CORRELATION OF SERUM PROLACTIN AND THYROID STIMULATING HORMONE CONCENTRATION AMONG INFERTILE WOMEN: A SYSTEMATIC REVIEW AND META-ANALYSIS

DR DELINI DEVI A/P RAMADRAS

DISSERTATION SUBMITTED IN PARTIAL

FULFILLMENT OF THE REQUIREMENTS FOR

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MAIN SUPERVISOR:

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LIST OF FIGURES AND TABLES

LIST OF ABBREVIATIONS AND SYMBOLS

PRL	Prolactin
TRH	Thyrotropin releasing hormone
GnRH	Gonadotrophin releasing hormone
TSH	Thyroid stimulating hormone
FSH	Follicle stimulating hormone
LH	Luteinizing hormone
WHO	World Health Organization
HPO	Hypothalamic-pituitary-ovarian
HPT	Hypothalamic-pituitary-thyroid axis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
JBI	Joanna Briggs Institute
CI	Confidence interval
CLIA	Chemiluminescence Immunoassay
ECLIA	Electrochemiluminescence Immunoassay
EIA	Enzyme Immunoassay
ELFA	Enzyme-Linked Fluorescence assay
ELISA	Enzyme-Linked Immunosorbent Assay
hPRL	hyperprolactinaemia
ns	not stated

r	correlation value
τ^2	tau-squared
I^2	Higgins I squared
Q	Cochran's Q
x^2	chi- square
df	degree of freedom

ABSTRAK

Latar Belakang: Ketidaksuburan menjejaskan berjuta-juta orang dalam usia reproduktif di seluruh dunia. Hormon tiroid dan prolaktin (PRL) menjejaskan reproduktif dan kehamilan; oleh itu, kedua-dua hormon ini mempengaruhi kesuburan. Kajian sistematik dan meta-analisis ini bertujuan untuk menentukan kesahihan kaitan di antara PRL dan "thyroid stimulating hormone" (TSH) dalam kalangan wanita yang tidak subur dan untuk mengenalpasti faktor-faktor yang mempengaruhi nilai korelasi yang dianggarkan.

Kaedah: Carian sistematik pangkalan data dalam talian (PubMed, Scopus, Science Direct, SAGE dan Google Scholar) sehingga Mac 2021 dan carian manual bibliografi kajian yang disertakan telah dijalankan untuk mengenal pasti kajian yang berkaitan. Kertas penyelidikan asal yang menerangkan korelasi atau perkaitan antara PRL dan TSH dalam kalangan wanita usia reproduktif dengan ketidaksuburan (primer dan sekunder) telah dirangkumkan. Penilaian risiko bias dijalankan secara kritis dan berobjektif dengan menggunakan soalan-soalan penilaian kritikal "Joanne Bridge Institut (JBI)". Model kesan rawak digunakan untuk menganggarkan korelasi terkumpul PRL dan TSH, diikuti dengan penilaian heterogeniti dan analisa sensitiviti.

Keputusan: Daripada sejumlah 822 artikel berkaitan yang dikenal pasti, sebanyak sebelas artikel layak dan dimasukkan dalam kajian sistematik dan meta-analisis ini. Anggaran korelasi model kesan rawak antara PRL dan TSH ialah 0.431 (95% CI: 0.251, 0.582) dengan heterogeniti yang ketara antara kajian (I^2=80%, τ2=0.067, p<0.001). Tiada bias penyelidikan yang ketara diperhatikan. Tambahan pula, tempat kajian, jenis ketidaksuburan, saiz sampel dan tahun kajian tidak mempengaruhi anggaran korelasi.

Kesimpulan: Keputusan kami menunjukkan korelasi sederhana positif yang signifikan antara serum PRL dan TSH dalam kalangan wanita yang tidak subur.

