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Evaluation of Selenium Status among Iranian Pregnant Women: A Systematic Review and Met-Analysis

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ABSTRACT

Background: Selenium (Se) plays an important role in numerous immunological functions of human health. It has been shown that maternal Se deficiency contributes to many pregnancy complications such as pre-eclampsia, gestational diabetes mellitus (GDM), miscarriage, and even fetal growth restriction. Due to the evidence of importance of Se in pregnancy outcomes and the inconsistency of current shreds of evidence on Se adequacy in Iranian pregnant women, this study aimed to provide a comprehensive evaluation of published studies. This systematic review explored studies reporting dietary Se intake, serum or plasma Se, and Umbilical cord Se in Iranian pregnant women. **Methods:** PubMed, Scopus, Web of Science, Embase, Google scholar (in English and Persian), and Persian databases, including Scientific Information Database, IranDoc, Iranian National Library, Magiran, and Regional Information Center for Science and Technology, were reviewed. **Results:** A total of 30 studies were included in the meta-analysis. Pooled effect sizes show an overall value of 90.09 µg/l (95% CI: 81.89, 98.29) and 75.08 µg/d (95% CI: 63.01, 87.16) for serum and dietary Se. Geographically, the lowest serum Se was in Fars and East-Azerbaijan with values of 61.97 µg/l (51.38, 72.55) and 55.12 µg/l (48.5, 61.74), respectively. Dietary intake pooled estimate showed that the lowest Se intake was in West-Azerbaijan with a value of 42.80 µg/d (95% CI: 38.95, 46.65). **Conclusion:** The current study shows that the overall serum and dietary intake of Se in Iranian pregnant women is acceptable. Some parts of the country need monitoring to prevent Se inadequacy and related-adverse complications in pregnant women.

Keywords: *Iran; Pregnancy; Pregnancy complications; Selenium; Systematic review*

Introduction

Selenium (Se) as an essential trace element, has attracted great attention due to its several roles in human health. Among the wide variety of functions in the body, Se has a structural role in enzymatically active proteins called selenoproteins, including Glutathione peroxidases (GPx), thioredoxin reductases, and deiodinases (Rayman, 2000, 2012). Selenoproteins are well-

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known for their Reactive Oxygen Species (ROS) scavenging activity, which may interpret Se importance in pregnancy, especially because of increased ROS production during this period (Pieczyńska and Grajeta, 2015, Zachara, 2018). The placenta has been considered the main source of oxidative stress during pregnancy, and accumulation of ROS during placental development can be exacerbated by Se insufficiency. On the other hand, increasing mass of erythrocytes in the fetus, and increased oxygen demands in the body of a mother may alter Se homeostasis during pregnancy (Kyozuka *et al.*, 2021, Pieczyńska and Grajeta, 2015). ROS agglomeration, as a consequence of inadequate maternal Se concentration and/or impaired antioxidant defense, may lead to different pregnancy complications such as pre-eclampsia (PE), gestational diabetes mellitus (GDM), preterm birth, and abortion. These conditions can threaten maternal and neonatal health (Kyozuka *et al.*, 2021, Mariath *et al.*, 2011).

Se exposure has been assessed in epidemiologic studies through several biomarkers, including its concentrations in erythrocyte, whole blood, serum or plasma (Sieniawska *et al.*, 1999), and also hair and toenail (Filippini *et al.*, 2017). Serum and plasma Se reflect short-term status; nonetheless, they are the most commonly used indicators in pregnant women (Stoffaneller and Morse, 2015). Some studies also evaluated Se status in pregnancy by measuring dietary intake (Kyozuka *et al.*, 2021, Solé-Navais *et al.*, 2021) or urinary Se (Koukkou *et al.*, 2014). Sufficient plasma concentration of Se is estimated by reaching optimal plasma GPX activity, which is achieved at approximately 90 µg/l (Duffield *et al.*, 1999, Kipp *et al.*, 2015); however, the lower limit of 70 µg/l (0.89 µmol/l) has been reported due to obtaining normal Se levels (Okunade *et al.*, 2018); the latter has been suggested to prevent GDM (Liu *et al.*, 2021).

Studies on dietary Se intakes have demonstrated that Se intake varies markedly worldwide ranging from approximate values of 7-30 µg/d in Eastern European countries and some parts of China to even toxic amounts with an approximate value of 5 mg/d resulting in selenosis (Rayman, 2008). Dietary Se intake in Europe has been estimated as 30 µg/d, while in the U.S., the intake is more than 90 µg/d (Kieliszek, 2019). This variation in dietary intake of Se mainly depends on the concentration of Se in soils (Al-Othman *et al.*, 2012), moreover, other factors such as geochemistry, rainfall, and dietary habits can affect total Se intake. The main food sources of Se in diet are cereals, organ meat, and fish (Chun *et al.*, 2010, Solé-Navais *et al.*, 2021), followed by eggs and dairy products (Solé-Navais *et al.*, 2021). Considering the Se concentration in food crops and soil, Se rich fertilizers can improve its concentration in soils where plants and animals are produced as food (Al-Othman *et al.*, 2012, Nazemi *et al.*, 2012). In 2010, Xia *et al.* indicated that 49 µg/d Se is desired to obtain selenoprotein P saturation in Se-deficient Chinese subjects (Xia *et al.*, 2010). In 2015, joint nutrition societies of Germany, Austria, and Switzerland revised the reference value to 60 µg/d in adult women (Kipp *et al.*, 2015); finally, in 2019, the European Food Safety Authority recommended 70 µg/d Se in pregnancy (Hubalewska-Dydejczyk *et al.*, 2020). Se status expansively varies throughout middle eastern countries, since suboptimal and supra-optimal Se status has been reported in parts of Saudi Arabia and Jordan, respectively (Ibrahim *et al.*, 2019). However, between-population variation is also noticeable, where the Se status in the North-Western population (Tabriz), is considerably lower than North-Eastern (Mashhad) in Iran (Vanderlelie and Perkins, 2011).

Given the remarkable role of Se in health and complications related to pregnancy, there is a need to have a comprehensive assessment of the current status of Se among Iranian pregnant women. Therefore, the present study aimed to estimate the Se status in different provinces of Iran.

Materials and Methods

The current study was conducted based on

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the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (PRISMA statement).

