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The Value of Serum B-Subunit of Human Chorionic Gonadotropin Level in Prediction of Treatment Response to Methotrexate in Management of Ectopic Pregnancy; a Systematic Review and Meta-Analysis

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Abstract

***Background*:** No consensus has been reached on prognostic value of serum concentration of β (beta) subunit of human chorionic gonadotropin (β-hCG) in treatment response to methotrexate in management of ectopic pregnancy. Therefore, the present study aimed to evaluate this subject through a systematic review and meta-analysis.

***Materials and Methods*:** An extensive literature search on online databases was performed. All studies performed on ectopic pregnancy patients treated by methotrexate from all age groups were included. After collecting data, random effect models were used to calculate the pooled standardized mean difference (SMD) of β-hCG level in treatment success and treatment failure groups. Finally, pooled performance screening characteristics of serum β-hCG level were assessed in different cut offs.

***Results*:** Finally, 51 articles were included in meta-analysis. Overall treatment success rate of methotrexate was 84% [95% confidence interval (CI): 84-85 percent]. A negative association was found between serum β-hCG level and the treatment response before intervention (SMD= -1.10, 95% CI: -1.39 to -0.88). In addition, pooled sensitivity, specificity, and prognostic odds ratio of β-hCG in the 2000 mIU/mL cut off were: 0.75 (0.65-0.82), 0.68 (0.58-0.82), and 6.0 (5.0-8.0), respectively.

***Conclusion*:** The present meta-analysis showed that serum β-hCG concentration before treatment could predict success of methotrexate in management of ectopic pregnancy.

***Key Words*:** Beta Subunit, Chorionic Gonadotropin, Ectopic, Methotrexate, Pregnancy.

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1- INTRODUCTION

Ectopic pregnancy (EP) is a major public health problem worldwide and its incidence has been increasing recently (1, 2). Although maternal death due to ectopic pregnancy has recently decreased, it is still a leading cause of mortality in the first trimester (3). Therefore, early management of ectopic pregnancy is very important.

Expectant management, surgical, and medical strategies are alternative treatments for EP (4). Methotrexate as a folic acid antagonist is routinely used in medical treatment of EP (5, 6). It has been shown that Methotrexate is safe and its efficacy is similar to that of surgical interventions (7, 8). However, the success rate of Methotrexate has been reported to vary from 47% to 95% (9, 10). Various prognostic factors have been proposed for predicting treatment response to methotrexate including serum concentration of β-subunit of human chorionic gonadotropin (β-hCG), ectopic pregnancy diameter and etc. (11-13). However, no consensus has been reached on many of these factors.

Several studies have found association between lower pre-treatment concentrations of β-hCG with high success rates of methotrexate in management of EP (14, 15). However, no comprehensive conclusion has been made about the prognostic value of β-hCG in treatment response to methotrexate. Therefore, the study aimed to assess this subject through a systematic review and meta-analysis.

2- MATERIALS AND METHODS

2-1. Search strategy

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (16). A literature search using a structured predefined search string was performed in online databases (Medline, SCOPUS, Cochrane library, and EMBASE databases) with no temporal restrictions. The search was limited to studying human participants. Validated combinations of MeSH and EMTREE terms and key words were used.

These search terms in PubMed were: "Pregnancy, Ectopic"[Mesh] OR "Ectopic Pregnancies"[tiab] OR "Pregnancies, Ectopic"[tiab] OR "Pregnancy, Interstitial"[Mesh] OR "Interstitial Pregnancy"[tiab] OR "Pregnancy, Extrauterine"[tiab] OR "Pregnancy, Abdominal"[tiab] OR "Extrauterine Pregnancy"[tiab] OR "Extrauterine Pregnancies"[tiab] OR "Pregnancy, Cornual"[tiab] OR "Pregnancy, Ovarian"[tiab] OR "Pregnancy, Angular"[tiab] OR "Pregnancy, Heterotopic"[tiab] OR "Ectopic Pregnancy"[tiab] OR "tubular pregnancy"[tiab] OR "pregnancy"[tiab] OR "Chorionic Gonadotropin, beta Subunit, Human"[Mesh] OR "Chorionic Gonadotropin"[tiab] OR "Beta-hCG"[tiab] OR "β-hCG"[tiab] OR "Human Chorionic Gonadotropin"[tiab] AND "Methotrexate"[Mesh] OR "Amethopterin"[tiab] OR "Methotrexate, (D)-Isomer"[tiab] OR "Methotrexate, (DL)-Isomer"[tiab] OR "Mexate"[tiab] OR "Methotrexate Sodium"[tiab] OR "Sodium, Methotrexate"[tiab] OR "Methotrexate, Disodium Salt"[tiab] OR "Methotrexate, Sodium Salt"[tiab] OR "Methotrexate Hydrate"[tiab] OR "Hydrate, Methotrexate"[tiab] OR "Methotrexate, Dicesium Salt"[tiab] OR "Dicesium Salt Methotrexate"[tiab].

