

# The correlation between serum Ca-125 level and clinical pregnancy in in vitro fertilization (IVF): A meta-analysis

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## Research

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## Abstract

**Background** Several studies had investigated the role of serum Ca-125 in clinical pregnancy of patients undergoing in vitro fertilization (IVF); however, their conclusions had been inconsistent. This study aimed to evaluate the correlation between serum Ca-125 level and clinical pregnancy in IVF.

**Methods** We systematically review the studies in the databases of Medline OvidSP, EMBASE OvidSP and Cochrane (CENTRAL Central Register of Controlled Trials). Studies on the correlation between serum Ca-125 level and clinical pregnancy in patients undergoing IVF with or without Intracytoplasmic sperm injection (ICSI) were considered. The pooled standardized mean difference (SMD) with 95% confidence intervals (CIs) was used in the analysis.

**Results** Seven studies involving 558 patients were included. The meta-analysis showed that there was no significant difference in the serum Ca-125 level before embryo transfer (ET) between clinical pregnant group and nonpregnant group (SMD 0.72; 95% CI [0.01, 1.43],  $P = 0.05$ ,  $I^2 = 88\%$ ), and the same conclusion was also reached in patients without endometriosis (SMD 0.31; 95% CI [-0.53, 1.16],  $P = 0.47$ ,  $I^2 = 89\%$ ); However, after embryo transfer, the result showed that the Ca-125 level has a small but significantly increase in the clinical pregnant group than in the nonpregnant group (SMD 0.39; 95% CI [0.09, 0.69],  $P = 0.01$ ,  $I^2 = 0\%$ ).

**Conclusions** Before ET, there was no significant correlation between serum Ca-125 level and clinical pregnancy in IVF; After ET, the Ca-125 level has a small but significantly increase in the clinical pregnant group than in the nonpregnant group, and it might reflect a successful interaction between the embryo and the endometrium in that time period.

## Background

Prediction of clinical pregnancy is rapidly becoming an important objective in in vitro fertilization (IVF). On the one hand, pregnancy in IVF have a higher risk of obstetric and perinatal complications than spontaneous pregnancies; on the other hand, most IVF patients are successfully fertilized and get embryos transferred (ET), but only a relatively small percentage of transferred embryos actually implant and develop into viable pregnancies.

Successful implantation after ET has been shown to depend on two factors: good quality of transferred embryos; and well-prepared endometrium [1]. At present, endometrial receptivity is judged generally by Ultrasound parameters, such as endometrial thickness and pattern, and Doppler study of uterine arteries and subendometrial flow [2]. However, morphological assessments of endometrial receptivity have been subjective and disregards embryo interaction [1]. The idea that some objective parameters could ascertain the endometrial receptivity in a non-invasive and cost efficient way in an Assisted Reproductive Technology cycles is interesting and has important clinical significance.

Cancer antigen 125 (Ca-125) is a cell-surface antigenic determinant on a high molecular-weight glycoprotein, as a well-established marker it is mainly used to diagnose endometriosis and epithelial cell ovarian cancer [3, 4]. Ca-125 can be measured in the serum. Although the primary source of serum Ca-125 levels is controversial, some studies have found that endometrium may be one of the sources of serum Ca-125: (1) Ng et al. detected Ca-125 in the uterine flushings fluid [5]; (2) Ca-125 was detected in vitro endometrial tissue culture medium [6]; (3) The serum Ca-125 level was increased due to endometrial destruction during menstrual period [7]. If endometrium is the main source of serum Ca-125, then Ca-125 may be used as an indicator of endometrial receptivity in IVF. In addition, several studies had investigated the role of serum CA-125 in clinical pregnancy of patients undergoing IVF; however, their conclusions were inconsistent. Therefore, we conducted a meta-analysis to evaluate the correlation between serum Ca-125 level and clinical pregnancy in in vitro fertilization.

## Methods

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [8].

### Exclusion criteria and inclusion criteria

Inclusion and exclusion criteria were established prior to literature search. This meta-analysis focused on the correlation between serum Ca-125 level and clinical pregnancy in patients undergoing IVF with or without Intracytoplasmic sperm injection (ICSI). The inclusion criteria were as follows: (1) Case-control, cohort or cross-sectional studies; (2) All patients were women who underwent IVF treatment with or without ICSI, regardless of the ovarian stimulation protocol employed; (3) Study provided data on serum Ca-125 levels in clinical pregnant and nonpregnant groups, no limit was given for Ca-125 measurement methods; (4) Clinical pregnancy was clarified as a positive heart action or Intrauterine pregnancy sac in transvaginal ultrasound after ET; (5) When multiple studies may contain the same study population, only the most complete study was included; (6) Available full text in English. We excluded: (1) Study contained overlapping or insufficient data; (2) Reviews, editorials, commentaries, animal experiments, and individual case reports.