Search strategy and data collection: Searching was performed up to 3 May 2021 and the following databases were searched: PubMed, Scopus, Web of Science, Embase, and google scholar (in English and Persian), along with Persian databases including Scientific Information Database (SID) (http://www.sid.ir/), Iranian Research Institute for Information Science and Technology (IranDoc) (https://irandoc.ac.ir), Iranian National Library (http://www.nlai.ir/), Magiran (http://www.magiran.com/), and Regional Information Center for Science and Technology (RICST) (http://en.ricest.ac.ir/).

The following medical subject heading terms and words were used for the search: ("selenium" OR Microelement OR "trace element" OR micronutrient OR minerals OR antioxidant OR selenium OR selen* OR selepen OR organoselen* OR natriumselen* OR methylseleninic OR methylselenium OR selenomethionin* OR selenite* OR selenate*) AND (Iran OR Iranian) AND (maternal OR prenatal OR peripartum OR pregnancy OR premature OR preterm OR preeclampsia OR "intrauterine growth restriction" OR "Pregnancy" OR pregnant OR gestational OR gestation* OR gravid OR preconception* OR conception OR miscarriage OR abortion). No country or study type limitation was applied. Finally, the reference list of eligible articles was checked for related studies.

Study selection: The inclusion criteria were determined as follows: 1) Studies on the Iranian population living in Iran; 2) Pregnant women with or without gestational and or delivery complications in mother or neonate; 3) evaluation Se in maternal serum, plasma, dietary intake, or in umbilical cord serum; and 4) Estimating overall Se status in Iranian pregnant women. The exclusion criteria were as follows: 1) Non-Iranian subjects; 2) Non-pregnant subjects; 3) insufficient statistical data; 4) unavailable full-text; and 5) duplicate data.

Data extraction: Data extraction was performed independently by one author (Daneshvar M**)** and was checked by another author (Hasanzadeh M) to reach more accuracy. The information was extracted including the author's name, publication year, study design, characteristics of the participants (maternal age, gestational age, health conditions, province and city, and sample size), mean and standard deviation (SD)/or standard error (SE) of Se level. Conversion of units and statistical values of measurements were performed accordingly, using Cochrane methods.

Quality assessment: The risk of bias (RoB) assessment tool for non-randomized studies (RoBANS) was used to evaluate the quality of observational studies. RoBANS contains six domains including selection, performance, detection, attrition, and reporting bias. RoB for each domain was categorized as low, high, or unclear (Kim *et al.*, 2013). For interventional trials, RoB was assessed in each study using the Cochrane RoB assessment tool which assesses sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, and selective outcome reporting (Higgins *et al.*, 2011).

Data analysis: Meta-analyses were performed using random-effects models based on mean and standard error. For studies that reported a standard deviation, the standard error was calculated using relevant formulas (Higgins and Deeks, 2011). Moreover, for two studies with missing standard deviation, appropriate values were imputed from the nearest studies, using the *Furukawa* method (Higgins and Green, 2019). In two studies, plasma Se was reported, and they were considered as serum levels due to non-noticeable differences (Johnson *et al.*, 2010, Stoffaneller and Morse, 2015). Heterogeneity between the studies was evaluated by the Cochrane Q test and I^2 statistic, with values greater than 50%, indicating substantial heterogeneity (Higgins and Thompson, 2002).

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Subgroup analyses were carried out to find probable sources of heterogeneity, according to the predefined variables including health condition, province, year, trimester, maternal age, maternal body mass index (BMI), language, and study design. Egger's linear regression and Begg's test were used to evaluate the publication bias (Lin and Chu, 2018), with P-values < 0.05 were considered significant. Sensitivity analysis was also achieved to evaluate the impact of each study, based on the results of the overall serum Se. All statistical analyses were conducted by the use of the STATA, version 11.2 (StataCorp). *A P*-value < 0.05 was considered a significant level.

Results

Study selection: A total of 437 articles were identified through an initial search, and following the removal of duplicates, the title and abstracts of 251 articles were screened. By skimming the title and abstracts, 136 articles were excluded due to irrelevancy in context (animal/cell study, review, gene study, etc.). After evaluating full-text of the remaining studies, 85 papers were excluded based on pre-defined criteria, and eventually, 30 studies (Aalami-Harandi *et al.*, 2015, Akhlaghi *et al.*, 2012, Alipour *et al.*, 2015, Asemi *et al.*, 2015, Asemi *et al.*, 2012, Atarod *et al.*, 2015, Boskabadi *et al.*, 2012, Daneshzad *et al.*, 2020, Davaryari *et al.*, 2011, Farzin and Sajadi, 2012, Ghaemi *et al.*, 2013, Iranpour *et al.*, 2009, Jalili *et al.*, 2015, Kazemian *et al.*, 2013, Khoigani *et al.*, 2012, Kooshki *et al.*, 2009, Kushki *et al.*, Maleki *et al.*, 2011, Mazloomi *et al.*, 2021, Mohammadzadeh *et al.*, 2009, Mohammadzadeh *et al.*, 2012, Monafi *et al.*, 2003, Moshfeghy *et al.*, 2020, Mostafa-Gharehbaghi *et al.*, 2012, Nazemi *et al.*, 2015, Noormohammadi Isa *et al.*, 2004, Parast and Paknahad, 2017, Peirovifar *et al.*, 2013, Sheykhi *et al.*, 2015, Tara *et al.*, 2010b) were included in the meta-analysis (**Figure 1**).

Characteristics of the included studies: The included studies were published between the year 2004 to 2020. Study designs included RCT, cohort, cross-sectional, and case-control studies. Health conditions in women and neonates differed across studies including healthy, PE, GDM, and abortion for women and healthy, low birth weight (LBW), and preterm labor for neonates.

Fifteen studies reported the serum Se status of 1381 women in 8 provinces (1245 pregnant women during gestation and 136 women at the time of delivery). Dietary Se intake was evaluated between 2512 pregnant women in 5 provinces. Also, 523 umbilical cord serum Se was measured in 6 studies from 4 provinces. The total number of participants in the umbilical cord, dietary intake, and serum Se evaluation studies ranged from 19-177, 44-584, and 38-125, respectively. Se status was measured mostly using atomic absorption spectrometry in sera. Food frequency questionnaire (FFQ), food recall, and dietary record were used for a dietary intake assessment. Detailed study characteristics are illustrated in **Table 1**. The quality of the included studies is provided in **Table 3**. The overall score was evaluated by the number of domains, in which low RoB was determined. Only one study had a high RoB (overall score =< 2), and 12 studies were found with low RoB (overall score = 6). The remaining 17 papers presented moderate quality (overall score 3 to 6).

