

A case control study of stress and infertility in hypothyroid reproductive age group women residing in Udaipur, Rajasthan, India

Neha Sharma^{1,*}, Pooja Gandhi², K.L. Mali³, Arjun Lal Jain⁴

¹Assistant professor, ³Professor & HOD, Dept. of Biochemistry, ²HOD & Consultant IVF Department,

⁴Assistant professor, Blood Bank Incharge, Dept. of Pathology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan

***Corresponding Author:**

E-mail: nehal6.sharma@gmail.com

Abstract

Introduction: Challenges to human being fertility may occur from numerous conditions caused through hereditary abnormalities, communicable or else environmental agents, as well as certain behaviors. Reproduction is one of the essential functions for every life form. The age of male or female is a reason along with others to be able to have an effect on fertility. Owing to chase of education as well as supplementary factors, lots of couple is choose to wait for childbearing.

Methods: This study was done on hypothyroid reproductive age group women at Geetanjali Medical College and Hospital, Udaipur, Rajasthan after obtaining GMCH ethical committee approval. Serum TSH, FSH LH, PRL was performed on automated system cobas e-411 (CLIA) and IL-6 was done by ELISA method.

Results and conclusions: Significant changes were occurred in serum FSH, LH and PRL along with IL-6 in 20-36 years of age group of subjects and changes in menstrual pattern along with the stress. Positive correlation between IL-6 and TSH was found in hypothyroid reproductive age group women, individuals who were childless.

Key words: Hypothyroid, Infertility, Oligomenorrhoea, Prolactin, Thyroid hormone

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Introduction

The wish for to have kids be important and common, also for a great minority this is not simply fulfilled. Challenges to reproduction take place from inherited abnormalities, contagious and environmental agents, belated childbearing, actions, or certain diseases. Consciousness of the probable risk may direct some community to adopt corrective behaviors and preserve fertility. A lot of people, however, locate themselves cope with sterility [1]

Less than 30 year, a woman's probability of conceive possibly as 71%, while over 36, just be 41% [2]. Challenges to human being fertility may perhaps develop beginning lots of conditions caused through genetic abnormality, transmittable or environmental factors, or certain behaviors.

Natural aging process also situates a limit toward human fertility. In some persons, fertility window close prior than predictable. New trends in the direction of postpone period on first pregnancy cover highlighted natural restrictions of fertility with accelerate the development as well as make use of medical knowledge to triumph over such limits. The amount of primary birth to women 30 years as well as elder has

improved additional, fourfold ever since 1975, beginning 5% to 24% in to 2006. The total figure of these births amplified starting above 69,000 to just about 405,000 throughout this period [3, 4]

It is predictable that worldwide 60-80 million couple undergo infertility each year, of which most likely among 15-20 millions (25%) are within India only [5,6]. Particular factors disturbing women infertility consist of hormonal or endocrine disorder (menstrual or ovulatory disturbances), tubal factor (occlusions, pelvic adhesions and extra tubal abnormalities), acquire non-tubal factor (cervical or uterine disturbances), sexual dysfunction with innate abnormalities. [7]

Thyroid hormones are closely interacting through the women's reproductive hormones (estrogens and progesterone) to defend normal role of the ovaries along with maturation of egg (oocyte) [8]. Normal level of thyroid hormone is therefore compulsory for usual fertility. In women, the occurrence was superior, at 11.4%, while compare with men, within whom the occurrence was 6.2%. The frequency of subclinical hypothyroidism improved with age.[9] Hormones are liable for maintain mood, reproduction, be asleep, sexual characteristics drive, and ability to switch stress, now to name a few function [10]. Therefore it stand to cause that as they are not in balance, the range of symptom is extensive and variable depends on the individual and what life is dishing out at that moment. (Health and Wellness Institute.)