## **Search Strategy**

The studies in the databases of Medline OvidSP, EMBASE OvidSP and Cochrane (CENTRAL Central Register of Controlled Trials) were systematically reviewed until October 25, 2019. The search strategy was shown in Additional file 1. We also manually searched the references of the included studies and reviews for additional studies.

## **Study selection and quality assessment**

After importing the search results into EndNote X9, duplicated studies were excluded. Two review authors (Li Z and Wang XL) independently screened the studies based on both the titles and abstracts of the selected studies, then retrieved the full text articles for those relevant and determine whether it meets the inclusion criteria. The quality of the included studies were assessed using the Newcastle–Ottawa scale (NOS) for cohort studies, which evaluates studies according to the following three domains: selection of subjects, comparability, and assessment of the results [9]. We rated the studies as 'high quality' if they had a score  $\geq 5$ ; otherwise, the studies were rated as 'low quality'. A discrepancies between Li and Wang was resolved through discussion and consensus with a third reviewer (Zhang Han).

## **Extraction of data**

Two researchers (Wang XL, Li Z) extracted data independently using a pre-designed data extraction table. A third review author (Zhang Han) resolved any disagreements between the two researchers. We extracted data on study design, number of participants, patients' age, publication year, included and excluded criteria of patients, ovarian stimulation protocols, and time of blood sample collection, methods of Ca-125 detected, the mean and standard deviation (SD) of serum Ca-125 level (In case no means and SD were reported, we used medians, interquartile ranges (IQRs), or ranges to estimate them based on the methods advocated by Wan et al) [10].

## **Synthesis of results and assessment of heterogeneity**

All analyses were performed using Review Manager 5.0 software. Statistical heterogeneity was tested with the Q test (chi-square) and calculated  $I^2$  values. When chi-square test  $p < 0.1$  and the  $I^2 > 50\%$ , we thought that there was significant heterogeneity among studies, in which case, we used the randomized effect model, otherwise the fixed effects model was used. We assessed clinical heterogeneity by performing subgroup analyses for different detection methods of Ca-125. We expected the different methods of Ca-125 detected among studies, so the serum Ca-125 level was shown as standardized mean difference (SMD) with corresponding 95% confidence intervals (95% CIs). The  $P < 0.05$  values could be considered as statistically significant.

## **Sensitivity analysis and assessment of publication bias**

To evaluate stability and reliability of the meta-analysis, we performed sensitivity analysis whereby: 1. Assessed the influence of each individual study on the pooled SMD by removing each study individually; 2. Different models (fixed effect model or randomized effect model) were used. If enough studies (10 or more) were found, we planned to use a funnel plot to explore the possibility of publication bias.

## Result

### Study selection

The preliminary database search retrieved 185 citations. After the initial exclusion of 32 duplicate articles, the remaining 157 articles were screened based on title and abstract. Then we retrieved 32 full-text articles reading, of which we excluded 25. Finally, seven articles were included in our analysis. No articles were included by manual search. The details of study selection was shown in Fig. 1.

#### Characteristics and quality assessment of the included studies

The various baseline characteristics of including studies were shown in Table 1. A total of 7 studies involving 558 patients were included, and the sample sizes of included studies were ranged from 33 to 182. Three studies directly reported mean and SD [11–13], while data for 4 studies [14–17] that did not were transformed according to the method proposed by Wan et al [10]. Two studies detected serum Ca-125 by enzyme immunoassay method [15, 17], while four studies [11, 12, 14, 16] used Immunoradiometric methods and only one [13] used Chemiluminescence method. The quality assessment of the included studies was summarised in Table 2. All studies had a score  $\geq 5$  and were rated as 'high quality'.