Meta-analysis results

Serum Se: Thirty effect-sizes with a total sample size of 1245 participants were included in the Meta-analysis using a random-effect model. The overall mean serum Se concentration in the Iranian pregnant population during gestation was 90.09 µg/l (95% CI: 81.89, 98.29 µg/l), with significant heterogeneity between studies (P < 0.001, I^2=98.8). Reported values varied from 39.87 µg/l in Fars province to 137.43 µg/l in Razavi Khorasan. Serum Se data was stratified into healthy (no diagnosed complication in the mother or neonate) and unhealthy (at least one diagnosed complication in the mother or neonate) groups. The combined analysis of mean serum Se concentration for a healthy group including 17 effect sizes revealed a mean value of 95.75 µg/l (95% CI: 85.72, 105.79 µg/l) and for the

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unhealthy group including 13 effect sizes revealed a mean value of 82.69 µg/l (95% CI: 68.38, 96.99 µg/l). Moreover, subgroup analysis by province evaluated mean serum Se values as follows: Razavi Khorasan 113.99 µg/l (95% CI: 96.67, 131.30 µg/l), Fars 61.97 µg/l (95% CI: 51.38, 72.55 µg/l), East-Azerbaijan 55.12 µg/l (95% CI: 48.50, 61.74 µg/l), Tehran 90.93 µg/l (95% CI: 82.20, 99.65 µg/l), Hamadan 94.25 µg/l (95% CI: 64.88, 123.63 µg/l), Kermanshah 87.16 µg/l (95% CI: 75.91, 98.41 µg/l), and Mazandaran 87.68 µg/l (95% CI: 68.67, 106.69 µg/l) (**Figures 2, 3**). Trimester subgroup analysis presented mean values of 90.42 µg/l (95% CI: 57.54, 123.29 µg/l) for the first trimester, 87.68 µg/l (95% CI: 68.67, 106.69 µg/l) for the second trimester, and 91.20 µg/l (95% CI: 80.07, 102.33 µg/l) for the third trimester. Subgroup analysis for serum Se was also performed based on the trimester of pregnancy, maternal age (<26 and >26 years old), maternal BMI (<26 and >26 kg/m^2), language (English and Persian), year of publication (=<2012, >2012), and study design (**Table 2**).

Meta-analysis of serum Se at delivery was fulfilled separately from maternal Se during pregnancy. The overall analysis of 4 effect sizes from 2 studies revealed a mean serum Se concentration of 94.73 µg/l (95% CI: 72.78, 116.67 µg/l) at delivery with considerable heterogeneity among studies (P < 0.001, I^2 = 98.3%). The studies were categorized into two groups including the healthy group combining 2 effect sizes with a mean value of 98.62 µg/l (95% CI: 62.6, 134.65 µg/l), the PE group containing 1 effect size with a mean value of 71.22 µg/l (95% CI: 65.83, 76.61 µg/l), and the preterm bearing mothers group containing 1 effect size with the mean value of 110.56 µg/l (95% CI: 104.30, 116.82 µg/l, **Table 2**).

Dietary Se: Combined analysis of 23 effect sizes demonstrated that the mean dietary intake of Se in the Iranian pregnant population is 75.08 µg/d (95% CI: 63.04, 87.13 µg/d, **Figure 2**), with a considerable between-study heterogeneity (P < 0.001, I^2 = 100%). Reported values of intake ranged from 40.95 µg/d in Isfahan to 124.7 µg/d in North-Khorasan. Subgroup analysis by trimesters and the health state of participants was conducted. In trimester subgroups, there was only one study reporting first-trimester intake with the mean value of 124.70 µg/d (95% CI: 124.29, 125.11 µg/d); for second-trimester subgroup combined analysis of 3 effect sizes revealed the mean value of 43.41µg/d (95% CI: 41.16, 45.66 µg/d) and for the third-trimester subgroup combined analysis of 19 effect sizes revealed the mean value of 76.61 µg/d (95% CI: 70.60, 82.62 µg/d). Also combined analysis of 12 and 10 effect sizes for healthy and unhealthy groups, demonstrated that mean dietary intakes were 73.91µg/d (95% CI: 56.65, 91.16 µg/d) in the healthy group and 71 µg/d (95% CI: 61.90, 80.10 µg/d) in the unhealthy group (definition of groups described earlier). Also, dietary Se intake was stratified by different Provinces and revealed that mean values of intake are as follows: Isfahan with the mean value of 74.90 µg/d (95% CI: 68.10, 81.69 µg/d), Tehran with a mean value of 60.16 µg/d (95% CI: 57.34, 62.98 µg/d), West-Azerbaijan with the mean value of 42.80 µg/d (95% CI: 38.95, 46.65 µg/d), North-Khorasan with the mean value of 71.07 µg/d (95% CI: 6.83, 135.32 µg/d), and Markazi with the mean value of 114.90 µg/d (95% CI: 105.69, 124.11 µg/d, **Figure 3**). Additionally, subgroup analysis was performed by different trimesters and health conditions (**Table 2**).

Umbilical cord serum Se: The overall analysis of 11 effect sizes reporting Se concentration in umbilical cord presented the mean value of 70.98 µg/l (95% CI: 58.95, 83.02 µg/l) with significant heterogeneity between studies (P < 0.001, I^2 = 97.9%). Subgroup analysis by healthy and unhealthy birth groups was conducted. The mean value in the healthy subgroup with 6 effect sizes was 72.66 µg/l (95% CI: 55.44, 89.89 µg/l) and in the unhealthy subgroup with 5 effect sizes was 68.93 µg/l (95% CI: 52.67, 85.20 µg/l). The unhealthy group contains at least one of the following conditions: bronchopulmonary

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dysplasia (BPD), respiratory distress syndrome (RDS), LBW, or preterm birth (**Table 2**).

Sensitivity analysis: The robustness of results was assessed by performing the sensitivity analysis. Based on estimates, serum Se levels may vary between 88.60 µg/l (95% CI: 80.42, 96.76) and 91.82 µg/l (95% CI: 83.89, 99.74). By excluding two studies (4 effect sizes) with some methodological or statistical errors (Akhlaghi *et al.*, 2012, Noormohammadi Isa *et al.*, 2004), the overall estimate altered to 86.01 µg/l (95% CI: 77.64, 94.37 µg/l). Moreover, by excluding data from Razavi Khorasan (highest values, effect sizes = 11), an overall estimate for the remaining country fell to 78.06 µg/l (95% CI: 70.04, 86.08 µg/l). After excluding RCTs (two effect-sizes from Tara *et al.*), the remaining observational studies revealed that overall serum Se was equal to 87.67 µg/l (95% CI: 79.82, 95.53 µg/l).