In addition, we checked cross-references of all articles meeting the inclusion criteria and previous reviews to identify additional articles. Moreover, non-indexed reports were also searched in Google search engine and Google scholar. The authors of the related articles were also asked to provide any unpublished data that were not registered or any unpublished dissertations. The ProQuest database was

also precisely searched for related theses. In cases where data were not available online, the corresponding author of article was contacted. A reminder was also sent to the author after one week of no response. If no answer was received, the co-authors were contacted through social networks such as ResearchGate and LinkedIn. We performed this wide search to include the maximum number of relevant patients. Also, contacting the authors of all the studies that met the inclusion criteria was attempted and unpublished data and abstracts were requested.

2-2. Selection of study and data extraction

All potentially eligible original papers were independently summarized by two authors (M.Y., P.G). A third author (S.S) was consulted in case of disagreement. We included all cohort studies, case-control studies, and clinical trials of ectopic pregnancy patients treated by methotrexate from all age groups. These studies should have measured serum or plasma concentrations of β-hCG at least before intervention and should have assessed the treatment outcome. The diagnosis of ectopic pregnancy should have been confirmed based on ultrasound assessment or presence of elevated level of β-hCG. Animal studies, lack of comparison results based on β-hCG level in treated and control groups, and poor quality of study were defined as exclusion criteria.

Data were extracted independently by two reviewers using a standardized data abstraction form. We collected information related to study design, patient characteristics (age, gestational age), protocol of treatment (single or multiple dose), type of drug administration (intramuscular, intravenous, local), sample size, data collection methods (prospective or retrospective), sampling (consecutive or convenience), success rate and failure rate, laboratory aspects of β-hCG testing (type of assay used, timing of sampling), treatment response criteria, β-hCG cut off value, and outcome of treatment. We contacted authors for clarification about the missing data.

3-2. Quality assessment

The quality of the eligible studies was assessed using Methods Guide for Effectiveness and Comparative Effectiveness Reviews developed by Agency for Healthcare Research and Quality (AHRO) (17). Two reviewers (M.Y., P.G.) independently reviewed and rated of the papers into three levels of "good", "fair", or "poor". Quality assessment was carried out based on impact of methodological quality on the reported outcomes, accounting for study design, and presence of bias (performance, recording, and reporting). Inter-rater reliability between two reviewers was 87%. Disagreements were discussed with a third reviewer.

4-2. Statistical analysis

Statistical analysis was performed using the Stata software, version 12.0 (Stata Corp, College Station, TX, USA). Data were extracted and mean and standard deviation value of serum β-hCG were recorded. Effect sizes were calculated as the standardized mean difference (SMD) with 95% confidence interval (CI) using Hedges' g. The authors were contacted if the paper did not report mean values or standard deviations (SD). If they did not respond, estimation methods were used to calculate the mean and SD (18). Sistrom and Mergo method was used in cases where the information were reported as graphs (19).

Statistical heterogeneity was measured using the I^2 and χ^2 –tests. For this purpose $P < 0.10$ represented a significant statistical heterogeneity (20). Random effects models were generated for data analysis because the test of heterogeneity

was significant. In addition screening performance characteristics (area under the curve, sensitivity, specificity, prognostic odds ratio) of serum β-hCG level were assessed. For this purpose, Patients were divided into two groups: successful response to treatment and failure. Treatment failure was defined as a drop of less than 15% in β-hCG concentration compared to the baseline value after one week or failure result yielded from ultrasound examination. Then, the cut off value of β-hCG level were recorded. Based on this value, data were summarized as true positive (true prediction of response to treatment), true negative (true prediction of treatment failure), false positive (false prediction of response to treatment), and false negative (false prediction of treatment failure) values. Finally, area under the curve, sensitivity, specificity, and prognostic odds ratio of serum β-hCG level in different cut points were evaluated.