Table 1  
The various baseline characteristics of including studies

Study author, year	Number of patients in study	Age (years)		Causes of infertility	Ovarian stimulation protocols	ART protocol	Sample time	Methods of CA-125 detection
		Clinical pregnant	Nonpregnant					
Urbancsek 2005	182	31 (28–35) Median (25–75 centile range)	32 (30–36) Median (25–75 centile range)	NR	GnRH-a, HMG, FSH	IVF, ICSI	post-ET day 11	Immunoradiometric
Hauzman 2005	112	31.1 ± 3.8 Mean ± SD	30.9 ± 3.5 Mean ± SD	male/tubal/unexplained	GnRH-a, HMG, FSH	IVF, ICSI	on day 1 and on the day of oocyte pickup	Immunoradiometric
Vujisic 2002	33	34 (28–42) Median (range)	35 (31–42) Median (range)	Tubal factor/ Unexplained Male factor	GnRH-a, HMG	IVF	on the day of human chorionic gonadotropin (hCG) administration and on the day of ET	enzyme immunoassay
Baalbergen 2000	44	33.0 (27–40) Median (range)	32.5 (24–41) Median (range)	NR	GnRH-a, HMG	IVF	before OPU, 14 days after ET (day ET + 14) and, after the establishment of a clinical pregnancy, on day ET + 21	enzyme immunoassay
Tavmergen 2001	75	31.54 ± 0.69 Mean ± SEM	32.6 ± 0.77 Mean ± SEM	Male factor, Idiopathic, Tubal, Tubal + male factor	GnRH-a, HMG, FSH	ICSI	on the day before and on the day of HCG administration, and on the day of oocyte retrieval	Chemiluminescence
Brandenberger 1998	86	34 (26–38) Median (range)	34 (25–41) Median (range)	NR	GnRH-a, HMG	IVF	2 and/or 3 days before OPU (day hCG/hCG-1), on the day of OPU, and on the day of ET	Immunoradiometric
Chryssikopoulos 1996	26	31.1 ± 4.3 <sup>a</sup> Means ± SD		NR	GnRH-a, FSH, HMG	IVF	on the day of hCG administration, on the day of oocyte retrieval, and on the day of ET	Immunoradiometric

NR = not report; GnRH-a = gonadotrophin-releasing hormone agonist; HMG = human menopausal gonadotrophin; FSH = Follicle-stimulating hormone; IVF = in vitro fertilization; ICSI = Intracytoplasmic sperm injection; ET = embryos transferred. <sup>a</sup>The data showed the age of the total population.

Table 2  
The NOS quality assessment of the included studies

Studies	Score for Selection				Score for Comparability		Score for Outcome			Aggregate score	Quality
	Item 1	Item 2	Item 3	Item 4	Item 1	Item 2	Item 1	Item 2	Item 3		
Urbancsek 2005	0	0	1	0	1	1	1	1	1	6	High
Hauzman 2005	1	1	1	0	1	1	1	1	1	8	High
Vujisic 2002	1	1	1	0	0	1	1	1	1	7	High
Tavmergen 2001	0	0	1	0	1	1	1	1	1	6	High
Baalbergen 2000	1	1	0	0	0	1	1	1	1	6	High
Brandenberger 1998	1	1	1	0	0	1	1	1	0	6	High
Chryssikopoulos 1996	1	1	0	0	0	1	1	1	1	6	High
NOS: Newcastle-Ottawa scale											

The correlation between serum Ca-125 level before ET and clinical pregnancy in IVF

A total of 349 patients in 6 studies reported the correlation between serum Ca-125 level before ET and clinical pregnancy in IVF, including 132 clinical pregnant and 217 nonpregnant patients [11–13, 15–17]. When there were multiple blood sample collection times, we considered the values of the closest to the day of ET. The meta-analysis showed that there was no significant difference in the serum Ca-125 level before ET between clinical pregnant group and nonpregnant group (SMD 0.72; 95% CI [0.01, 1.43],  $P = 0.05$ ,  $I^2 = 88\%$ ; Fig. 2).

The correlation between serum Ca-125 level after ET and clinical pregnancy in IVF

A total of 229 patients in 2 studies reported the correlation between serum Ca-125 level after ET and clinical pregnancy in IVF, including 162 clinical pregnant and 67 nonpregnant patients [14, 17]. The result showed that the Ca-125 level has a small but significantly increase in the clinical pregnant group than in the nonpregnant group (SMD 0.39; 95% CI [0.09, 0.69],  $P = 0.01$ ,  $I^2 = 0\%$ ; Fig. 3).

The correlation between serum Ca-125 level before ET and clinical pregnancy in Patients without endometriosis in IVF

Considering that Ca-125 concentrations are known to be elevated in endometriosis [18], We excluded studies that might include patients with endometriosis [11, 16] before ET. The result showed that there was no significant difference in the serum Ca-125 level between clinical pregnant group and nonpregnant group (SMD 0.31; 95% CI [-0.53, 1.16],  $P = 0.47$ ,  $I^2 = 89\%$ ; Fig. 4).