Sensitivity analysis revealed that dietary Se can extend from 73.1 µg/d (95% CI: 60.8, 85.39 µg/l) to 76.58 µg/d (95% CI: 64.22, 88.93 µg/l). Six of 23 effect sizes are from khoigani (Khoigani *et al.*, 2012), which can affect the overall estimate; by excluding them, the overall value rose to 84.67 µg/d (95% CI: 70.59, 98.74 µg/l). After excluding RCTs (3 studies with 6 effect-sizes), the remaining observational studies revealed that overall dietary Se was equal to 61.82 µg/d (95% CI: 47.94, 75.70 µg/l).

Publication bias: Based on results from Egger and Begg's test, publication bias among serum Se studies was significant ($P < 0.001$ and $P = 0.005$). In the case of dietary Se intake, no evidence of publication bias was found by the Egger test ($P = 0.71$); however, Begg's test showed a significant bias ($P = 0.04$).

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Table 1. Characteristics of the included studies.

Study	Language	Year	Province (city)	Study design	Sample size Case/ Control	Maternal age (years) Case Control	Gestational age (weeks) Case Control	Condition in Cases	Se concentration Case Control	Sample	Unit	Se measuring method
Serum Se												
(Noormohammadi Isa *et al.*, 2004)	Per	2004	Tehran (Tehran)	Case-control	34/34	Total 29.0±6.7	≤20	MSCRG	97.41±34.94 100.36±38.97	Serum	µg/l	AAS
(Iranpour *et al.*, 2009)	Per	2009	Isfahan (Isfahan)	Case-control	30/30	27.96±5.12 25.23±5.45	(Delivery) 29.93±2.52 39.51±1.05	PRT	110.56±17.49 117.03±17.15	Serum	µg/l	GF-AAS
(Mohammadzadeh *et al.*, 2009)	Eng	2009	Khorasan (Mashhad)	Case-control	70/53	24.0±4.0 25.7±5.4	33.4±2.9 39.3±1.4	LBW	118.8±24.5 122.5±29.3	Serum	µg/l	GF-AAS
(Tara *et al.*, 2010b)	Eng	2010	Razavi-Khorasan (Mashhad)	RCT	61/64	21.6±2.5 21.6±3.4	≤12	HLTH	122.5±23.2 122.9±26.9	Serum	µg/l	ET-AAS
(Davaryari *et al.*, 2011)	Per	2011	Razavi-Khorasan (Mashhad)	Case-control	35/30	29.69 24.33	28-40	PE	103.03±27.38 132.7±29.65	Serum	µg/l	AAS
(Maleki *et al.*, 2011)	Eng	2011	east-Azerbaijan (Tabriz)	Case-control	40/40	27.62±5.25 26.42±3.73	34-36 37-39	PE	51.75±1.62 58.51±11.85	Plasma	µg/l	ET-AAS
(Akhlaghi *et al.*, 2012)	Eng	2012	Razavi-Khorasan (Mashhad)	Case-control	30/30	30 25	24-28	GDM	137.43 134.33	Serum	µg/l	AAS
(Farzin and Sajadi, 2012)	Eng	2012	Tehran (Tehran)	Case-control	60/60	26.66±3.72 27.43±3.91	35.27±1.20 35.48±1.14	PE	88.2±21 104.7±27.8	Serum	µg/l	GF-AAS
Ghaemi et al. (Ghaemi *et al.*, 2013)	Eng	2013	Fars (Shiraz)	Case-control	38/38	28.4±3.13 28.2±3.12	25.4±1.34 24.52±1.23	PE	70.63±21.41 82.03±15.54	Plasma	µg/l	GF-AAS
(Alipour *et al.*, 2015)	Per	2014	Kermanshah (Kermanshah)	Case-control	29/29	30.93±8.94 25.42±4.98	24-36 38-41	PRT	81.29±15.89 92.77±12.87	Serum	µg/l	AAS
(Atarod *et al.*, 2015)	Eng	2015	Mazandaran (Sari)	Case-control	43/43	20-40 20-40	12-14		77.9±16 97.3±11.2	Serum	µg/l	GF-AAS
(Nazemi *et al.*, 2015)	Eng	2015	Tehran (Tehran)	Case-control	91/86	28.41±6.32 28.7±5.44	28.82±13.66 38.12±0.91	LBW	80.69±28 78.48±25.54	Serum	µg/l	NR

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(Jalili *et al.*, 2015)	Per	2015	Razavi-Khorasan (Mashhad)	Cohort	18/20	16-35 16-35	n/a	HLTH	72.05±6.29 75.69±8.17	Serum	µg/l	AAS
(Mazloomi *et al.*, 2021)	Eng	2020	Hamadan (Hamadan)	Case-control	30/30	31(24-38) 31(24-38)	> 20	PE	80.15±23.16 110.18±46.7	Serum	µg/l	AAS
(Moshfeghy *et al.*, 2020)	Eng	2020	Fars (Shiraz)	Case-control	25/50	25.76±3.65 25.66±3.52	First trimester	GDM	50.6±10.88 66.02±10.57	Serum	µg/l	HG-AAS
Dietary Se												
Kooshki et al.(Kooshki *et al.*, 2009)	Per	2007	North-Khorasan (Sabzevar)	Cross-sectional	561		4.29±3.2	General population	124.7±4.9	3*24hr FR + FFQ	µg/d	FP
(Kushki *et al.*)	Per	2009	North-Khorasan (Sabzevar)	Case-control	100/100	Total 26.7±6	>20	HTN	45.04±37.32 43.1±55.96	3*24hr FR	µg/d	FP
(Asemi *et al.*, 2012)	Eng	2012	Isfahan (Kashan)	RCT	37/37	25.7±3.1 24.2±3.3	28	HLTH (both)	110±40 110±30	3*24hr FR	µg/d	NUT IV
(Khoigani *et al.*, 2012)	Eng	2012	Isfahan (Isfahan)	Cohort	23/561	27.73±6.04 25.36±4.84	11-15	PE	50.41±33.4 43.44±34.17	48hr DR	µg/d	NUT IV
(Kazemian *et al.*, 2013)	Per	2013	Tehran (Tehran)	Case-control	200/263	29.27±5.96 27.4±4.8	33.39±4.67 33.22±3.73	HTN	58.76±23.96 61.64±21.35	FFQ	µg/d	NUT III
(Aalami-Harandi *et al.*, 2015)	Eng	2014	Isfahan (Kashan)	RCT	37/37	24.2±3.3 25.7±3.1	27	HLTH (at risk of PE)	117.8±4.6 111±3.5	3*24hr FR	µg/d	NUT IV
(Monafi *et al.*, 2003)	Per	2014	West-Azerbaijan (Urmia)	Cross-sectional	118		12-16	HLTH	42.8±0	3*24hr FR	µg/d	FP II
(Sheykhi *et al.*, 2015)	Eng	2015	Isfahan (Isfahan)	Cross-sectional	55	Total 29.3±5.5	34.1±2.7	PE	81.5±40.7	FFQ	µg/d	NUT IV

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Table 1. Characteristics of the included studies.