Publication bias was assessed using funnel plots, formal Egger's and Begg's tests (21) and Deeks funnel plot asymmetry test (22). A two sided P-value <0.05 was considered as statistically significant.

3- RESULTS

3-1. The characteristics of included studies

A total of 4,630 non-duplicate articles were identified using search strategies from which 713 potentially relevant papers were screened. Finally, 155 studies were found to be eligible and 51 full-text articles (5, 9-13, 23-67) were included in meta-analysis and were studied in details (**Figure.1**). **Table.1** summarizes these articles. A study compromised two separate experiment (30). Overall, 5,599 women with EPs were included. The mean and standard deviation of pre-treatment β-hCG level was reported in 50 studies. In addition, these measurements were done in the fourth day in 11 studies (12, 38, 43, 45, 54-57, 63, 65, 67) and in the seventh day in 9 (10, 12, 38, 43, 55, 57, 63, 65, 67). The prognostic value of β-hCG in treatment response of EP to methotrexate was reported in 20 articles (10-13, 24-26, 30, 31, 34, 37, 39, 44, 45, 54, 57, 58, 63, 64, 66). Overall, treatment success rate of methotrexate was found to be 84% (95% CI: 84% to 85%).

3-2. Heterogeneity and publication bias

SMD of serum β-hCG levels were found to be heterogeneous between the two groups at the temporal cut offs of before intervention (I^2=87.6%; P<0.001), fourth day (I^2=90.2%; P<0.001) and seventh day (I^2=90.7%; P<0.001). Heterogeneity was also observed in the assessment of serum β-hCG level screening performance characteristics in predicting treatment response (**Table.2**). Therefore, we used random effect model in all analyses. No publication bias was found among the included studies (**Table.2**).

3-3. Meta-analysis

3-3-1. Relation between serum β-hCG level and treatment response to methotrexate

Forty nine studies were found from which mean and standard deviation values of serum β-hCG level was extracted (5, 9-13, 23, 24, 26-67). A total of 4,334 successful treatment cases and 1,073 failure cases were assessed. According to our analysis, there was negative association between serum β-hCG level and the treatment response before (SMD= -1.10, 95% CI: -1.39 to -0.88), four days (SMD= -1.97, 95% CI: -2.59 to -1.35), and seven days (SMD= -1.92, 95% CI: -2.66 to -1.18) after intervention (**Figure.2**).

3-3-2. Performance characteristics of β-hCG in predicting response to methotrexate treatment

Table.2 shows the area under the curve, sensitivity, specificity, and prognostic odds

ratio for serum β-hCG concentrations (before intervention level) of 1000 to 5000 mIU/mL. Pooled sensitivity, specificity, and prognostic odds ratio of β-hCG in the 1000 mIU/mL cut off were 0.85 (0.72-0.93), 0.51 (0.34-0.67), and 6.0 (4.0-9.0), respectively. These values for the 2000 mIU/mL cut off were 0.75 (0.65-0.82), 0.68 (0.58-0.82), and 6.0 (5.0-8.0), respectively. The performance characteristics for different cut offs are presented in **Table.2**. Although the best prognostic odds ratio was observed in the 4,000 mIU/mL cut off, these pooled values was calculated from 4 studies. Therefore, based on the sensitivity and specificity, the 2000 mIU/mL concentration could be considered as a rational cut off point in predicting treatment response of ectopic pregnancy to methotrexate.

4- DISCUSSION

To the best of our knowledge, the present study is the first quantitative meta-analytic approach to review all available evidence regarding the value of serum β-hCG levels in predicting treatment response of ectopic pregnancy to methotrexate. This meta-analysis showed that success of methotrexate treatment in the management of ectopic pregnancy may depend on pre-treatment β-hCG concentration. The lower the serum concentration of β-hCG, the higher the chance of successful methotrexate treatment. We found significant heterogeneity between the eligible studies. Therefore, a subgroup analysis was performed to assess its possible sources. However, the source of heterogeneity was not detected. The performance characteristics of β-hCG in predicting response to methotrexate treatment were also assessed in several cut off points (**Table. 2**). The area under the curve of β-hCG in different cut offs ranged from 0.76 to 0.81, which indicative of a moderate predictive value. Based on the prognostic odds ratio, sensitivity, and specificity, we suggest β-hCG concentration of 2000 mIU/mL as a rational cut off point for predicting treatment response. Our results showed higher likelihood of therapeutic success in patients with β-hCG concentrations lower than 2000 mIU/mL.