Kata kunci

‘Thyroid stimulating hormone’, prolaktin, ketidaksuburan, korelasi, meta-analisis

ABSTRACT

Background: Infertility affects millions of people of reproductive age worldwide. Thyroid hormones and prolactin (PRL) affect reproduction and pregnancy; therefore, these two hormones influence fertility. This systematic review and meta-analysis aimed to summarise the strength of the correlation between serum PRL and thyroid stimulating hormone (TSH) among infertile women and to explore selected factors influencing the correlation.

Method: Systematic search of online databases (PubMed, Scopus, Science Direct, SAGE and Google Scholar) from inception until March 2021 and manual search of bibliographies of the included studies was conducted to identify relevant studies. The original research paper describing the correlation or association between PRL and TSH among reproductive-age women with infertility (primary and secondary) was included. The risk of bias was assessed using the Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies. A random effect model was used to estimate the pooled correlations of PRL and TSH, followed by an assessment of heterogeneity and sensitivity analysis.

Results: From a total of 822 relevant articles identified, eleven articles were eligible and included in this systematic review and meta-analysis. The random effect pooled correlation estimates between PRL and TSH was 0.431 (95% CI: 0.251, 0.582) with substantial heterogeneity between the included studies (I^2=80%, τ^2=0.067, p<0.001). No significant publication bias was observed. Furthermore, study region, types of infertility, sample size and year of the study did not influence the correlation estimates.

Conclusion: Our results highlighted a significant positive moderate correlation between serum PRL and serum TSH among infertile women.

Keywords

Thyroid stimulating hormone, prolactin, infertility, correlation, meta-analysis

CHAPTER 1

INTRODUCTION

1.1 Infertility among women: prevalence

Infertility affects millions of people of reproductive age worldwide and it is known to be a critical component of reproductive health. It is characterized by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce either as an individual or with his/her partner(1). Infertility may be primary if the participation of either partner does not turn out to be successful in achieving pregnancy or secondary if the couple has achieved a pregnancy previously but is currently having difficulty with conception (2).

In 2010, an estimated 48.5 million couples worldwide were infertile (3). In 2010, 1.9% of child-seeking women of reproductive age were unable to have a first live birth (primary infertility),and 10.5% of child-seeking women with a prior live birth were unable to have an additional live birth (secondary infertility) (3).

In Malaysia, the infertility rate is estimated to be around 10 – 15 %. Even though the infertility rate seems quite high, people often undermine this problem since it is not a life-threatening disease, unlike heart attack or diabetes (4).

1.1.1 Serum prolactin and infertility

Prolactin (PRL) is a polypeptide hormone composed of 199 amino acids which are produced at the anterior pituitary. This hormone mainly exerts its function in lactation, breast development during pregnancy and several other actions needed to maintain homeostasis (5). Other factors that stimulate PRL production include thyrotropin-releasing hormone (TRH) and estrogen. TRH has a stimulatory effect on PRL; thus, with

low thyroid hormone in hypothyroidism, the negative feedback on TRH is removed, allowing for excessive (PRL) release (6).

Elevated PRL level is also known to potentially affect fertility by suppressing hypothalamic- pituitary gonadal axis and gonadotropin releasing hormone (GnRH) pulsatility.

This occurs when the elevated PRL level interferes with the secretion and action of gonadotrophins at growing follicles in the ovary, thus impairing gonadal steroid secretion, which further affects positive feedback on gonadotropins. This would further lead to follicle immaturity and, consequently, infertility with anovulation (7).

1.1.2 Serum thyroid stimulating hormone and infertility

Thyroid-stimulating hormone (TSH) is a glycoprotein hormone produced by the anterior pituitary. It consists of two chains which is composed of an alpha chain and a beta chain. The hypothalamic-pituitary axis regulates TSH release (8).