Study	Language	Year	Province (city)	Study design	Sample size Case/ Control	Maternal age (years) Case Control	Gestational age (weeks) Case Control	Condition in Cases	Se concentration Case Control	Sample	Unit	Se measuring method
(Asemi *et al.*, 2015)	Eng	2015	Markazi (Arak)	RCT	35/35	27.6±5.3 29.6±3.6	24-28	GDM (both)	114.9±45.5 114.9±35.1	3*24hr DR	µg/d	NUT IV
(Parast and Paknahad, 2017)	Eng	2017	Isfahan (Isfahan)	Case-control	40/40	29.4±4.9 28.9±5.2	26±1.5 26.1±1.5	GDM	81±26 95±36	FFQ	µg/d	NUT IV
(Daneshzad *et al.*, 2020)	Eng	2020	Isfahan (Isfahan)	Case-control	35/35	27.6±5.3 29.6±3.6	25-28	GDM	60±2 70±2	3*24hr DR	µg/d	NUT IV
Umbilical cord Se												
(Mostafa-Gharehbaghi *et al.*, 2012)	Eng	2011	East-Azerbaijan (Tabriz)	Longitudinal	8/11		32 >=	BPD	42.7±17.0 31.9±13.9	Serum	µg/l	HG-AAS
(Boskabadi *et al.*, 2012)	Eng	2012	Razavi-Khorasan (Mashhad)	RCT	(End-point in placebo group) 34		39	HLTH	106.3±18.2 101.9±15.9	Serum	µg/l	ET-AAS
(Mohammadzadeh *et al.*, 2012)	Eng	2012	Razavi-Khorasan (Mashhad)	Cross-sectional	27/123		37 >=	RDS	96.5±20.1 96.6±18.7	Serum	µg/l	ET-AAS+GF tubes
(Peirovifar *et al.*, 2013)	Eng	2013	East-Azerbaijan (Tabriz)	Longitudinal	25/29	27.95±6.02 27.85±6.28	20>=	BPD	69.82±28.47 60.11±24.59	Serum	µg/l	ET-AAS
(Alipour *et al.*, 2015)	Per	2014	Kermanshah (Kermanshah)	Case-control	29/29	30.93±8.94 25.42±4.98	24-36 38-41	PRT	56.98±13.13 70.11±11.6	Serum	µg/l	AAS
(Nazemi et al., 2015)	Eng	2015	Tehran (Tehran)	Case-control	91/86	28.41±6.32 28.7±5.44	28.82 38.12	LBW	77.32±26.12 73.89±24.37	Serum	µg/l	n/a

AAS: Atomic absorption spectrometry, GF: Graphite furnace, HG: Hybrid generation, ET: Electro-thermal, FP: Food processor, NUT: Nutritionist, Se: Selenium, Per: Persian, Eng: English, RCT: Randomized clinical trial, PRT: Preterm birth, GDM: Gestational diabetes mellitus, PE: Pre-eclampsia, HLTH: Healthy, LBW: Low birth weight, MSCRG: Miscarriage, HTN: Hypertension, BPD: Bronchopulmonary dysplasia, RDS: Respiratory distress syndrome, n/a: not applicable, Note: For trial studies, baseline Se levels are reported.Values are as mean ± SD

Table 2. Subgroups analysis results.

Subgroups	Effect sizes	Mean	95% CI	Heterogeneity test	
				I^2 (%)	P-value
Maternal serum Se concentration (µg/l)					
Total	30	90.09	81.89, 98.29	98.8	< 0.0001
Age (y)					
<26	11	96.68	78.30, 115.05	99.4	< 0.0001
>26	15	87.81	77.44, 98.17	97.6	< 0.0001
Not specified	4	80.74	68.73, 92.75	97.8	< 0.0001
Body mass index (kg/m^2)					
<26	5	93.83	74.29, 113.36	98.5	< 0.0001
>26	7	108.19	83.88, 132.49	98.8	< 0.0001
Not specified	18	82.11	72.29, 91.93	98.8	< 0.0001
Health condition					
Healthy	17	95.75	85.72, 105.79	98.7	< 0.0001
Gestational diabetes mellitus	3	75.61	36.80, 114.42	99.4	< 0.0001
Pre-eclampsia	5	78.57	59.55, 97.60	98.0	< 0.0001
Abortion	2	86.89	67.83, 105.95	89.0	0.003
Low birth weight or preterm	3	93.59	68.85, 118.34	98.2	< 0.0001
Trimesters					
First	4	90.42	57.54, 123.29	99.5	< 0.0001
Second	2	87.68	68.67, 106.69	97.6	< 0.0001
Third	20	91.20	80.07, 102.33	98.8	< 0.0001
Not specified	4	83.73	74.67, 92.78	90.8	< 0.0001
Province					
Razavi Khorasan	10	113.99	96.67, 131.30	98.9	< 0.0001
Fars	6	61.97	51.38, 72.55	97.7	< 0.0001
East-Azerbaijan	2	55.12	48.50, 61.74	84.9	0.010
Tehran	6	90.93	82.20, 99.65	89.0	< 0.0001
Hamadan	2	94.25	64.88, 123.63	90.0	0.002
Kermanshah	2	87.16	75.91, 98.41	89.1	0.003
Mazandaran	2	87.68	68.67, 106.69	97.6	< 0.0001
Year					
2004-2012	14	106.68	89.17, 124.19	99.0	< 0.0001
2013-2020	16	75.66	67.98, 83.34	98.0	< 0.0001
Language					
English	22	88.72	78.20, 99.25	99.0	< 0.0001
Persian	8	93.64	83.01, 104.28	96.5	< 0.0001
Study design					
Randomized clinical trial	2	122.68	118.31, 127.04	0.0	0.929
Case-control and cross-sectional	26	88.84	79.93, 97.76	98.7	< 0.0001
Cohort	2	73.71	70.16, 77.27	58.2	0.122
Maternal serum Se concentration at delivery (µg/l)					
Total	4	94.73	72.78, 116.67	98.3	< 0.0001
Health condition					
Healthy	2	98.62	62.60, 134.65	98.7	< 0.0001
Pre-eclampcia	1	71.22	65.83, 76.61		
Preterm	1	110.56	104.30, 116.82		
Dietary Se intake (µg/d)					
Total	23	75.08	63.04, 87.13	100	< 0.0001
Health condition					
Healthy	12	73.91	56.65, 91.16	99.9	< 0.0001
Gestational diabetes mellitus	4	94.36	72.81, 115.92	97.0	< 0.0001
Hypertension	2	53.64	37.38, 69.89	93.5	< 0.0001
Pre-eclampcia	4	57.09	37.55, 76.62	89.9	< 0.0001
Not specified	1	124.70	124.29, 125.11		

