

Correlation of Menstrual Irregularities with Thyroid Disorders in Infertile Women

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Submitted for Publication: 15-09-2023
Accepted for Publication 11-12-2023

How to Cite: Rahman R, Jan F, Faisal N, Aftab L, Salman A, Waheed A. Correlation of Menstrual Irregularities with Thyroid Disorders in Infertile Women. *APMC* 2023;17(4):533-539. DOI: 10.29054/APMC/2023.1509

ABSTRACT

Background: In current era menstrual irregularities are very common problem mainly in adulthood age. It creates a lot of stress not only on the social behavior of females but can also leads to infertility especially if it is related to hormonal imbalance. Among them, thyroid dysfunction can result in reproductive cycle problems like menorrhagia which is commonly seen in hypothyroid females. **Objective:** The aim of this study was to highlight menstrual disorders & investigate thyroid hormone levels in both fertile & infertile women. As it will help us to evaluate the correlation between menstrual irregularities & hypo- and hyperthyroidism. **Study Design:** A case control study, patients were analyzed by the help of questionnaire which include history, clinical examination & laboratory investigations. **Settings:** This clinical study was done in Gynecology Department of Madinah Teaching Hospital, Faisalabad Pakistan. **Duration:** 6 months from February 2018 to July 2018. **Methods:** Almost 132 females belonging to 20-35 years of age were selected, among them 86 females were infertile & 46 were fertile. **Results:** Results were evaluated by SPSS version 20. Most of the infertile women were euthyroid and hyperthyroidism was more common among them. The prevalence of hyperthyroidism and hypothyroidism was about 26.7% and 9.3% respectively. Almost all infertile females with thyroid disorders showed menstrual irregularities. Thyroid hormonal status was also assessed with different types of menstrual disarrays and it was non-significant. **Conclusion:** Thyroid profile should be recommended to those infertile women who are having menstrual irregularities so that other needless investigations can be avoided. Evaluation of thyroid status in an infertile couple is important and easy. Its treatment is simple and has reversible or preventable effects on subfertility.

Keywords: Hypothyroidism, Hyperthyroidism, Amenorrhoea, Menorrhagia.

INTRODUCTION

Menstruation is cyclical phenomena that happens at regular intervals and involves the discharge of blood via vagina from uterus occurring at regular intervals in the duration of reproductive cycle of females.¹ Some women may experience their monthly cycle with a little bit or no symptoms at all. While other females may get some emotional or physical symptoms either before or during their cycles.² Studies have exposed a number of menstrual cycle disorders in a large proportion of women in their reproductive age.³ Not only the women but young girls may also have the problems of heavy menstrual flow

or missed cycle along with mood swings which may disturb the daily activities of their lives.² The disproportion of socioeconomic status of a country has a serious impact not only on general health of a population but the menstrual disorders are also more prevalent in females belonging to lower socioeconomic class.⁴

A complex endocrine axis regulates the menstrual cycle by controlling the activities of ovaries & endometrium. The cyclical length of menstrual cycle is usually associated with fertility & reproductive health of females.⁵ Hence the characteristics of menstrual cycle may provide a non-invasive parameter for the

determination of reproductive health of women making them suitable for epidemiologic research.⁵

A network of hormones like gonadotrophin releasing hormones, follicle stimulating hormones & luteinizing hormones along with steroid hormones like progesterone & estrogen play a key role in menstrual cycle regulation by modifying hypothalamic-pituitary-ovarian axis. This coordination is closely resembled to hypothalamic-pituitary-thyroid axis which overwhelms the thyroid function.⁶ Thus hypothalamic-pituitary-ovarian axis (HPO) and hypothalamic-pituitary-thyroid axis (HPT) both act together in a cohesive manner.² But the association of thyroid function & female reproductive system is very much complex.⁷ As compared to men, thyroid disorders are about four to five times more common in women⁸ and can be greatly seen during the time of puberty, pregnancy & menopause.⁷ Both hypo & hyperthyroidism are linked with reproductive cycle disarrays including infertility, abnormal sexual development and menstrual irregularities.^{2,8,9}