Normal thyroid function is necessary for fertility as thyroid hormones have profound effects on reproduction and pregnancy. Serum TSH is elevated when it is stimulated by the increased production of TRH. This increment, along with follicle-stimulating hormone(FSH) and luteinizing hormone (LH) have synergistic action at granulosa cell and thus have a stimulatory effect on its growth as well as on the secretion of steroid hormones from the ovary that are responsible for normal reproductive function and thus causing infertility (7,9)

1.2 Role of serum PRL and serum TSH among infertile women

Issues pertinent to the female reproductive system are contributed mainly by dysfunction in hypothalamic-pituitary-ovarian axis (10). GnRH is secreted by the hypothalamus in a pulsatile fashion and transported to the anterior pituitary, where it binds to specific receptors on the gonadotrope cells. This results in the biosynthesis and secretion of FSH and LH from the pituitary gonadotrope cells (11).

However, pulsatile secretion of GnRH is affected when there is increased TRH production, especially in hypothyroidism, which concomitantly promotes hyperprolactinaemia (12). This leads to a delayed LH response leading to abnormal follicular development and anovulation. In addition, a decrement in sex hormone-binding globulin production occurs as hypothyroidism also alters the peripheral metabolism of estrogen. Potentially this could be another pathway by which it may have resulted in abnormal feedback at the pituitary level, impairing fertility (13). Furthermore, hyperprolactinaemia could also contribute towards infertility due to elevated levels of dopamine affecting steroidogenesis due to GnRH inhibition (14).

1.3 Rational of this study

Infertility associated with elevated TSH and PRL level is reversible with treatment, irrespective of the type of treatment. Therefore, assessment of serum PRL and TSH is considered important for the evaluation of the cause of infertility. This systematic review and meta-analysis would be the first of its kind conducted in Malaysia, thus, we believe the correlation results between serum TSH and PRL among infertile women would carry a good weightage to the Malaysian population, especially pertaining to infertility management.

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CHAPTER 2

STUDY PROPOSAL

2.1 Introduction and study background

Infertility affects millions of people of reproductive age worldwide. The World Health Organization (WHO) estimates that 8-12 % of couples world worldwide experience difficulty conceiving a child. It is characterised by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce either as an individual or with his/her partner (1).

According to WHO the term primary infertility is used when a woman has never conceived, and secondary infertility is the incapability to conceive in a couple who have had at least one successful conception in the past (2). Infertility is a common problem (up to 21.9%), with primary infertility accounting for 3.5% and secondary infertility for 18.4% (3). It is widely acknowledged that inaccurate estimates of infertility rates exist. Several factors could make it difficult to determine the prevalence, including faulty assessment techniques and unidentified types of infertility brought on by cultural prejudices (4).

Among the factors contributing to reduced fertility are endocrine factors such as hypothyroidism and hyperprolactinaemia. Most issues with the female reproductive system are due to hypothalamic-pituitary-ovarian (HPO) axis dysfunction. The hypothalamus releases GnRH to control the pituitary gland, which affects the pituitary gland, thyroid, and ovaries and results in hormonal abnormalities (5). Hyperprolactianemia and hypothyroidism may result from these disorders. It is well established that hyperprolactinaemia leads to infertility because high dopamine levels

interfere with steroidogenesis by inhibiting GnRH (6). Hypothyroidism may cause ovulation failure leading to infertility and menstrual abnormalities (7).

2.2 Literature review

2.2.1 Prolactin

Prolactin (PRL) is a polypeptide hormone composed of 199 amino acids which are produced at the anterior pituitary. This hormone mainly exerts its function in lactation, breast development during pregnancy, and other actions needed to maintain homeostasis (8). Other factors that stimulate PRL production include thyrotropin-releasing hormone (TRH) and estrogen. TRH has a stimulatory effect on prolactin; thus, with low thyroid hormone in hypothyroidism, the negative feedback on TRH is removed, allowing for excessive PRL release (8).

2..2.2 Thyroid Stimulating Hormone (TSH)

Thyroid-stimulating hormone (TSH) is a glycoprotein hormone produced by the anterior pituitary. It consists of two chains composed of an alpha chain and a beta chain. The hypothalamic-pituitary axis regulates TSH release

Normal thyroid function is necessary for fertility as thyroid hormones affect reproduction and pregnancy. Serum TSH is elevated when it is stimulated by the increased production of TRH. This increment, along with follicle-stimulating hormone(FSH) and luteinising hormone (LH) have synergistic action at granulosa cell and thus have a stimulatory effect on its growth as well as on the secretion of steroid hormones from the ovary that are responsible for normal reproductive function and thus causing infertility (9) (10).