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Table 2. Subgroups analysis results.

Subgroups	Effect sizes	Mean	95% CI	Heterogeneity test	
				I^2 (%)	P-value
Trimesters					
First	1	124.70	124.29, 125.11		
Second	3	43.41	41.16, 45.66	0.0	0.575
Third	19	76.61	70.60, 82.62	99.8	< 0.0001
Province					
Isfahan	15	74.90	68.10, 81.69	99.9	< 0.0001
Tehran	2	60.16	57.34, 62.98	5.2	0.304
West-Azerbaijan	1	42.80	38.95, 46.65		
North-Khorasan	3	71.07	6.83, 135.32	99.7	< 0.0001
Markazi	2	114.90	105.69, 124.11	0.0	1.000
Umbilical cord Se concentration (µg/l)					
Total	11	70.98	58.95, 83.02	97.9	< 0.0001
Health condition					
Healthy	6	72.66	55.44, 89.89	98.5	< 0.0001
Unhealthy	5	68.93	52.67, 85.20	96.1	< 0.0001

Table 3. The quality assessment of the included studies.

Study	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome assessments	Incomplete outcome data	Selective outcome reporting	Total score[a]
Noormohammadi et al. 2004	L	U	L	L	L	L	5
Kooshki et al. 2007	L	H	L	L	L	L	5
Iranpour et al. 2009	L	U	L	L	L	L	5
Mohammadzadeh et al. 2009	L	L	L	L	L	L	6
Mortazavi et al. 2009	L	L	L	L	L	L	6
Tara et al. 2010	U	U	L	U	L	L	3
Davaryari et al. 2011	L	U	L	L	L	L	5
Gharehbaghi et al. 2011	L	H	L	L	L	L	5
Maleki et al. 2011	L	L	L	L	L	L	6
Akhlaghi et al. 2012	L	U	L	L	L	L	5
Asemi et al. 2012	U	U	H	H	L	L	4
Boskabadi et al. 2012	U	L	L	U	H	L	3
Farzin and sajadi 2012	L	U	L	L	L	L	5
Khoigani et al. 2012	L	L	L	L	H	L	5
Mohammadzadeh et al. 2012	L	L	L	L	L	L	6
Ghaemi and Foroohari 2013	L	L	L	L	L	L	6
Kazemian et al. 2013	L	L	L	L	L	L	6

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Table 3. The quality assessment of the included studies.

Study	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome assessments	Incomplete outcome data	Selective outcome reporting	Total score[a]
Peirovifar et al. 2013	L	L	L	L	L	L	6
Harandi et al. 2014	L	U	L	L	L	L	5
Monafi et al. 2014	L	H	L	L	L	L	5
Asemi et al. 2015	L	U	L	L	L	L	5
Atarod et al. 2015	L	U	L	L	L	L	5
Jalili et al. 2015	L	H	L	L	H	L	4
Sheykhi et al. 2015	L	H	L	L	L	L	5
Nazemi et al. 2015	L	L	L	L	L	L	6
Mohammad parast et al. 2017	L	L	L	L	L	L	6
Arabpour et al. 2018	U	U	U	L	U	L	2
Daneshzad et al. 2020	L	L	L	L	L	L	6
Mazloomi et al. 2020	L	L	L	L	L	L	6
Moshfeghy et al. 2020	L;	L	L	L	L	L	6

L: low risk, H: high risk, U: unclear risk; [a] overall score considered as number of low risk domains.

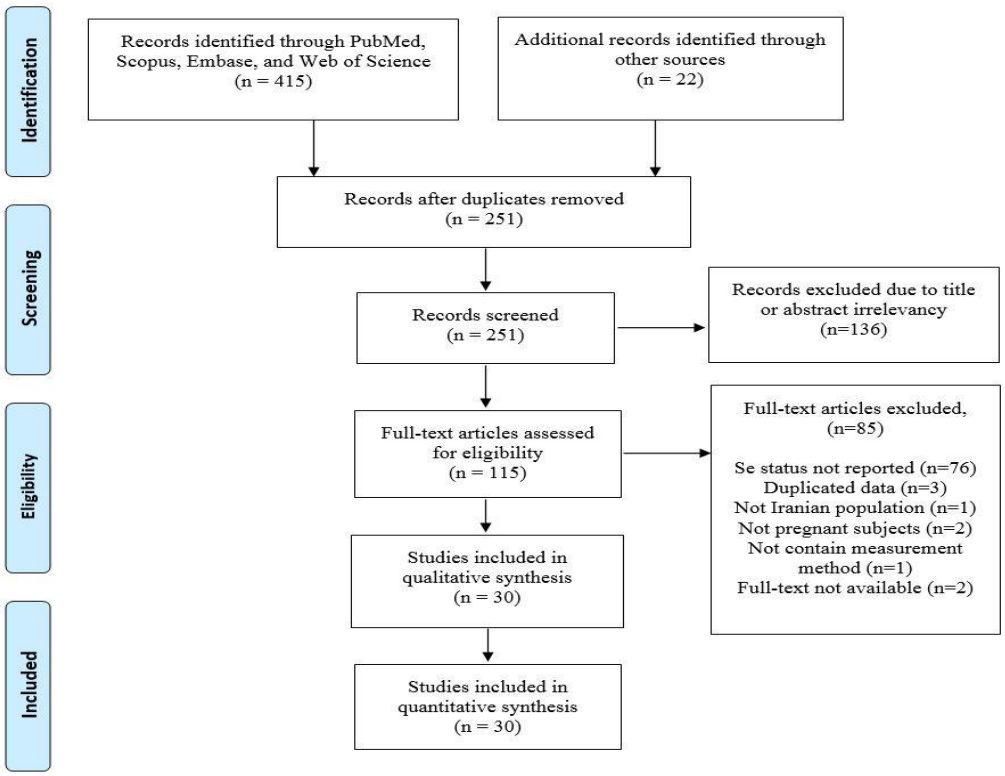

Figure 1. Flow diagram of study selection.