Previous studies reported the initial β-hCG concentration properly predict treatment success with a single dose of methotrexate. Barnhart et al. showed the difference in success rate of single dose and multi dose treatment protocol are affected by β-hCG concentration (68). In their meta-analysis, success rate of multi dose management of methotrexate
was estimated to be 1.96 times higher than the use of single dose regime. This value reached to 2.34 after adjusting the analysis for β-hCG levels. In addition, Bachman and Barnhart in a narrative review stated that there is no established true cut-off for initial β-hCG levels for predicting outcome of methotrexate therapy (69). In the present study we suggest β-hCG concentration of 2000 mIU/mL as a rational cut off point for predicting treatment response of EP to Methotrexate.

Three facts have improved the quality of the present study. First we assessed the confirmed cases of ectopic pregnancy and excluded patients with suspected diagnosis from our analysis. Second, we calculated SMDs as the effect size estimate using Hedges' g to be able to make comparisons across the articles and to correct for the bias caused by the small sample size. In addition we included studies with a minimum of 10 samples. Third, we performed subgroup analysis stratified by β-hCG assessment time (days 0, 4 and seven) and β-hCG cut off points, since heterogeneity is expected to affect meta-analyses of observational studies. Moreover, we designed an extensive search and used a comprehensive analytical approach which allowed inclusion of studies presenting not only

means and standard deviations, but also medians and ranges.

4-1. Study limitations

The present review and meta-analysis has a number of potential limitations. First, there is the issue of heterogeneity between the studies. Therefore, a random effects model was used which yielded more conservative results. Second, absence of adjustment for potential confounding factors that might have affected the serum levels of β-hCG.

5- CONCLUSIONS

The present meta-analysis showed that low serum β-hCG concentration may be able to predict success of methotrexate treatment in management of EP. Our results showed higher likelihood of therapeutic success in patients with β-hCG concentrations lower than 2000 mIU/mL. However, the pooled sensitivity and specificity of β-hCG in this cut off point were 0.75 and 0.68, which indicates that β-hCG concentration alone cannot properly predict the treatment outcome. We suggest that the future studies design a predictive model, in which β-hCG concentration is entered along with other factors.

6- AUTHOR CONTRIBUTIONS

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors.

7- CONFLICT OF INTEREST: None.

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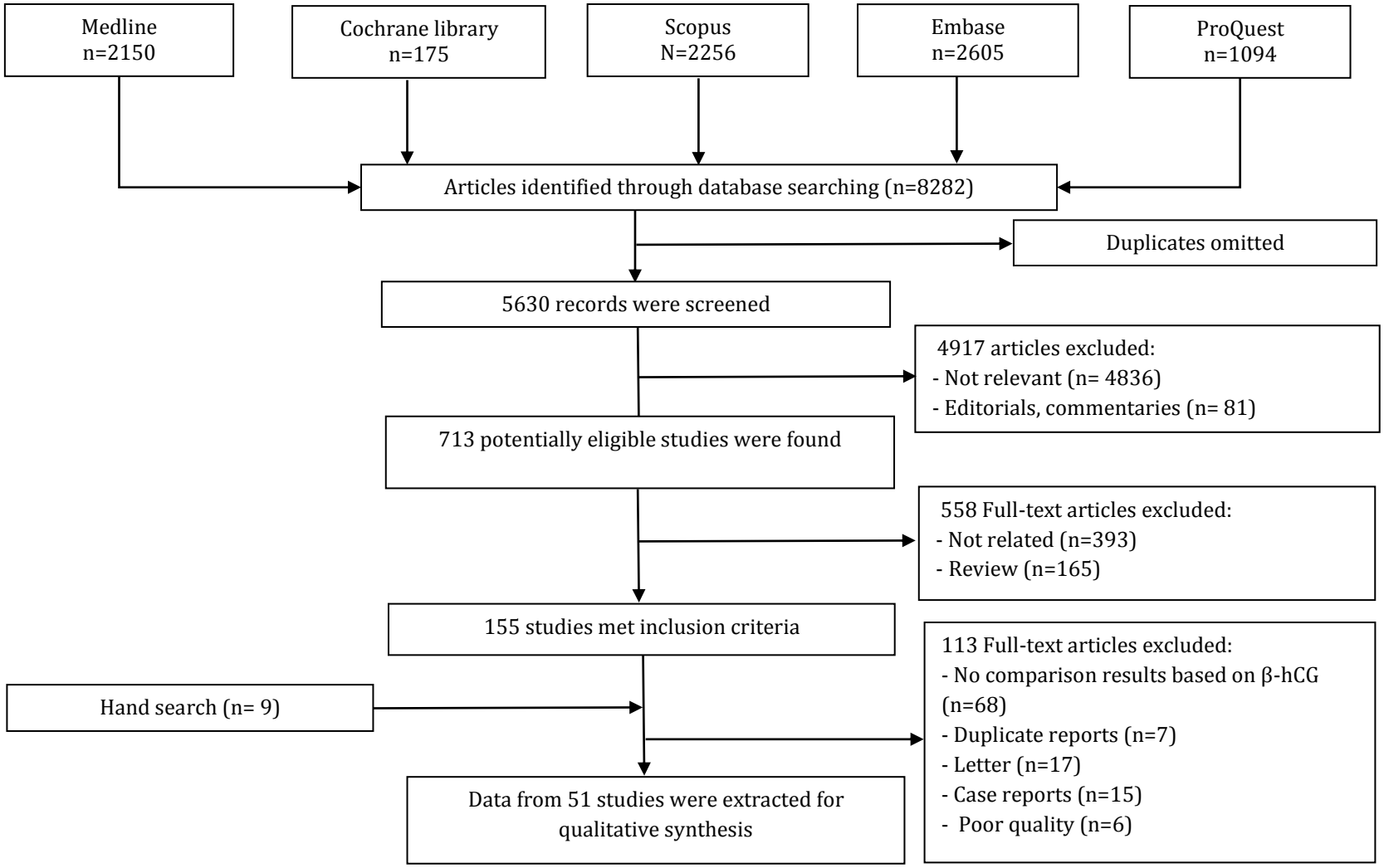