The global prevalence of thyroid disorders, considered to be as a most important public health dilemma is about 5%-10%. In Pakistan the prevalence of hyperthyroidism and hypothyroidism is almost 5.1% and 4.1% respectively.¹⁰

Hypothyroidism is the most common cause of infertility due to its effect on reproductive cycle causing anovulation, luteal phase defect, menstrual irregularities & hyperprolactinemia.^{2,11} Abnormal uterine bleeding can occur in many ways like Menorrhagia, Oligomenorrhea, Polymenorrhagia, Amenorrhea and dysfunctional uterine bleeding.¹¹ Thyroid hormones regulate the female reproductive cycle by either directly acting on ovaries or indirectly by acting along with sex hormone binding globulins.⁹

Low level of T₃ & T₄ causes increase production of TSH from pituitary gland and it also stimulates release of TRH from hypothalamus which in turn controls the release of prolactin from pituitary gland.^{2,12,13} A positive correlation of about 4:1 was found in infertile women between hypothyroidism and hyperprolactinemia.¹⁴

Decreased level of thyroid hormones can also inhibit the release of GnRH from hypothalamus and LH & FSH levels decline in turn.¹⁵ Some studies have appreciated the presence of thyroid hormones receptors in human oocytes & they work in concert with the LH/HCG receptors facilitated by FSH in order to employ direct stimulation on granulosa cell activity and trophoblastic differentiation.² The significant increased concentration of TSH was found in those females who produced oocytes but unable to achieve fertilization.²

Ovulation occurring in mid-cycle phase is regulated by the coordinate control of luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin and thyroid hormones on hypothalamic-pituitary-ovarian axis.¹⁶ For ovulation to happen ovaries are stimulated by LH. By upsetting the levels of reproductive hormones hypothyroidism halts ovulation.² The growth of follicles occurs due to FSH stimulation but ovulation fails to take place because of lack of LH surge hence menorrhagia associated with anovulatory cycle can occur. Thus, hypothyroidism along with hyperprolactinemia can lead to delayed LH response followed by inadequate corpus luteum development.¹⁷ No progesterone can be produced subsequently. The proliferative phase of endometrium continues markedly. As a result, most cases of anovulatory cycles occur regularly but along with normal menstrual flow. On the other hand, menorrhagia can occur because of irregular shedding of proliferative endometrium.²

When follicle involutes, the outcome will be the withdrawal bleeding due to low estrogen level. But hypothyroidism can lead to raised estrogen level because of less SHBG production and its low peripheral metabolism. This persistent elevated level of estrogen also interferes with ovulation by disrupting midcycle preovulatory FSH and LH surge and can upset the menstrual cycle.¹⁸ Estrogen also enhances the response of prolactin under the effect of TRH.¹⁹

Maturation of fertilized egg occurs in a normal luteal phase which is about 13 to 15 days.

Luteal phase generally starts after ovulation and lasts till the commencement of menstruation. Short luteal phase has been observed in hypothyroid women. Thus, the fertilized ovum is unable to sustain in a shortened luteal phase and loss of early pregnancy can be seen in such women. The risk of conception failure & abortion are the hall mark of luteal phase defect due to hormonal imbalance which will affect the ovarian functions & endometrial lining of uterus leading impaired fertilization.^{2,16,20}

It has been confirmed that TSH plays a pivotal role in successful implantation as it directly controls the nature of endometrium by up regulating the expression of growth factors.²¹ After implantation, the further growth of gestational sac also depends upon assembly of systemic and local endocrine functions. Endocrine disarrays are responsible for miscarriages in almost ~20-25% cases.²² For effective implantation, LIF (Leukemia inhibitory factor), is also required which is under control of TSH. LIF is a cytokine which is expressed in endometrium during mid-secretory phase.²¹ Threatened abortion, placental abruption, preterm labor, preeclampsia and postpartum hemorrhage are the

complications of pregnancy which can be seen in those mothers who have thyroid problems. High rate of miscarriages was found among hyperthyroid women.²³

Along with it, fetal complications seen in hyperthyroid females are intrauterine growth retardation (IUGR), increase risk of neonatal death and still birth. Also, the risk of neonatal hypothyroidism and hyperthyroidism, neonatal hyperbilirubinemia and rate of perinatal mortality is high.²³