### Subgroup analysis

Before embryo transfer, two studies detected serum Ca-125 level by enzyme immunoassay [15,17], whereas three studies used Immunoradiometric methods [11,12,16], and the remain one used Chemiluminescence [13]. Subgroup analysis showed Ca-125 level was significantly higher in the clinical pregnant group than in the nonpregnant group by Chemiluminescence (SMD 1.49; 95% CI [0.97, 2.01],  $P < 0.001$ , 1 study) or Immunoradiometric methods (SMD 1.12; 95% CI [0.18, 2.05],  $P = 0.02$ , 3 study), but not in the enzyme immunoassay subgroup (SMD -0.34; 95% CI [-0.83, 0.14],  $P = 0.16$ , 2 study) (Fig 5).

### Sensitivity analysis and publication bias

Considering that the number of the included studies on Ca-125 level after ET was small, we didn't conduct sensitivity analyses about it. We performed a sensitivity analysis for the Ca-125 level before ET, and found that Ca-125 level before ET was significantly higher in the clinical pregnant group compared with the nonpregnant group when the study by Baalbergen et al. [17] or Vujisic et al. [15] was excluded. In addition, the conclusion on Ca-125 level before ET also changed when we used different models. There were insufficient data for any publication bias analysis.

## Discussion

This meta-analysis aimed to assess the correlation between serum Ca-125 level and clinical pregnancy in in vitro fertilization. Before ET, our meta-analysis showed that there was no significant correlation between serum Ca-125 level and clinical pregnancy in IVF, and the same conclusion was also reached in patients without endometriosis; After ET, the result revealed that there was a significant correlation between serum Ca-125 level and clinical pregnancy in IVF.

Although we included women who underwent IVF treatment with or without ICSI, five studies excluded patients with endometriosis [12–15, 17]. It is likely that Ca-125 concentrations are known to be elevated in endometriosis [18]; therefore, evidence related to the correlation between serum Ca-125 level in endometriosis and pregnant outcome is still lacking, which may reduce the overall applicability of the evidence.

We found that there was significant heterogeneity among studies on the outcome of correlation between serum Ca-125 level before ET and clinical pregnancy in IVF ( $I^2 = 88\%$ ). The sources of heterogeneity might be explained by the differences in the methods of Ca-125 detected, the time of sample collected, the inclusion and exclusion of patients (eg. Some studies excluded patients with endometriosis), and the ovarian stimulation protocols. However, we found no reduction in heterogeneity when we excluded studies that might include patients with endometriosis, and the same as we only included studies which used Immunoradiometric methods. This suggests that patient inclusion criteria or testing methods are not at least the only sources of heterogeneity. The sensitivity analysis found that the conclusion where there was no significant difference in the serum Ca-125 level before ET between clinical pregnant group and nonpregnant group had changed after excluding the study by Baalbergen et al. or Vujisic et al [15,17], which may be attributed to Ca-125 assay used, both of them used enzyme immunoassay. Unfortunately, enzyme immunoassay is a less sensitive detection methods of Ca-125 compared with Immunoradiometric and Chemiluminescence methods [19]. In addition, subgroup analyses showed that there was a significant correlation between serum Ca-125 level before ET and clinical pregnancy in IVF by Immunoradiometric or Chemiluminescence methods; which indicated that detecting Ca-125 using more sensitive assays can better predict pregnant outcome in IVF. We should be cautious to assess the impact of conclusion on Ca-125 level before ET, because we used randomized effect model that dealt with the heterogeneity of data by increasing the weight of small sample data and reducing the weight of large sample data [20], and the direction of effect altered when we used fixed effect model; Therefore, further studies should increase sample sizes to reduce accidental errors.