[DOR: 20.1001.1.24767417.2023.8.2.18.6]
[DOI: 10.18502/jnfs.v8i2.12604]

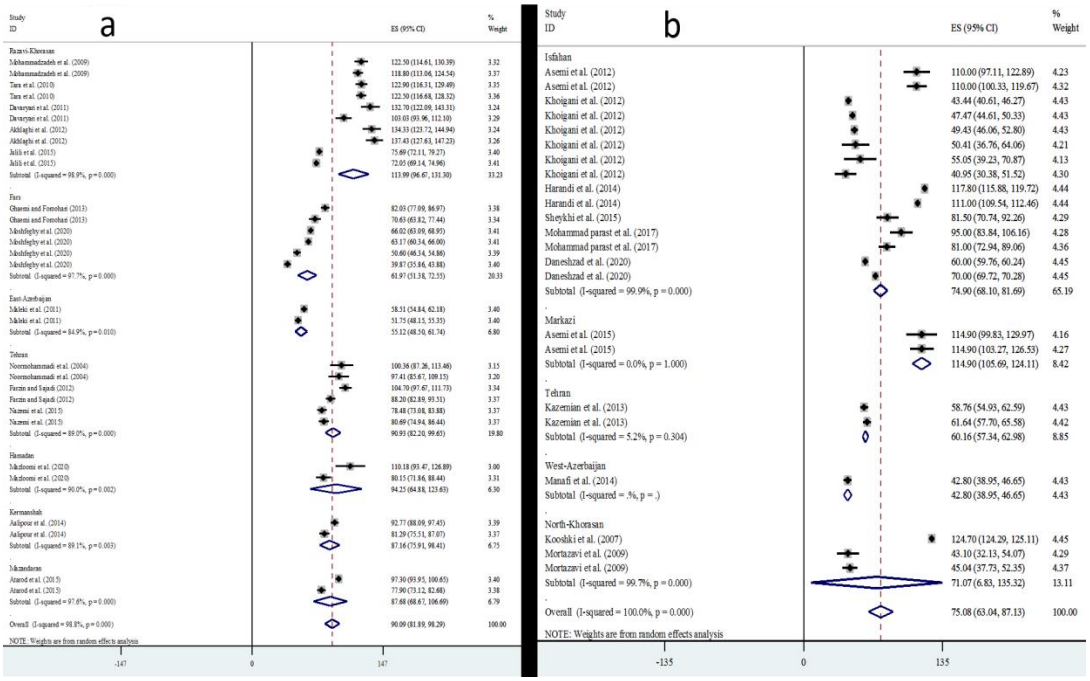

Figure 2. Forest plot included studies that assessed Serum (a) and Dietary (b) Se status in Iranian pregnant women.

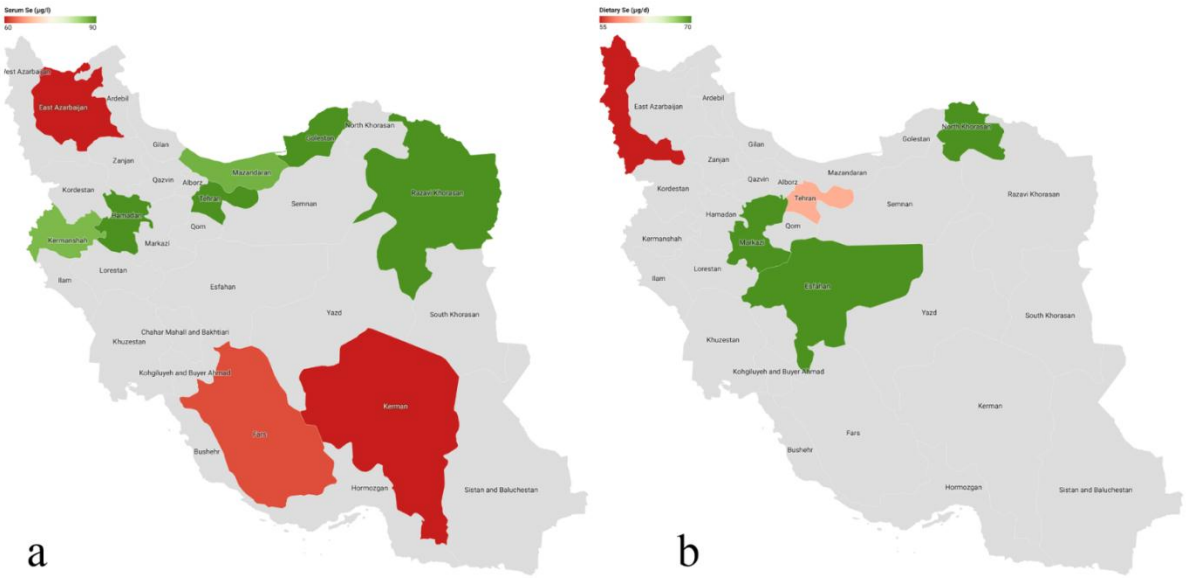

Figure 3. Provincial distribution of serum (**a**) and dietary (**b**) Se in Iranian pregnant women (values of Kerman and Golestan gathered from unpublished reports; Kerman: Arabpour E. Comparison of serum levels of maternal and umbilical cord Se in LBW and normal weight infants (http://eprints.kmu.ac.ir/31684/1/7318.pdf); and Golestan: Kiahosseini M. Evaluation of serum Se levels in pregnant women with preeclampsia and healthy patients referred to Shahid Sayad Shirazi Hospital http://thesis.research.ac.ir/faces/search/bibliographic/ biblioFullView. jspx?_ afPfm=124c2wegry)

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Discussion

To the best of the authors' knowledge, this is the first meta-analysis of Se status conducted on Iranian pregnant women. The meta-analysis of 1245 Iranian pregnant women from 30 studies enabled the authors to assess reliable estimates of serum Se at the national level, and the results showed that the overall estimate of serum Se was 90.09 µg/l. The pooled result was close to the results reported in Korea and Spain (Choi *et al.*, 2016), but it was higher than the results reported in Turkey (Kilinc *et al.*, 2008), Iraq (Alawad *et al.*, 2019), and Poland (Polanska *et al.*, 2016), and lower than that results reported in the United States (Hawkes *et al.*, 2004), and probably Japan (Nakayama *et al.*, 2019) (third trimester was considered).

