from types of HT. Hence, excluding the study performed by Akin et al., the subgroup analysis on the basis of types of HT was conducted. The preliminary results from two studies revealed AMH values were significantly higher in adolescent patients with euthyroid HT compared with healthy adolescent girls. Serum total testosterone and dehydroepiandrosterone sulfate(DHEAS) levelswere significantly higher in adolescents with HT than in controls.Therefore, some researchers thought higher AMH levels in adolescent girls with HT may result from hyperandrogenaemia [32]. Furthermore, impaired systemic antioxidant capacitymay causethe oxidative environment in the follicles, which inturn increasing the serum AMH level, indicating a systemicoxidant–antioxidant imbalance [33].

The pooled results in the subgroup of female adults with euthyroid HT showed AMH values were not significantly different between patients with HT and healthy women [15–18]. The pooled results in the two subgroups of female adults with subclinical hypothyroidism and overt hypothyroidism both showed AMH values were significantly lower in the HT group compared with healthy women
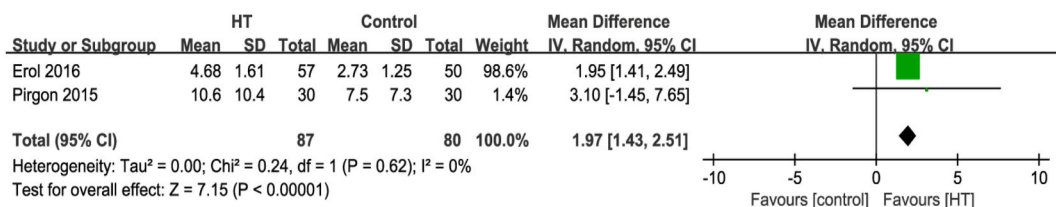

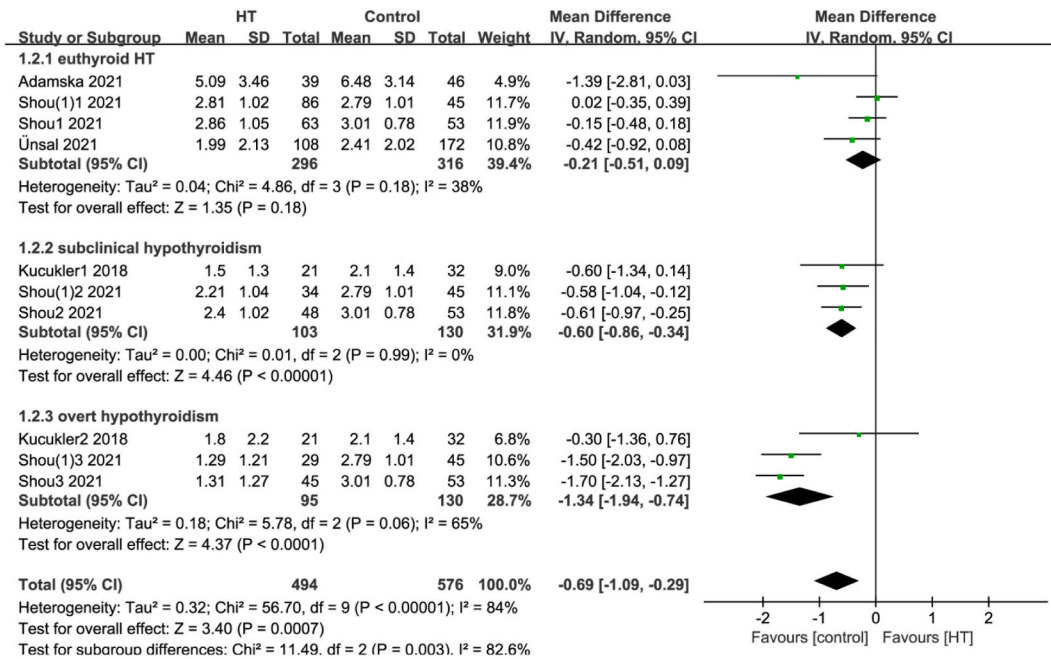**Fig. 3.** Meta analysis of AMH level in subgroup of adolescent girls.