First of all, the concentration of serum Ca-125 fluctuated throughout the menstrual cycle. The different observations reveal that Ca-125 levels were significantly elevated during menstruation [21, 22]. The reason may be that the endometrium was destroyed during menstruation, which caused Ca-125 to be released into the blood; So Ca-125 was somehow associated with the integrity of the endometrium. Secondly, immunohistochemistry of Ca-125 showed that the concentration of Ca-125 in endometrium was 20-fold higher than that in ovary and 2-fold higher than those in fallopian tubes; In addition, only in the endometrium Ca-125 content has a significant circulatory change [23]. This suggests that endometrium might be the main source of serum Ca-125, and therefore, an endocrine or a paracrine function would be possible. However, our meta-analysis showed no correlation between serum Ca-125 level before ET and clinical pregnancy in IVF, the same as patients without endometriosis. The reasons for this phenomenon may be as follows: (1) Although there is some evidence that endometrium is one of the sources of serum Ca-125, other factors (eg. Endometrial thickness, endometrial volume, endometrial pattern, pulsatility index and resistance index of the subendometrial blood flow) play a greater role in the endometrial receptivity [24]; (2) The achievement of a clinical pregnancy in IVF results from too many factors, such as maternal age and embryo quality, so serum CA-125 level can not directly predict the success of pregnancy in an IVF cycle; (3) Despite the controversy, studies have shown changes of Ca-125 concentration during ovarian stimulation [16, 25], hence, changes of the serum Ca-125 level due to ovarian stimulation may mask the changes caused by endometrium.

After ET, the meta analysis showed that the serum Ca-125 level had a small but significantly increase in the clinical pregnant group than in the nonpregnant group. In the first trimester of pregnancy, serum Ca-125 level rised in patients with vaginal bleeding and miscarriage [26, 27]. Therefore, the increase of Ca-125 concentration might indicate the destruction of decidua. However, these observations were all made over 5 weeks gestation. In our meta analysis, there were 2 studies which reported the correlation between serum Ca-125 level after ET and clinical pregnancy in IVF, one study detected Ca-125 on or closer to post-ET day 11, the another one was on 14 days after ET. Hence, higher Ca-125 levels might reflect a successful interaction between the embryo and the endometrium in that time period.

This study has several limitations. Firstly, we conducted a comprehensive search of the corrlation between serum Ca-125 level and clinical pregnancy in IVF. However, It is possible that our findings on serum Ca-125 level before ET cannot be interpreted as truly negative because of the small sample sizes and significant heterogeneity between studies; Secondly, the evidence on Ca-125 level after ET between clinical pregnancy and nonpregnancy is limited, as only two trials were included for our investigation, and needs to be further investigated; Third, publication bias could not be assessed because of the limited number of studies; Fourth, four studies didn't directly report mean and its SD, and we employed the method recommended by Wan et al to handle the dates [10], and it may result certain deviation.

## Conclusion

Our meta-analysis was the first systematic review to confirm the correlation between serum Ca-125 and clinical pregnancy in IVF. This meta-analysis revealed that there was no significant correlation between serum Ca-125 level before ET and clinical pregnancy in IVF, and the same conclusion was also reached in patients without endometriosis; After ET, the Ca-125 level had a small but significantly increase in the clinical pregnant group than in the nonpregnant group, and it might reflect a successful interaction between the embryo and the endometrium in that time period.

## Declarations

**Abbreviations:** IVF:in vitro fertilization, ET:embryos transferred, Ca-125:Cancer antigen 125, ICSI:Intracytoplasmic sperm injection.

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There was no funding source in this study.

## Availability of data and material

All data generated or analysed during this study are included in this published article.

## Authors' contributions

Took part in the literature search, study characteristics assessment, study quality assessment: WXL, LZ, ZH; took part in the data analysis, interpretation of statistics: SC, TT; conducted the preliminary idea and drafted the paper: XQ; critically reviewed the paper XQ, LRZ.



## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Competing interests

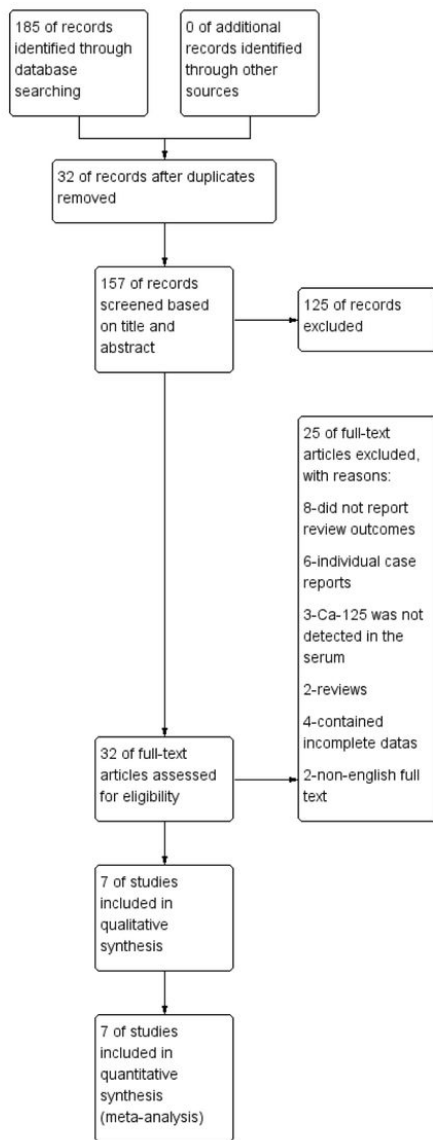
The authors declare that they have no competing interests.