Women frequently are diagnose and treated among major depressive disorder (MDD) throughout reproductive age. [8] As a consequence of their

childless status, they experience physical or mental violence, overlook, rejection, financial scarcity and communal barring and segregation from certain societal actions and customary ceremonies.[11] The IL-6(interleukin-6) previously described as a significant factor concerned in a broad variety of psychiatric disorder, finding to depression frequently co-exists with few subclinical autoimmune sickness, such like thyroiditis or lupus, suggest that sadness may cause alteration within immune system and in fact this is an autoimmune disorder itself. Acute stress possibly started with a transient, defensive immunological response. Therefore, extended or inadequately prohibited psychosocial stressor's May consequence alters in unlike components of immune system, mostly cytokine IL-6. [7]

A great need for research into several issues regarding the complexity of infertility and their true negative late impact on woman's health. Measurement of serum prolactin, FSH, LH, thyroid stimulating hormone and IL-6 have been considered important components of the evaluation of women presenting with infertility. In view of the aforementioned controversial literature, it was decided to evaluate the relationship between stress and infertility in hypothyroid reproductive age group women.

Materials and Methods

The study has been carried out at Geetanjali Medical College and Hospital, Udaipur, Rajasthan after obtaining GMCH ethical committee permission. The data of each patient was recorded in identical pre-designed written informed consent. Initial assessment was carried out by taking a detailed history, duration and type of infertility, age of the patient, menstrual cycle.

Inclusion Criteria: It was included 168 women between age 20-36 years with hypothyroidism having normal pregnancy or infertility, along with 50 normal healthy age and sex matched control.

Exclusion Criteria: Exclusion criteria were women without hypothyroidism. Women with Hyperthyroidism, Diabetes mellitus, liver failure, or having any renal disease, malignancy or taking any lipid lowering drug were also excluded from our study.

Patients were divided into following two groups depending upon their age.

Group I: Hypothyroid women between age group 20-28 years.

Group II: Hypothyroid women between age group 29-36 years.

Further these were divided into --

A. Normal pregnant hypothyroid [NPH] between age group 20-28 years and age group 29-36 years.

B. Primary infertile hypothyroid [PIH] between age group 20-28 years and age group 29-36 years.

C. Secondary infertile hypothyroid [SIH] between age group 20-28 years and age group 29-36 years.

Blood collection, separation, storage and analysis of sample:

Unique ID number was given to each participant of the study and same ID was given on sample container. After obtaining informed consent from all patients and healthy control, 5 mL of venous blood was collected in a sterile plain vial under all aseptic precautions. Blood was drawn from antecubital vein in plain vial. After samples collection, samples were centrifuged in REMI centrifuge at 3000 RPM for a period of 15 minutes at central laboratory of Geetanjali Hospital. Serum was made in two aliquots. Serum for IL-6 was kept frozen at -20 °C until assayed. While another aliquot was analyzed for the following parameters:-T₃ (3,5,3'-triiodothyronine), T₄(Thyroxine), Thyroid stimulating hormone (TSH), Follicle-stimulating hormone (FSH), Luteinizing hormone (LH), Prolactin (PRL). They were done by electrochemiluminescence immunoassay "ECLIA method on Roche Cobas e-411 along with quality control sera for accurate result. Interleukin 6 (IL-6) was done by ELISA method [12]

Statistically analysis

All results were expressed in mean \pm SD. Differences between means were calculated by Student's t-test by using the Graph Pad software QuickCalcs. The level of significance was set as $p < 0.05$.

Results

In our study, subjects were divided in to two groups according to age. One group of 102 subjects with 20-28 years of age, another group of 66 subjects with 29-36 years of age, were found respectively. According to their history they were further divided in to NPH –normal pregnant hypothyroid women, PIH- primary infertile hypothyroid women, SIH- secondary infertile hypothyroid women.

Here, 61 NPH, 30 PIH, 11 SIH subjects were found in 20-28 years of age. While 8 NPH 18 PIH, 40 SIH subjects were found in 29-36 years of age. In present study Table 1 represented the mean \pm Sd (T₃, T₄, TSH) and p- value of age group 20-28 years subjects and control. In these subjects comparisons between NPH and PIH and NPH and SIH for T₃ was non-significant ($p=0.366$, $p=0.1624$, respectively) in the same manner T₄ was non-significant between NPH and PIH ($P=0.2676$), while remaining all parameters were significant.. Table 2 showed the mean \pm sd (T₃,T₄,TSH) between age group of 29-36 years subjects along with it's comparison of control. In this Table showed that comparisons between NPH and PIH was ($p=0.4899$)

non significant, while remaining all were significant. Table 3 represented the comparisons between both age group of s infertile objects and control in T₃,T₄,TSH respectively. All parameters were statistically significant in infertile women.