Fig.1: PRISMA Flowchart

Table-1: The characteristics of eligible studies

Author	Year	Age	Gestational age	Type of injection	Treatment protocol	Success rate (n)	Failure rate (n)
Ransom et al.	1994	32	NR	IM	Single	15	6
Lipscomb et al.	1999	26	NR	IM	Single	320	30
Tawfiq et al.	2000	27-42	NR	IM	Single	44	16
Olofsson et al.	2001	29.6	42	IM	Single	20	6
Gamzu et al.	2002	31	NR	IM	Single	44	6
Lipscomb et al.	2002	24.5	NR	IM	Single	18	3
Natale et al.	2002	NR	41	IM	Single	39	11
Gervaise et al.*	2003	31.1	48	IM	Single	54	19
Gervaise et al.*	2003	30.6	47.6	Local	Single	43	4
Nazac et al.	2003	30.7	NR	IM	Single	109	28
Potter et al.	2003	NR	NR	IM	Single	69	12
Erdem et al.	2004	NR	NR	IM	Single	30	4
Kumtepe et al.	2004	28.2	NR	IM	Single	18	11
Lipscomb et al.	2004	27	NR	IM	Single	448	47
Bixby et al.	2005	29	NR	IM	Single	45	17
Cassik et al.	2005	49	NR	Local/IV	Single	35	5
Cho et al.	2006	NR	NR	IM	Single	33	6
Gabbur et al.	2006	32	NR	IM	Single	60	23
Soliman et al.	2006	27.1	56.8	IM	Single	26	4
Srivichai et al.	2006	27	51.2	IM	Single	96	10
Behnamfar et al.	2007	27.8	NR	IM	Single	32	9
Kirk et al.	2007	31.5	43	IM	Single	47	22
Skandar et al.	2007	29.2	NR	IM	Single	66	4
Lipscomb et al.	2009	25.9	NR	IM	Single	60	13
Nowak-Markwitz et al.	2009	30	42	IM	Single	53	11