2.2.3 Relationship between serum prolactin and serum thyroid stimulating hormone

PRL secretion is controlled by the PRL inhibitor factor that is secreted from the hypothalamus (11). TRH stimulates PRL and TSH release, causing raised prolactin levels; however, a higher prevalence of hyperprolactinaemia in hypothyroidism is found in females than males because estrogen is required for this effect. The elimination of prolactin is decreased in hypothyroidism patients (12). The inhibitory action of dopamine and dopamine agonists is reduced due to a decrease in sensitivity to dopamine. The thyroid hormone itself is a cause of hyperprolactinaemia (12).

2.2.4 Correlation of serum prolactin and serum thyroid stimulating hormone among infertile women

Hypothyroidism and hyperprolactinaemia are found to be closely interrelated. Hypothyroidism may cause a failure in ovulating regularly in women of the reproductive age group. Some of the women with high PRL levels have been diagnosed with hypothyroidism, which is characterised by high levels of serum TSH (13).

Tasneem et al., stated that there was a higher prevalence of hyperprolactinaemia, together with a greater propensity for thyroid disorders in infertile subjects as compared to those in females with normal fertility (7). This study stated that some of the women with high PRL levels had been observed to have hypothyroidism which was characterised by high levels of serum TSH and low levels of triiodothyronine (T3) and thyroxine (T4). A subclinical hypothyroidism which was associated with hyperprolactinaemia was also reported in some cases.

Clinical and experimental studies have suggested a close relationship between the Hypothalamic-Pituitary-Thyroid axis (HPT) and the HPO axis (14). The specific thyroid

hormone receptors at the ovarian level may regulate the reproductive function and influence of oestrogens at higher levels of the HPT axis, which seem to integrate the reciprocal relationship between these two major endocrine axes (14). Viau et al. stated that patients with increased PRL values were often seen with low thyroid levels. Hyperprolactinaemia which results from longstanding primary hypothyroidism, has been implicated in ovulatory dysfunctions due to inadequate corpus luteal progesterone secretion. Also, when the circulating PRL levels are high, they lead to oligomenorrhoea or amenorrhoea (15).

Kumkum et al. stated that amenorrhoea occurs in hypothyroidism due to hyperprolactinaemia, which results from a defect in the positive feedback of oestrogen on LH, and because of the suppression of LH and FSH. It also mentioned that the prevalence of ovulatory dysfunction was one of the causes of female infertility. The significant association between the abnormal menstrual patterns, as well as the anovulatory cycles, with hyperprolactinaemia in the infertile group, was noted (16).

A study by Prasad Bheem found that decreased levels of LH in the midcycle clearly indicated that there was a possibility of anovulation, which could result in infertility. According to this study, the elevated prolactin values in infertile women clearly showed that there was a mechanism which operated at the anterior pituitary level, which showed an abnormal distribution of FSH and LH, which could further explain the abnormal or delayed ovum maturation. This study showed lower concentrations of serum FSH and LH and higher concentrations of prolactin in primary infertile women than in the control group (17)

Matsuzaki et al. stated that hyperprolactinaemia was associated with a marked reduction in both the frequency and the amplitude of the LH pulses, which indirectly suggested that both the brain and the pituitary gland might be targets for prolactin. According to this

study, the increase which was observed in prolactin may be the cause of the low oestrogen and progesterone concentrations in the infertile subjects, which showed that higher serum prolactin concentrations resulted in decreased serum LH and FSH levels in infertile women. This study also showed that there were lower concentrations of serum FSH and LH and higher concentrations of PRL in primary infertile women than in the control group (18).