In this study Table 4 showed level of FSH, LH, PRL and IL-6 in subjects of age between 20-28 years along with control and also showed their level of significance. In it all parameter were statistically significant instead of comparison between PIH and SIH, NPH and PIH, NPH and SIH, Control and NPH, control and NPH ($p=0.1739$, $p=0.2789$, $p=0.1935$, $p=0.2399$, $p=0.6575$) for FSH, LH, PRL, IL-6 respectively. In Table 5 represented mean \pm Sd of FSH, LH PRL and IL-6 along with their control. This Table showed statistically significant parameters, remaining of PIH and SIH, NPH and PIH, NPH and SIH ($P=0.741$, $P=0.8572$, $P=0.7195$ respectively) for FSH. Table 6 showed a comparison of total no of infertile subjects with control in age group of 20-28 and 29-36 years of FSH, LH, PRL, IL-6 respectively. There were a non-significant difference ($p=0.0719$, $p=0.5632$) in

FSH and LH respectively for Primary and secondary infertile women in both age group. In it showed a very statistically significant ($p=0.0001$) difference between both age group of infertile women and with control for IL-6.

Table 7 showed distribution of the subjects according to their menstrual pattern in normal menstrual cycle, oligomenorrhoea, amenorrhoea and polymenorrhoea. A regular menstrual cycle between 21 to 35 days was called normal. A prolonged cycle of more than 35 days but less than 6 months was termed oligomenorrhoea while a cycle longer than 6 months was called amenorrhea. A cycle shorter than 21 days was called polymenorrhoea. Figure 1, 2, 3 represent IL-6 level in infertile hypothyroid women of age group of 20-28 years and 29-36 years and infertile women of both age groups respectively. Figure 4, showed a positive linear correlation between hypothyroid and depressed infertile subjects. Figure 5 and 6 represented menstrual distribution between subjects of 20-28 years and 29-36 years, respectively.