Stratified analysis based on the provincial distribution of Se (**Figure 2**), Fars, East-Azerbaijan, West-Azerbaijan, and likely Kerman (unpublished), may require more attention by monitoring Se status during pregnancy.

Different serum Se levels in pregnant women have been reported in various countries and could be due to different soil Se, dietary habits, and lifestyle (Stoffaneller and Morse, 2015, Wang *et al.*, 2020), as well as differences in other environmental exposure in the population of each country (Tan *et al.*, 2018). It is noteworthy that the Se status could be compensated in some Se deficient countries by improving policies.

Finland and New Zealand are two countries with experience of Se deficiency in the 1980s. Finland has experienced Se deficiency, which was mainly attributed to low soil Se. Finnish government mandated Se improvement strategies by Se-rich fertilizers for cereal and grassland crops which resulted in a notable improvement in Se status in the Finnish population. The New Zealand government implemented the same in recent years, by enhancing Se concentration in livestock by promoting animal feed Se supplementation in deficient regions and importing wheat from Se-rich countries such as the USA and Australia. Decreased incidence of PE in these two countries has been attributed to the improvement of Se status (Vanderlelie and Perkins, 2011).

Moreover, interventional studies have demonstrated potential benefits of Se supplementation during pregnancy, such as reducing the incidence of PE (Tara *et al.*, 2010a), improving glucose homeostasis (Asemi *et al.*, 2015) and oxidative stress (Asemi *et al.*, 2015, Tara *et al.*, 2010b), and reducing the effect on pulsatility index (an indicator of intrauterine growth restriction) (Mesdaghinia *et al.*, 2017). On the other hand, results from observational studies are still contradictory (Farzin and Sajadi, 2012, Liu *et al.*, 2021, Mohammadzadeh *et al.*, 2009, Solé-Navais *et al.*, 2021).

Stratified analysis by maternal age showed that the mean values for <26-year-old women were 96.68 µg/l (95% CI: 78.30, 115.05 µg/l) and for >26-year-old subgroup were 87.81 µg/l (95% CI: 77.44, 98.17 µg/l). Also, mean values for maternal BMI <26 and >26 subgroups were 93.83µg/l (95% CI: 74.29, 113.36 µg/l) and 108.19µg/l (95% CI: 83.88, 132.49 µg/l), respectively. Subgroup analysis based on years of publication showed that studies published in 2004-2012 including 14 effect sizes had a mean value of 106.68 µg/l (95% CI: 89.17, 124.19 µg/l) and studies published in 2013-2020 including 16 effect sizes had the mean value of 75.66µg/l (95% CI: 67.98, 83.34 µg/l). The decreasing trend in serum Se can be associated with an increasing prevalence of PE among pregnant women in Iran (Kharaghani *et al.*, 2016, Vanderlelie and Perkins, 2011).

According to the result of the meta-analysis, the overall estimate of dietary Se intake revealed 75.08 µg/d by pooling 23 effect sizes from 5 provinces. Of the eleven studies, 6 of them were conducted in Isfahan (54%), 2 in North-Khorasan (18%), and only one study (9%) was conducted in three provinces (Tehran, West-Azerbaijan, Markazi). Data of Isfahan can be divided into two cities, Kashan with dietary Se intake of 113.12 µg/d (95% CI: 105.69, 124.11 µg/d) and Isfahan with 60.50 µg/d (CI: 55.48, 65.51), which can be interpreted as within provincial variation in Se intake.

Considerable differences in dietary Se intake between studies could be due to different

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measurement methods (NUT4, FP), or year of study; moreover, seasonal variation (Ma *et al.*, 2006) and anthropometric indices (Nazemi *et al.*, 2012, Zhong *et al.*, 2018) may affect dietary Se intake. Also, in a study by Jalili *et al.*, a positive relationship between physical activity and serum Se was reported (Jalili *et al.*, 2015).

Signs of Se inadequacy have been seen in different parts of Iran. A study by Hashemipour *et al.* showed a probable Se deficiency in schoolchildren of Semirom (Isfahan) (Hashemipour *et al.*, 2008). In a study conducted in Marvdasht (Fars), Se deficiency was considered an effective factor in goiter prevalence (Dabbaghmanesh *et al.*, 2007). Furthermore, in the south-east of Iran (Zahedan), 22.9% and 29.1% of male and female Thalassemia adolescent patients were diagnosed as Se deficient (Mashhadi *et al.*, 2014). Rafraf *et al.* reported that 53.33% of women of childbearing age in Tabriz (East-Azerbaijan), were Se deficient (<80 µg/l) (Rafraf *et al.*, 2008). These reports, in addition to the provincial Se status, emphasize that more studies on Se status are needed in regions suspected of Se inadequacy such as East and West-Azerbaijan, Isfahan and Fars, and South-East provinces of the country.

The present study represents the first comprehensive meta-analysis examining the Se status in Iranian pregnant women. However, several limitations should be considered in the interpretation of the results. First, the sample size in some of the included studies was not sufficiently large. Second, significant heterogeneity between studies resulted from variation in a year, city, maternal age, and maybe measurement method. A well-designed national assessment is needed to have a reliable evaluation on Se status among pregnant women.

Conclusions

The present study shows that the overall serum and intake of Se in Iranian pregnant women is acceptable. Some parts of the country need monitoring to prevent Se inadequacy and related-adverse complications in pregnancy and conception.

Conflict of interest

The authors declare that they have no conflict of interest.

Authors' contributions

Daneshvar M, Hasanzadeh M, and Djafarian K contributed to the study concept and design; Daneshvar M, Yadegari A, and Djafarian K designed the search strategy and screened papers; Daneshvar M performed statistical analysis; Daneshvar M, Yadegari A, and Hasanzadeh M wrote the manuscript. Finally, all authors approved the manuscript for publishing.

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