According to Binita Goswami's study, there is a significant association between abnormal menstrual patterns, as well as the anovulatory cycles, with hyperprolactinaemia in infertile women. Amenorrhoea occurs in hypothyroidism due to hyperprolactinaemia which results from a defect in the positive feedback of oestrogen on LH, and because of LH and FSH suppression (19). Hyperprolactinaemia adversely affects the fertility potential by impairing the pulsatile secretion of GnRH and hence interfering with ovulation. This disorder has been implicated in menstrual and ovulatory dysfunctions like amenorrhoea, oligomenorrhoea, anovulation, an inadequate corpus luteal phase and galactorrhoea (19).

2.3 Justification of Study

Infertility associated with elevated TSH and prolactin level is reversible with treatment, irrespective of the type of treatment. Therefore, assessment of serum prolactin and TSH is considered important for the evaluation for the cause of infertility. This systematic review and meta-analysis would be the first of its kind conducted in Malaysia, thus, we believe the correlation results between serum TSH and prolactin among infertile women would carry a good weightage to the Malaysian population especially pertaining to infertility management.

2.4 Research Objectives

2.4.1 General objective

To review and analyse the correlation between serum PRL and serum TSH among infertile women

2.4.2 Specific objective

To explore selected factors influencing the correlation between serum PRL and serum TSH among infertile women

2.5 Methodology

a. Inclusion criteria

Women with infertility (primary and secondary) of reproductive age

b. Exclusion criteria

- Male factor infertility and among the female factors were a tubal factor, any congenital anomaly of the urogenital tract, or any apparent organic lesion.
- Any history of thyroid disease or previous thyroid surgery or being on thyroid medications.

c. Recruitment

Not applicable

d. Research tools/tools materials

As attached below

Data extraction form

Review title	
Study ID	

General Information

Name/ID of person extracting data	
Reference citation	
Publication type	

Study Characteristics	Eligibility criteria	Eligibility criteria met? Yes	No	Unclear	Location in text or source
Type of study	cross-sectional /cohort/longitudinal	☐	☐	☐	
Participants	Female in reproductive age	☐	☐	☐	
Types of intervention	Measure serum prolactin and serum thyroid stimulating hormone among infertile women	☐	☐	☐	
Types of comparison	Correlation between prolactin and thyroid stimulating hormone	☐	☐	☐	
Types of outcome measures	Pearson correlation – r value	☐	☐	☐	
INCLUDE ☐		EXCLUDE ☐			
Reason for exclusion					

Participants

	Description		Location in text or source
Population description			
Mean age of subjects			
Inclusion criteria			
Exclusion criteria			
Confounding factors mentioned			
Informed consent obtained	☐ ☐ ☐ Yes No Unclear		
Race/Ethnicity			
Notes:			

Outcomes

	Description as stated in report/paper	Location in text or source
Number of subjects with hyperprolactinaemia		
Number of subjects with elevated TSH		
Method of prolactin measurement		
Method of TSH measurement		
Pearson R value:		

JBI CRITICAL APPRAISAL CHECKLIST FOR ANALYTICAL CROSS-SECTIONAL STUDIES

Author:

Year:

	Yes	No	Unclear	Not applicable
1. Were the criteria for inclusion in the sample clearly defined?	□	□	□	□
2. Were the study subjects and the setting described in detail?	□	□	□	□
3. Was the exposure measured in a valid and reliable way?	□	□	□	□
4. Were objective, standard criteria used for measurement of the condition?	□	□	□	□
5. Were confounding factors identified?	□	□	□	□
6. Were strategies to deal with confounding factors stated?	□	□	□	□
7. Were the outcomes measured in a valid and reliable way?	□	□	□	□
8. Was appropriate statistical analysis used?	□	□	□	□

Overall appraisal: Include □ Exclude □ Seek further info □

Comments (Including reason for exclusion)

Ethical Consideration

Not applicable.