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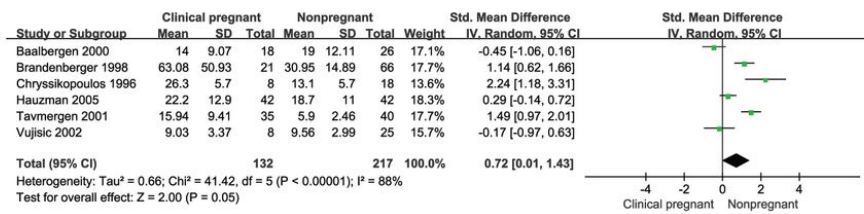
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## Figures



**Figure 1**

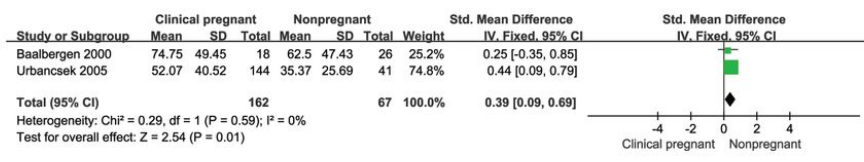
The details of study selection



**Figure 2**

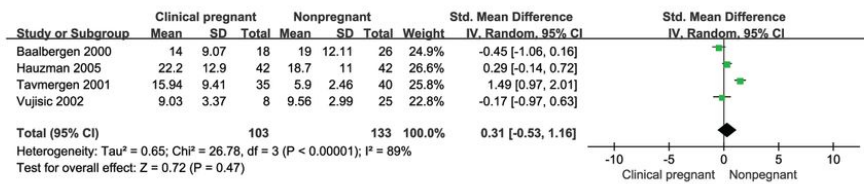
Forest plot of comparison: Clinical pregnant group vs Nonpregnant group, Outcome: serum Ca-125 level before embryos transferred.

Fig 3: Forest plot of comparison: Clinical pregnant group vs Nonpregnant group, Outcome: serum Ca-125 level after embryos transferred.



**Figure 3**

Forest plot of comparison: Clinical pregnant group vs Nonpregnant group, Outcome: serum Ca-125 level after embryos transferred.



**Figure 4**

Forest plot of comparison: Clinical pregnant group vs Nonpregnant group in patients without endometriosis, Outcome: serum Ca-125 level before embryos transferred.

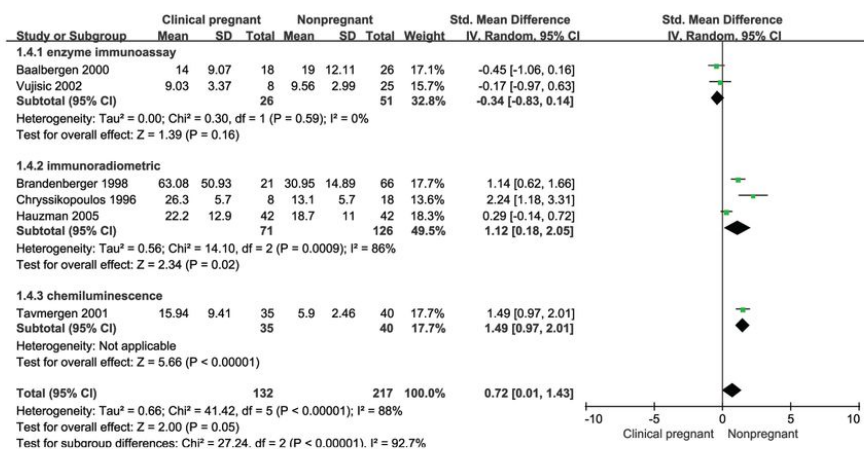


Figure 5

Forest plot of comparison: Clinical pregnant group vs Nonpregnant group, Outcome: Subgroup analysis of different methods of Ca-125 detected before embryos transferred.

## Supplementary Files

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