Balci et al.	2010	30.7	46.2	IM	Multiple	230	64
Butts et al.	2010	27	41	IM	Single	160	29
Rabischong et al.	2010	15-45	NR	IM	Single	316	103
Jiang et al.	2011	34.46	50.22	IM	Single	42	3
Kasum et al.	2012	NR	NR	IM	Single	32	3
Sagiv et al.	2012	30.3	NR	IM	Single	167	71
Kimiaei et al.	2013	31.4	58.1	IM	Single	165	20
Krissi et al.	2013	31.5	NR	IM	Single	92	10
Ustunyurt et al.	2013	27.5	NR	IM	Single	63	24
Avcioglu et al.	2014	30.5	NR	IM	both	68	29
Azargoon et al.	2014	29.8	NR	IM	Single	54	16
Cohen et al.	2014	30	NR	IM	Second	58	15
Cohen et al.	2014	31	47	IM	Single	356	53
de Waard et al.	2014	24.4	NR	IM	Single	59	65
Gnisci et al.	2014	32	NR	IM	Single	69	24
Helmy et al.	2014	30.57	NR	IM	Single	162	36
Hiersch et al.	2014	32.6	46.1	IM	Single	12	5
Kilic et al.	2014	30.72	47	IM	Single	67	32
Poon et al.	2014	33	NR	IM	Single	17	2
Sinprasertnavin et al.	2014	25.3	47	IM	Single	48	48
Vaswani et al.	2014	28.7	NR	IM	Single	30	10
Wu et al.	2014	32.3	NR	IM	Single	99	19
Alsammani et al.	2015	29.6	45	IM	Single	66	43
Cok et al.	2015	33.7	46	IM	Single	11	7
Orozco et al.	2015	31.4	NR	IM	Single	111	15
Peng et al.	2015	32.6	56	Local/IV	Single	71	33
Shaamash et al.	2015	NR	NR	IM	Single	38	11

*This study had two separate experiment. NR: not reported; IM: intramuscular; IV: intravenous.

Table-2: Primary meta-analyses of βhCG level in patients with ectopic pregnancy.

Characteristic	Number of included studies	Number of subjects (Success/Failure)	P-value (publication bias)[a]	P (heterogeneity %)	Effect size (95% CI)	P-value
βhCG level						
Day 0	50	4334/1073	0.21	<0.001 (87.6)	-1.10[b] (-1.39- -0.88)	<0.001
Day 4	11	603/207	0.22	<0.001 (90.2)	-1.97[b] (-2.59- -1.35)	<0.001
Day 7	9	499/160	0.06	<0.001 (90.7)	-1.92[b] (-2.66- -1.18)	<0.001
Area under curve						
Cut off (mIU/mL)						
1000	11	1257/293	0.88	<0.001 (100.0)	0.76 (0.72-0.79)	NA
2000	18	1567/386	0.89	<0.001 (99.0)	0.77 (0.73-0.81)	NA
3000	5	331/120	0.47	<0.001 (94.0)	0.78 (0.74-0.82)	NA
4000	4	208/88	0.42	<0.001 (92.0)	0.81 (0.78-0.85)	NA
5000	8	789/195	0.37	<0.001 (96.0)	0.81 (0.77-0.84)	NA
Sensitivity						
Cut off (mIU/mL)						
1000	11	1257/293	0.88	<0.001 (100.0)	0.85 (0.72-0.93)	NA
2000	18	1567/386	0.89	<0.001 (99.0)	0.75 (0.65-0.82)	NA
3000	5	331/120	0.47	<0.001 (94.0)	0.68 (0.37-0.85)	NA
4000	4	208/88	0.42	<0.001 (92.0)	0.63 (0.28-0.88)	NA
5000	8	789/195	0.37	<0.001 (96.0)	0.36 (0.19-0.58)	NA
Specificity						
Cut off (mIU/mL)						
1000	11	1257/293	0.88	<0.001 (100.0)	0.51 (0.34-0.67)	NA

2000	18	1567/386	0.89	<0.001 (99.0)	0.68 (0.58-0.82)	NA
3000	5	331/120	0.47	<0.001 (94.0)	0.78 (0.58-0.90)	NA
4000	4	208/88	0.42	<0.001 (92.0)	0.82 (0.61-0.93)	NA
5000	8	789/195	0.37	<0.001 (96.0)	0.89 (0.81-0.93)	NA
Prognostic odds ratio						
Cut off (mIU/mL)						
1000	11	1257/293	0.88	<0.001 (100.0)	6.0 (4.0-9.0)	NA
2000	18	1567/386	0.89	<0.001 (99.0)	6.0 (5.0-8.0)	NA
3000	5	331/120	0.47	<0.001 (94.0)	7.0 (4.0-12.0)	NA
4000	4	208/88	0.42	<0.001 (92.0)	8.0 (3.0-23.0)	NA
5000	8	789/195	0.37	<0.001 (96.0)	4.0 (2.0-9.0)	NA

[a]Begg's and Egger's test for standardize mean difference and Deeks funnel plot asymmetry test for performance characteristics values. [b]Standardized mean difference. CI: Confidence interval; NA: Not applicable.