Proposed data analysis and expected results

Author	Author year	Country	Region	Design	Healthy control	Study subjects	Age	Mean Age	Test TSH	Reference range for TSH	Test PRL	Reference range for prolactin	Upper reference range	Blood taking procedure	Elevated TSH (n)	Elevated prolactin (n)	Correlation (r)

Study characteristics	Number of studies	Random effect of pooled prevalence	95% CI of pooled prevalence	Within group heterogeneity			Between group heterogeneity	
				I^2(%)	r^2	p-value	x^2 (df)	p-value
Region								
South East Asia								
Eastern Mediterranean Region								
Type of Fertility								
Primary								
Secondary								
Primary and secondary								

PRISMA Flow Chart

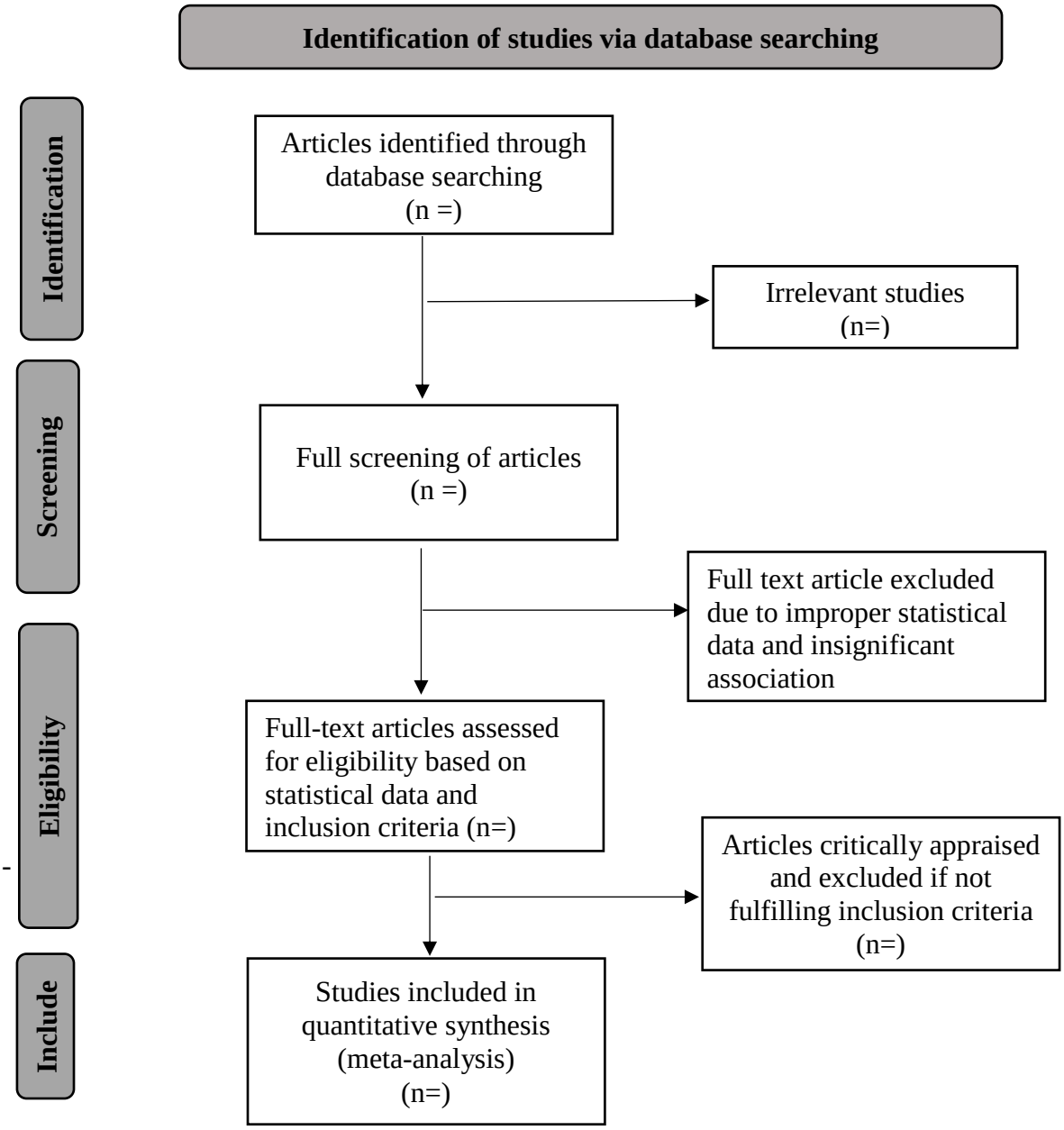