Taking in view the basic aim of this study is to identify thyroid disorders in infertile females as majority of females presenting in MTH belong to low socioeconomic status. Keeping in mind also that about 50% population of Pakistan is at risk of iodine dearth which is required for thyroid hormone synthesis. This study also emphasizes the correlation of menstrual irregularities with thyroid disorders as it is noninvasive & cost effective as compared to other invasive investigations. Also, the drug therapy may be a much better choice than surgical interventions, if thyroid disorder is found out.²

METHODS

A case control study was done in outdoor of gynecology department of Madinah Teaching Hospital (MTH) Faisalabad in collaboration with MTH laboratory.

Study was basically focused on infertile females of reproductive age groups. 86 infertile females of age 20-35 years were selected as a case group and 46 fertile females of similar age group were included as a control group. The duration of marriage was more than 1 year.

The excluding criteria was women ages below 20 and above 35 years. History of any congenital disorders, intake of drugs like L-thyroxin, any chronic illness like hypertension, diabetes mellitus, chronic renal failure, endometriosis and tuberculosis, any liver and cardiac diseases was also ruled out.

Before the start of study informed consents were taken from all individuals by describing the topic of study and highlighting the impact of study on general population while assuring the confidentiality of their personal information. A questionnaire was designed to assemble all relevant data. A thorough clinical history, general physical examination & laboratory investigations were done in selected females and all information was noted on individual Performa.

Clinical history includes lifestyle of every couple, family history of goiter, contraceptive history, menstrual history, history of lactational amenorrhea and all previous deliveries was asked in detail. In clinical examinations, general physical examination, pelvic examination and thyroid examination was done. General physical

examination include temperature, pulse rate, blood pressure & BMI was also calculated and recorded.

After counseling of patients, husband semen analysis was indorsed as a definite test to rule out any male pathology. Transvaginal ultrasonography of pelvis of all individuals was done to assess the condition of adnexa, any pathology in ovaries, endometrium & myometrium to find out any pelvic mass.

The blood samples of all participants were analyzed for hormonal profile including T₃, T₄ & TSH at Madinah Teaching Hospital laboratory by means of chemiluminescent Microparticle Immunoassay (CMIA) technology (Abbott / ARCHITECT i1000SR) with the help of a flexible assay known as Chemiflex.

Results were obtained and Statistical Package for Social Sciences (SPSS) software version 20 was used to analyze and assemble all these results.

RESULTS

The research was done on 132 patients and out of them 86 infertile females were belong to case group while 46 fertile group were belonging to control group. For further evaluation, TVS & thyroid profile including T₃, T₄ & TSH along with TVS was done. In order to make a definite diagnosis, all individuals were categorized into three sub groups: Euthyroid, Hypothyroid and Hyperthyroid by doing their thyroid function tests at MTH laboratory Faisalabad. Menstrual irregularities were asked in detail from all participants and correlation of menstrual irregularities with thyroid disorders was found out.

The females were divided in two main groups as case and control. The case group individuals were further subcategorized into primary infertile and secondary infertile groups.

Table 1: Patients examined in MTH Faisalabad (O.P.D)

Case Group		Control Group
Primary Infertile Group	Secondary Infertile Group	
45	41	46

In order to rule out pregnancy especially in females having amenorrhea, urine test for β -HCG was done and it was observed negative in all participants. Also the TVS report of every individual was normal. Thyroid profile was performed in all subjects and participants were divided into euthyroid, hypothyroid & hyperthyroid.

Table 2: Thyroid Status of infertile women

Thyroid Profile	Primary Infertile (n=45)	Secondary Infertile (n=41)	Total Infertile (n=86)	Control Group (n=46)
Euthyroid	28 (62.2%)	27 (65.9%)	55 (64%)	38 (82.60%)
Hypothyroid	05 (11.11%)	03 (7.3%)	08 (9.3%)	04 (8.70%)
Hyperthyroid	12 (26.67%)	11 (26.83%)	23 (26.7%)	04 (8.70%)

The hypo & hyperthyroid females were further subcategorized into clinical & subclinical cases depending upon their results obtained from laboratory.