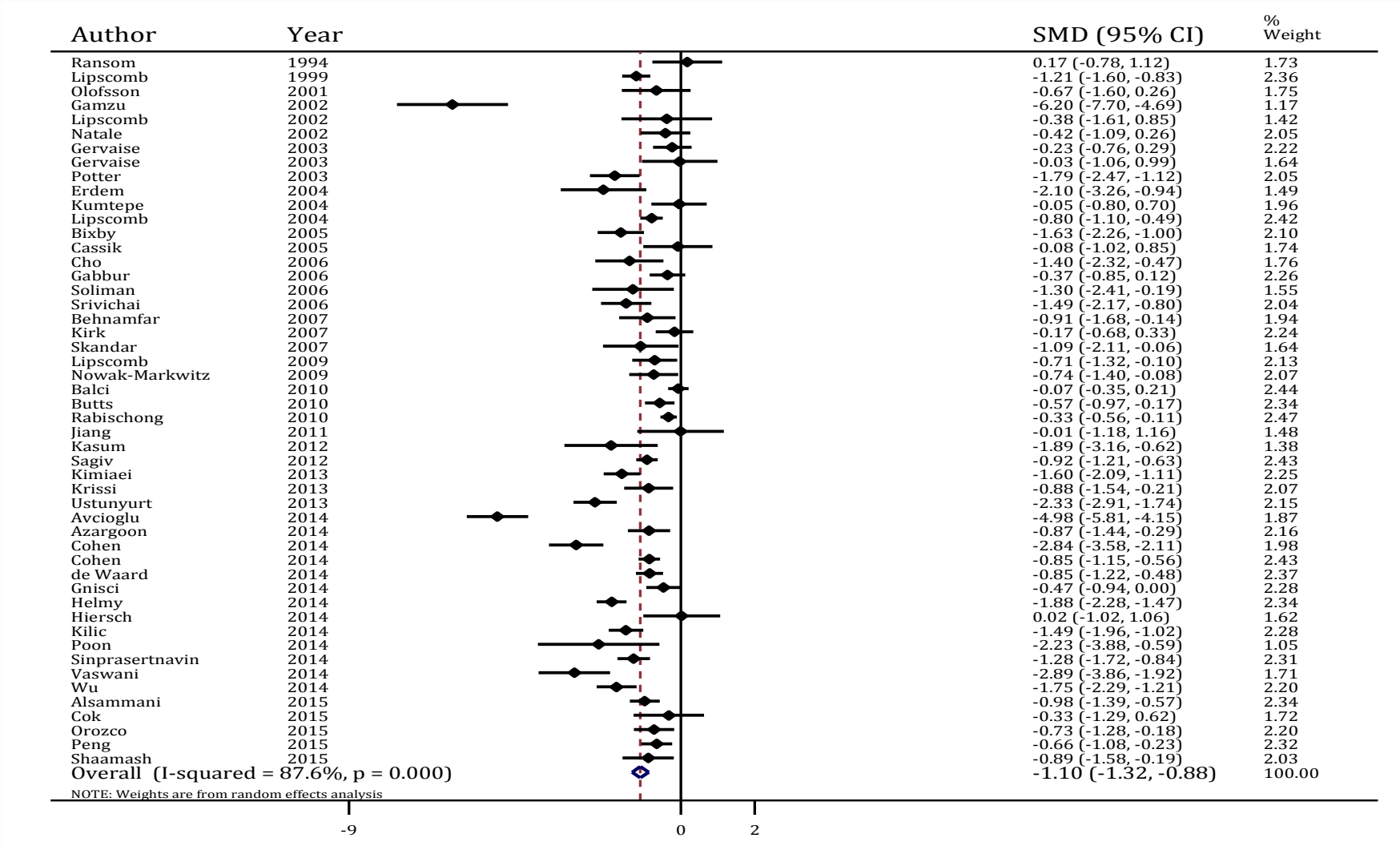

Fig.2: Standardize mean difference (SMD) of serum β-subunit of human chorionic gonadotropin level for predicting treatment response of ectopic pregnancy to methotrexate