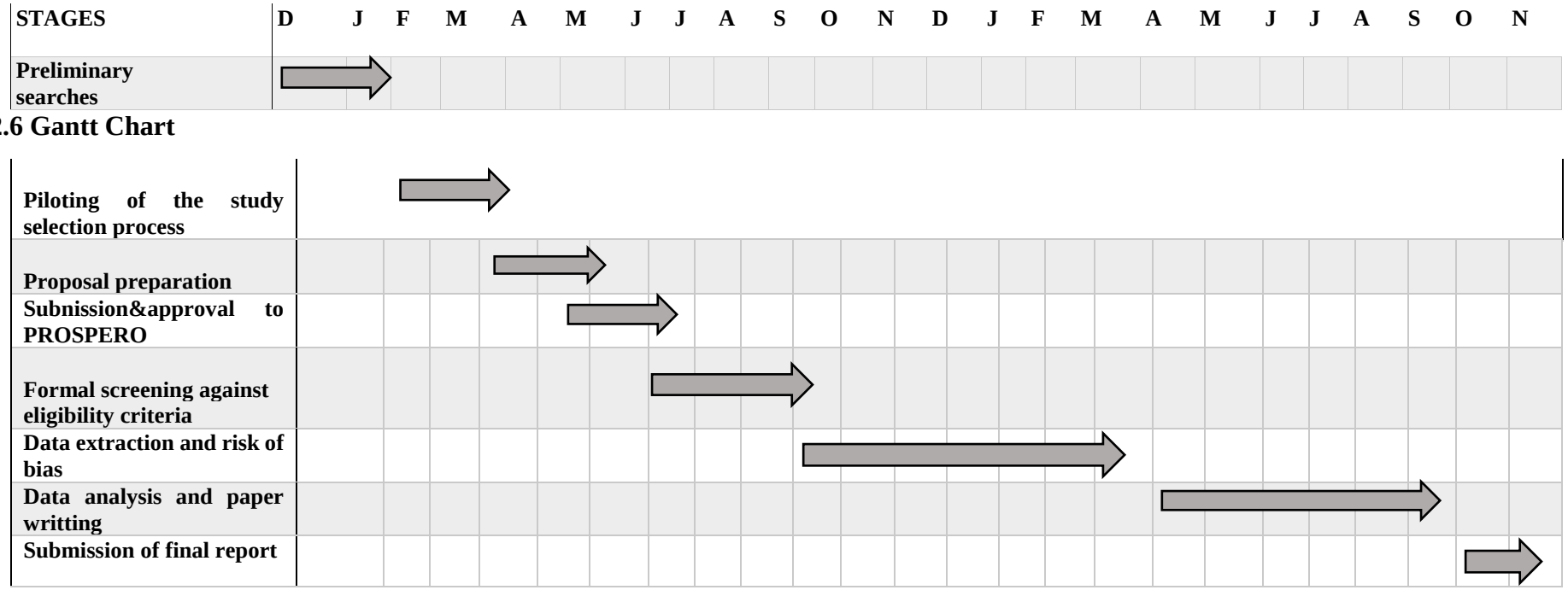


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

2.6 Gantt Chart



2.7 Ethical exemption

This study entitled correlation of serum prolactin and serum thyroid stimulating hormone among infertile women: a systematic review and meta-analysis had been reviewed by the Human Research Ethics Committee USM and was exempted from the ethical review. Letter of exemption has been attached (Appendix A)

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CHAPTER 3

MANUSCRIPT

Title page

Correlation of Serum Prolactin and Thyroid Stimulating Hormone Concentration Among Infertile Women: A Systematic Review and Meta-Analysis.

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