For example, clinical hypothyroidism was confirmed by increased TSH level along with decreased FT3 and FT4 levels. Whereas in subclinical hypothyroidism only TSH was raised and FT3 and FT4 were remain normal. (Normal ranges for FT4; 0.70-1.48 ng/ dL, FT3; 1.71-3.71 pg/ mL & TSH; 0.35-4.94 μ IU/mL).

Table 3: Categories of hypo- & hyperthyroid infertile women

Thyroid Profile		Primary Infertile (n=45)	Secondary Infertile (n=41)	Total Infertile (n=86)	Control Group (n=46)
Hypothyroid	Subclinical	01 (20%)	0	01 (12.5%)	04 (100%)
	Clinical	04 (80%)	03 (100%)	07 (87.5%)	0
	Total	05 (11.11%)	03 (7.3%)	08 (9.3%)	04 (8.70%)
Hyperthyroid	Subclinical	03 (25%)	02 (18.18%)	05 (21.73%)	04 (100%)
	Clinical	09 (75%)	09 (81.81%)	18 (78.26%)	0
	Total	12 (26.67%)	11 (26.83%)	23 (26.7%)	04 (8.70%)

Proper menstrual history was taken from all participants of both primary & secondary infertile groups and depending upon the flow & duration, the menstrual disorders were categorized as Irregular cycle, amenorrhea and menorrhagia. While some patients were also having complaints of dysmenorrhea.

Table 4: Correlation of thyroid dysfunction with menstrual disorders in primary infertile women

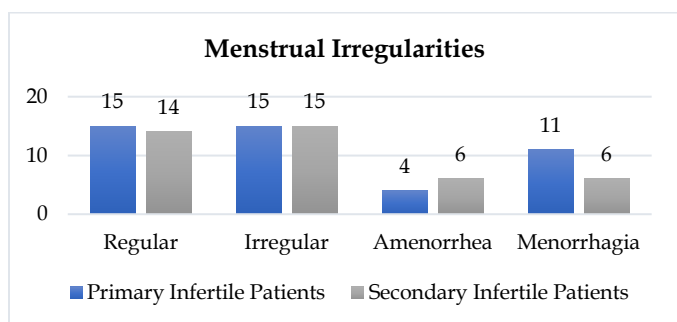
Presenting complaints	Euthyroid	Hypothyroid		Hyperthyroid	
		Subclinical	Clinical	Subclinical	Clinical
Regular menstrual cycle (n=15)	11 (39.29%)	0	01 (20%)	01 (8.33%)	02 (16.67%)
Menstrual disorders	Irregular (n=15)	10 (58.8%)	0	02 (22.22%)	03 (33.33%)
	Amenorrhea (n=04)	01 (5.88%)	0	0	03 (33.33%)
	Menorrhagia (n=11)	06 (35.29%)	01 (25%)	03 (75%)	0
Total (n=45)	28 (62.2%)	01 (2.2%)	04 (8.9%)	03 (6.7%)	09 (20%)
*p-value	0.213 ^{NS}	-	0.238 ^{NS}	0.238 ^{NS}	0.261 ^{NS}

The data is expressed as number (percentage). *p-value was calculated by using chi-square test.

Table 5: Correlation of thyroid dysfunction with menstrual disorders in secondary infertile women

Presenting complaints	Euthyroid	Hypothyroid		Hyperthyroid	
		Subclinical	Clinical	Subclinical	Clinical
Regular (n=14)	13 (48.14%)	0	0	0	01 (9.1%)
Menstrual disorders	Irregular (n=15)	10 (71.42%)	01 (33.33%)	01 (10%)	03 (30%)
	Amenorrhea (n=06)	01 (7.14%)	0	01 (10%)	04 (40%)
	Menorrhagia (n=06)	03 (21.42%)	0	02 (66.67%)	0
Total (n=41)	27 (65.9%)	0	03 (7.3%)	02 (4.9%)	09 (22.0%)
*p-value	0.213 ^{NS}	-	0.238 ^{NS}	0.261 ^{NS}	0.238 ^{NS}

The data is expressed as number (percentage). *P-value was calculated by using chi-square test.

