INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Polymorphisms and premature ovarian insufficiency and failure: A comprehensive meta-analysis update, subgroup, ranking, and network analysis

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Review question / Objective: **Early identification of women potentially who develop POI and POF is essential for early screening and treatment to improve clinical outcomes. We aim to conduct a comprehensive meta-analysis update, subgroup, ranking and network analysis for all available genetic polymorphism and associated with the POI and POF risk.**

Information sources: **Six electronic databases will be included such as PubMed, Web of Science, Embase, MEDLINE, WANFANG DATA, CNKI. Will contact with authors by emails when necessary.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 January 2022 and was last updated on 11 January 2022 (registration number INPLASY202210052).

INTRODUCTION

Review question / Objective: **Early identification of women potentially who develop POI and POF is essential for early screening and treatment to improve clinical outcomes. We aim to conduct a comprehensive meta-analysis update, subgroup, ranking and network analysis for all available genetic polymorphism and associated with the POI and POF risk.**

Rationale: **Premature ovarian insufficiency (POI) is a clinical syndrome, defined by impaired ovarian function before age of 40 years and characterized by menstrual disturbance with high serum gonadotrophins and low estradiol levels.**

Premature ovarian failure (POF) is a progression of POI with the total loss of ovarian function. POI and POF are complex and heterogeneous disorders presented with infertility, reduced bone mineral density and increased risk of cardiovascular disease and even reduced life expectancy. The diseases are influenced by multiple genetic components.

Condition being studied: Premature ovarian insufficiency (POI) is a clinical syndrome, defined by impaired ovarian function before age of 40 years and characterized by menstrual disturbance with high serum gonadotrophins and low estradiol levels. Premature ovarian failure (POF) is a progression of POI with the total loss of ovarian function. POI and POF are complex and heterogeneous disorders presented with infertility, reduced bone mineral density and increased risk of cardiovascular disease and even reduced life expectancy. The diseases are influenced by multiple genetic components. The prevalence of POI/POF is around 1% , it varies amongst different ethnicities. For example, 1.4% in African American and Hispanic; 1.0% in Caucasian; 0.5% in Chinese and 0.1% in Japanese. Lagergren had reported the highest prevalence as 1.9% in Swedish women. The etiopathogenesis of POI/POF included genetics, metabolic disorders, autoimmunity, iatrogenic procedures, infection and environment . It is a progressive, complex, heterogeneous disorder influenced by multiple components. Genetic factors contribute about 10.8% of cases, such as X chromosome defects, autosomal defects, and isolated point mutations.

METHODS

Search strategy: We will search English and Chinese articles in six electronic databases including PubMed, Web of Science, Embase, MEDLINE, WANFANG DATA, CNKI. All publications until 10 January 2022 will be searched without any restriction of countries or article type. Reference list of all selected articles will independently screened to identify additional studies lsft out in the initial search.

Participant or population: Case-controlled studies including that from the second stage of Genome wide association study (GWAS) compared relevant genes and their variants between POI/POF patients and healthy population will be included. The diagnostic criteria for POI and POF are based on ESHRE guideline on the serum FSH level according to the recommended GDG as POI when serum FSH level >25mIU/mL and POF when serum FSH level >40 mIU/mL on two occasions >4 weeks apart in women with amenorrhea or oligomenorrhea for at least 4 months. Women with chromosomal abnormalities or secondary causes of POI and POF, such as infection, autoimmune disease, ovarian surgery and chemo/radiotherapy treatment, will be excluded.All case-controlled studies of POI and POF will be included for analysis, but only more than 2 independent studies per variants will be included for meta-analysis. Studies included women with DOR will be excluded. Letters, comments and conference abstracts will be excluded as no extractable data available. Review, meta-analysis and animal studies will be excluded. Case report and family studies without control data will be also excluded. Publications language not in Chinese or English will be excluded.

Intervention: Relevant genes and their variants will be the main interventions.

Comparator: Healthy women with regular menstrual cycles and without infertility problem.

Study designs to be included: Randomized controlled trials (RCTs) will be included.

Eligibility criteria: Case-controlled studies including that from the second stage of Genome wide association study (GWAS) compared relevant genes and their variants between POI/POF patients and healthy population will be included. The diagnostic criteria for POI and POF are based on ESHRE guideline on the serum FSH level

according to the recommended GDG as POI when serum FSH level >25mIU/mL and POF when serum FSH level >40 mIU/mL on two occasions >4 weeks apart in women with amenorrhea or oligomenorrhea for at least 4 months.

Information sources: Six electronic databases will be included such as PubMed, Web of Science, Embase, MEDLINE, WANFANG DATA, CNKI. Will contact with authors by emails when necessary.

Main outcome(s): Overall effective size is contributed to POI/POF risk.

Additional outcome(s): Subgroup analysis; Gene networks by STRING database; Cytoscape software applied to perform modular analysis.

Data management: Hardy-Weinberg equilibrium (HWE) by χ2 test with Fisher's exact in the control population was tested for detecting genotyping errors in genotyping studies. Meta-analyses will be carried out with Stata software (Version 13, Stata Corporation, College Station, TX, USA). Heterogeneity will be assessed by Cochran's Q test as I^2 and PQ, significant heterogeneity was defined when I^2>40% and PQ0.05, there is no publication bias. P<0.05 will be considered as statistical significance. Sensitivity analysis will be carried out to recognize the uncertainty of the included studies.

Quality assessment / Risk of bias analysis: Using Cochrane risk of bias assessment tools for RCTs.

Strategy of data synthesis: Hardy-Weinberg equilibrium (HWE) by χ2 test with Fisher's exact in the control population was tested for detecting genotyping errors in genotyping studies. Meta-analyses will be carried out with Stata software (Version 13, Stata Corporation, College Station, TX, USA). Heterogeneity will be assessed by Cochran's Q test as I^2 and PQ, significant heterogeneity was defined when I^2>40% and PQ0.05, there is no publication bias. P<0.05 will be considered as statistical significance. Sensitivity analysis will be carried out to recognize the uncertainty of the included studies.

Subgroup analysis: Subgroup analysis will be conducted in ethnicity and genotype methods. Ethnicities of the study populations maybe include Asian, Caucasian and other populations. Different genotype methods will be include direct sequencing, restriction fragment length polymorphism (RFLP), Taqman polymerase chain reaction (PCR), Southern blot and capillary electrophoresis. RR and 95% CI in each subgroup will be calculated as above. Cochran Q test will be carried out to detect the heterogeneity between the subgroups.

Sensitivity analysis: Sensitivity analysis will be conducted to to recognize the uncertainty of the included studies by software (Stata)

Language: English.

Country(ies) involved: China.

Other relevant information: N.A.

Keywords: Keywords include premature ovarian insufficiency or POI; premature ovarian failure or POF; genetics; polymorphism and predisposition.

Dissemination plans: I intend to publish the review on completion.

Contributions of each author:

Author 1 - Ling Wu - will design and conduct this meta-analysis, go through all the included studies, complete study selection, analyze data and draft the manuscript.
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