Study or Subgroup	HT Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
1.2.1 euthyroid HT									
Adamska 2021	5.09	3.46	39	6.48	3.14	46	4.9%	-1.39 [-2.81, 0.03]	
Shou(1)1 2021	2.81	1.02	86	2.79	1.01	45	11.7%	0.02 [-0.35, 0.39]	
Shou1 2021	2.86	1.05	63	3.01	0.78	53	11.9%	-0.15 [-0.48, 0.18]	
Ünsal 2021	1.99	2.13	108	2.41	2.02	172	10.8%	-0.42 [-0.92, 0.08]	
Subtotal (95% CI)			**296**			**316**	**39.4%**	**-0.21 [-0.51, 0.09]**	
Heterogeneity: Tau² = 0.04; Chi² = 4.86, df = 3 (P = 0.18); I² = 38%									
Test for overall effect: Z = 1.35 (P = 0.18)									
1.2.2 subclinical hypothyroidism									
Kucukler1 2018	1.5	1.3	21	2.1	1.4	32	9.0%	-0.60 [-1.34, 0.14]	
Shou(1)2 2021	2.21	1.04	34	2.79	1.01	45	11.1%	-0.58 [-1.04, -0.12]	
Shou2 2021	2.4	1.02	48	3.01	0.78	53	11.8%	-0.61 [-0.97, -0.25]	
Subtotal (95% CI)			**103**			**130**	**31.9%**	**-0.60 [-0.86, -0.34]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 2 (P = 0.99); I² = 0%									
Test for overall effect: Z = 4.46 (P < 0.00001)									
1.2.3 overt hypothyroidism									
Kucukler2 2018	1.8	2.2	21	2.1	1.4	32	6.8%	-0.30 [-1.36, 0.76]	
Shou(1)3 2021	1.29	1.21	29	2.79	1.01	45	10.6%	-1.50 [-2.03, -0.97]	
Shou3 2021	1.31	1.27	45	3.01	0.78	53	11.3%	-1.70 [-2.13, -1.27]	
Subtotal (95% CI)			**95**			**130**	**28.7%**	**-1.34 [-1.94, -0.74]**	
Heterogeneity: Tau² = 0.18; Chi² = 5.78, df = 2 (P = 0.06); I² = 65%									
Test for overall effect: Z = 4.37 (P < 0.0001)									
Total (95% CI)			**494**			**576**	**100.0%**	**-0.69 [-1.09, -0.29]**	
Heterogeneity: Tau² = 0.32; Chi² = 56.70, df = 9 (P < 0.00001); I² = 84%									
Test for overall effect: Z = 3.40 (P = 0.0007)									
Test for subgroup differences: Chi² = 11.49, df = 2 (P = 0.003), I² = 82.6%									

Favours [control]   Favours [HT]

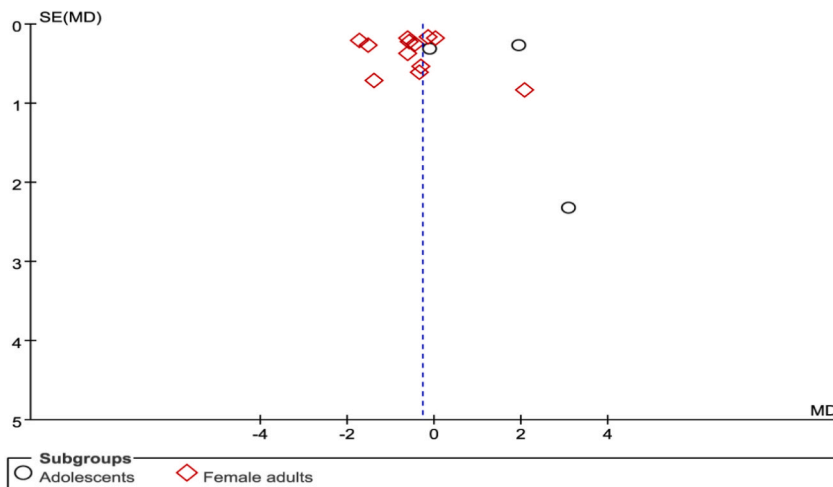**Fig. 4.** Meta analysis of AMH level in subgroup of female adults.

Fig. 5. The funnel plot of 10 studies.

[15,16,22]. Thyroid hormones(TH) are involved in regulating the menstrual cycle and oocytes possess triiodothyronine receptors and TH receptors on the cells' surface whichaffecting the secretion of follicle-stimulating hormone(FSH) and luteinizing hormone. Hence, the incidence of the disturbances of menstrual cycle and even the premature ovarian failure(POF) is increased in patients with thyroid dysfunction [34]. The thyroid function of the patients with euthyroid HT is still normal, so euthyroid HT didn't have impact on ovarian reserve.

It is obliged to admit the fact that there are still some limitations in the meta analysis including 10 studies involving 1202 individuals. Eventhough the results of Begg's ($P = 0.488$) and Egger's($P = 0.594$) also didn't show evidence of publicationbias, we did not try to uncover unpublished observations and not include studies with insufficient information to estimate an adjusted MD, which still could bring publication bias. Moreover, I^2 was larger than 50% for the subgroup of overt HT in female adults, but we couldn't have a further exploration with the limited numbers of included studies and the heterogeneity didn't have an obvious impact on the pooled results.Finaly, the sample size is not adequately large, especially in subgroup of adolescent girls, which limited its strengths of evidence. More multi-center case-control studies are still required.

5. Conclusions

With the present findings, AMH values were not significantly different between patients with euthyroid HT and healthy women. Ovarian reserve evaluated by serum AMH concentration is affected by adult patients with subclinical hypothyroidism and overt hypothyroidism. The AMH level was significantly higher in euthyroid adolescent girls. However, more large multi-center studies with more rigorous methodology are required to improve the quality of evidence before determining clinical decisions owing to the presence of limitations.

Author contribution statement

Juan Cui Shi: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Rui Tian Shao; Dong Xu Zhao: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Bin Wang: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e19204.

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