Figure 1: Menstrual disorders in primary & secondary infertile women

DISCUSSION

In our set up infertility is a social stigma and it must be rule out. This research was focused on infertile women of age 20-35 years coming to Madinah Teaching Hospital Faisalabad who belong to underprivileged areas. The drive of this study was to review the understanding of physiology, pathophysiology, and clinical aspects of interactions between thyroidal and gonadal axes.

Human body tissues are very much sensitive to fluctuating hormone levels that usually happen during a menstrual cycle. According to some studies, fluctuating

hormonal levels may also change the brain's neurotransmitters, mainly serotonin. However, it is unclear why some females may get the symptoms of premenstrual syndrome like bloatedness, fatigue, irritability & mood swings while others not, however the levels of progesterone & estrogen are same in all females. Thus the exact cause of PMS is unknown. It may be explained that sensitivity of some females to change in hormonal levels is variable.² In current study the premenstrual symptoms was observed in about 45% individuals.

As the menstrual cycle disorders create a lot of stress on the psychological behavior of women and all of them need proper evaluation. According to some studies, menstrual cycle problems are expected to occur in three out of four those infertile women who are having thyroid problems.²

In current study 62.2% primary infertile females were euthyroid. In these euthyroid infertile women, 39.29% came with no menstrual disorders while menstrual irregularities were observed in 60.7% cases. Among menstrual problems, about 58.8% cases were of irregular pattern which was followed by menorrhagia (35.29%) and then amenorrhea (5.88%). In case of secondary infertile females, 48.14% euthyroid females presented with regular menstrual cycle while 51.85% with menstrual disorders. Among them irregular pattern was the most common presentation and was observed in 71.4% females. Menorrhagia and amenorrhea were about 21.42% and 7.14% respectively. It can be shown that the total number of euthyroid females with regular cycle were about 43.6% cases while abnormal pattern was seen in 56% cases. Rahman *et al.*²⁴ also observed the normal cycle in 36.7% cases and abnormal pattern in 30% cases of euthyroid females.

Current studies showed that hypothyroidism is the cause of infertility in 9.3% of case group. In 8.9% hypothyroid primary infertile females, regular cycle was present in 20% individuals while menstrual irregularities were observed in 80% hypothyroid females in this study. Out of which menorrhagia was the most common symptom among all. And no case of amenorrhea and irregular cycle was reported. About 7.3% secondary infertile women were hypothyroid in above study. However, no hypothyroid females in this group came with amenorrhea and regular menstrual cycle while 66.67% cases were presented with menorrhagia and 33.3% cases with irregular pattern.

Subclinical hypothyroidism with menstrual irregularities was not so much common in present study which is in accordance to Sharma and Kumar *et al.*²⁵ However, Rahman *et al.*²⁴ found 23.3% cases of subclinical hypothyroid with menstrual problems. We also found

only 12% cases of clinical hypothyroid females with regular pattern & 6.7% by Rahman *et al.*²⁴ While 88% of total hypothyroid females in this study were presented with abnormal menstrual pattern and this was 62.5% according to Goswami *et al.*²⁶ The prevalence of irregular menstrual cycle seen in only clinical hypothyroid females and it was about 14.28% & 6.5% by Sharma and Gandhi *et al.*²⁷

In United States the incidence of primary & secondary amenorrhea was found to be 1% & about 4% per year respectively. There is no proof that prevalence of amenorrhea differs by ethnicity or country of origin. While environmental factors especially related to nutrition like intake of iodized salt & existence of any chronic disease can have an effect². Because of interaction of thyroid hormone with female reproductive cycle, Ovulatory dysfunction can be seen in severe hypothyroid females.² However, no case of amenorrhea in hypothyroid infertile females has been reported in present study.

Hypothyroidism is also correlated with menorrhagia & is the most common menstrual irregularities found in hypothyroid infertile women² due to decreased production of coagulation factors, like factors VII, VIII, IX, and XI.²⁸ In current study, menorrhagia (85%) was found as the most common problem among all hypothyroid females, out of which 71.4% females with menorrhagia were overt hypothyroidism and 14.28% cases were subclinical hypothyroidism and Ajmani and Sarbhai *et al.*⁹ observed it in 50% cases. It has been reported that after taking thyroxin as a therapy for hypothyroidism can not only improve the symptoms like depression & infertility but it can also improve the symptoms of menorrhagia.²

In present study, 26.7% cases were reported as hyperthyroidism. Among hyperthyroid primary infertile women, 25% cases were presented with regular cycle while 75% hyperthyroid cases had menstrual disorders. Those hyperthyroid females who had menstrual disorders, irregular pattern was observed in 55.55% cases which was followed by amenorrhea and menorrhagia in 33.33% & 11.11% cases respectively. Secondary infertile females who were hyperthyroid regular cycle was observed in 9.1% cases while about 91% females came with complaints of menstrual irregularities. Amenorrhea and irregular cycle were present in 50% cases and 40% cases respectively. Menorrhagia was observed in only 10% females in current studies & it was also found in hyperthyroid females by Sangeeta *et al.*²⁹ Subclinical hyperthyroidism with menstrual irregularities was observed in 23% cases in current study. Goswami *et al.*²⁶ also reported menstrual irregularities in 62.5% hyperthyroid infertile females.

Hyperthyroidism is usually associated with amenorrhea and oligomenorrhea according to Krassas and Poppe *et al.*²⁸ In this study among hyperthyroid females irregular cycle followed by amenorrhea was observed most commonly which is also reported by Khatiwada *et al.*³⁰

In short, normal menstrual pattern was observed in 33.7% of total infertile females as compared to 66.3% infertile females presented with menstrual irregularities. Out of which only 46% females were having thyroid problems and rest of them were euthyroid. The prevalence of menstrual disorders in hyperthyroid and hypothyroid infertile women was much greater than control group. Same was also observed by Ajmani and Sarbhai *et al.*⁹ & Khatiwada *et al.*³⁰ No significant difference in the thyroid functions according to menstrual pattern was assessed by Khatiwada *et al.*³⁰ which is in accordance to present study as p value showed. This may be due to less number of women presented with thyroid disorders.

CONCLUSION

Thyroid disorders are the risk factor of infertility, however in current study it is not much prevalent among infertile women. Even though thyroid hormones have a significant effect on menstrual cycle but many euthyroid females were also presented with menstrual irregularities. So one should kept in mind that some other physical or hormonal disorders can also cause menstrual irregularities. Like the level of thyroid peroxidase antibodies (anti-TPO) increases with age which may cause hypothyroidism so the levels of antithyroid antibodies like TPOAb along with TgAb & TRAb should also be a part of screening of thyroid profile among infertile women. As it will help us not only in diagnosis & monitoring but also in prognosis of those cases where clinical presentation is not clear.

On the other hand, menstrual irregularities were also very much common in both hypothyroid & hyperthyroid infertile females. So, if these individuals are properly identified, investigated & treated then they may get benefit and other procedures can be evaded. As the pharmacotherapy is a better choice than surgical intervention. Also, both fertility restoration and menstrual cycle normalization are possible. So it is endorsed that thyroid function test should be a part of routine investigations as there is strong correlation of menorrhagia with hypothyroidism in current study.

LIMITATIONS

We had a number of limitations. As majority of our participants were illiterate & belong to rural areas. They cannot give us proper history about dietary intake of iodized salt. They were also unable to give proper family history while the ratio of cousin marriage is high in our urban population. Furthermore, due to constraint

resources we were unable to check the levels of LH, FSH & prolactin hormones which can affect the reproductive cycle in women.

SUGGESTIONS / RECOMMENDATIONS

Thyroid hormonal profile should be a part of our routine investigation in order to rule out infertility. Also hypothyroidism decreases the levels of coagulation factors like VII, VIII, IX & XI. So the hypothyroid females should be treated with Thyroxine.

CONFLICT OF INTEREST / DISCLOSURE

There are no conflicts of interest.

ACKNOWLEDGEMENTS

We acknowledge the gynecology department & laboratory of Madinah Teaching Hospital for facilitation in data collection & analysis.

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