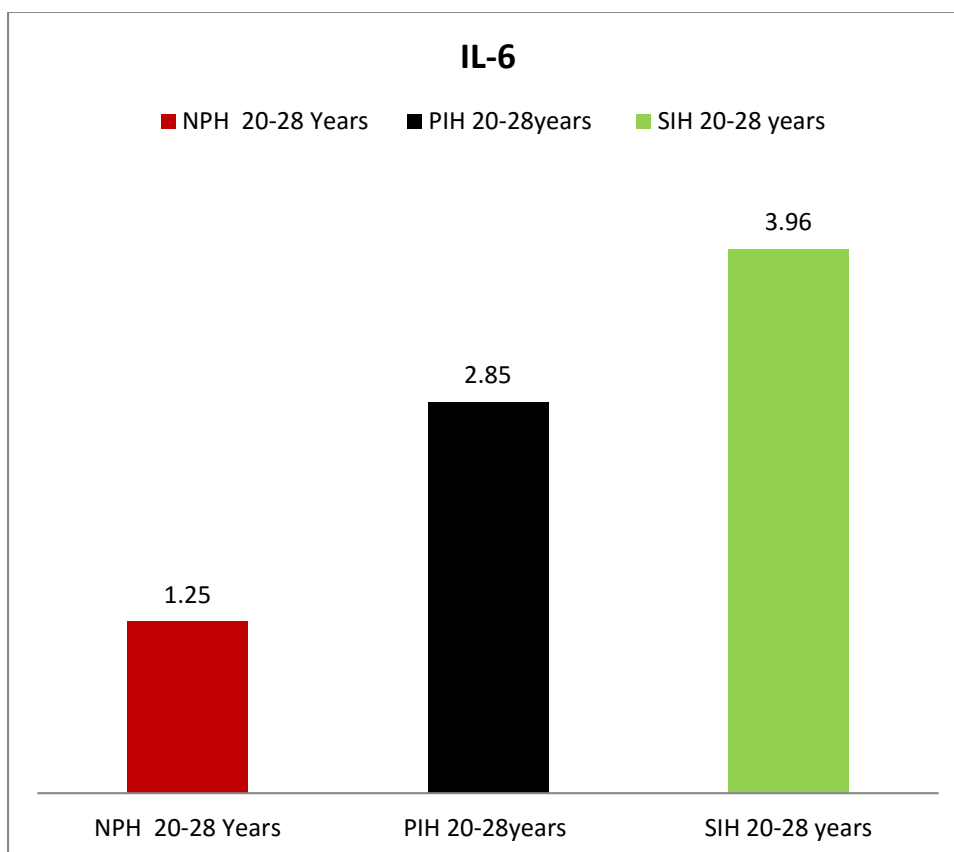


Fig. 1: Showed IL-6 level in control and 20-28 years age hypothyroid reproductive age group of women [NPH- normal pregnant hypothyroid, PIH-primary infertile hypothyroid women, SIH –secondary infertile hypothyroid women]

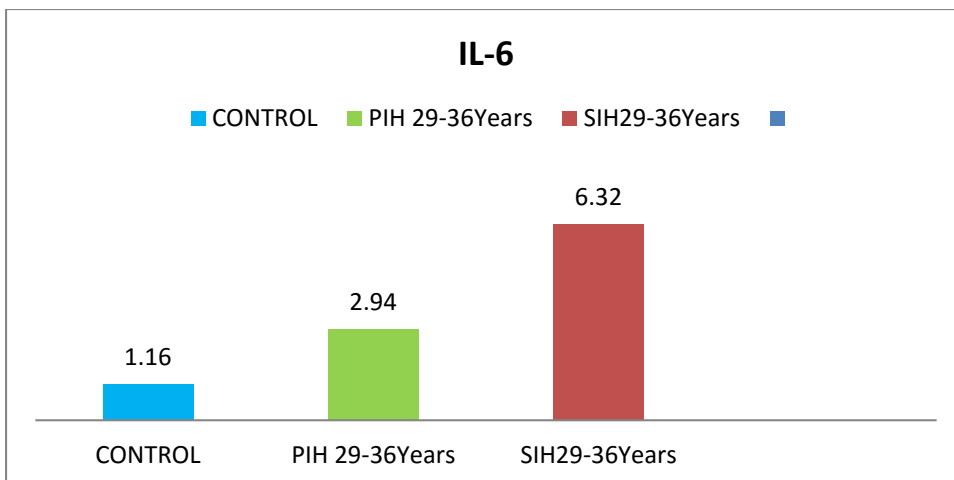


Fig. 2: Showed IL-6 level in control and 29-36 years age hypothyroid reproductive age group of women [NPH- normal pregnant hypothyroid ,PIH-primary infertile hypothyroid women, SIH –secondary infertile hypothyroid women]

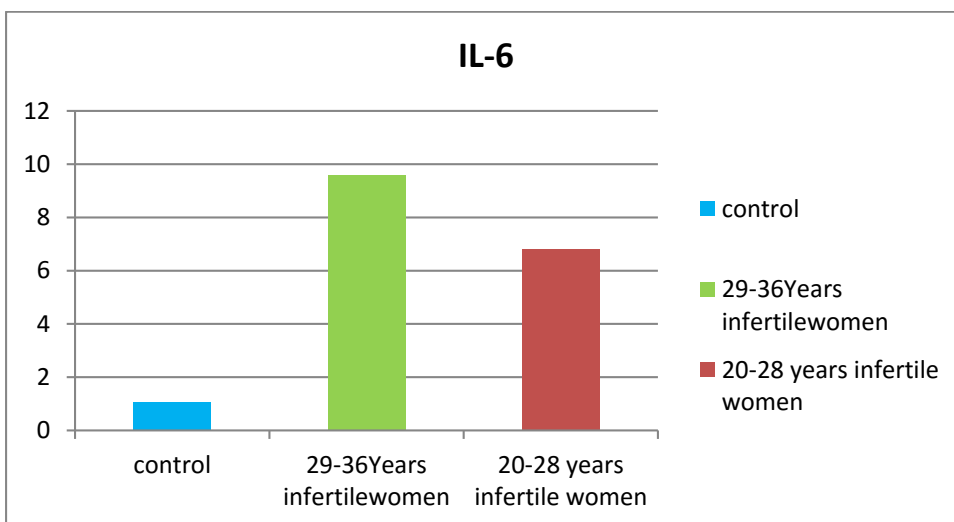


Fig. 3: Showed IL-6 level in infertile women of both age group along with control

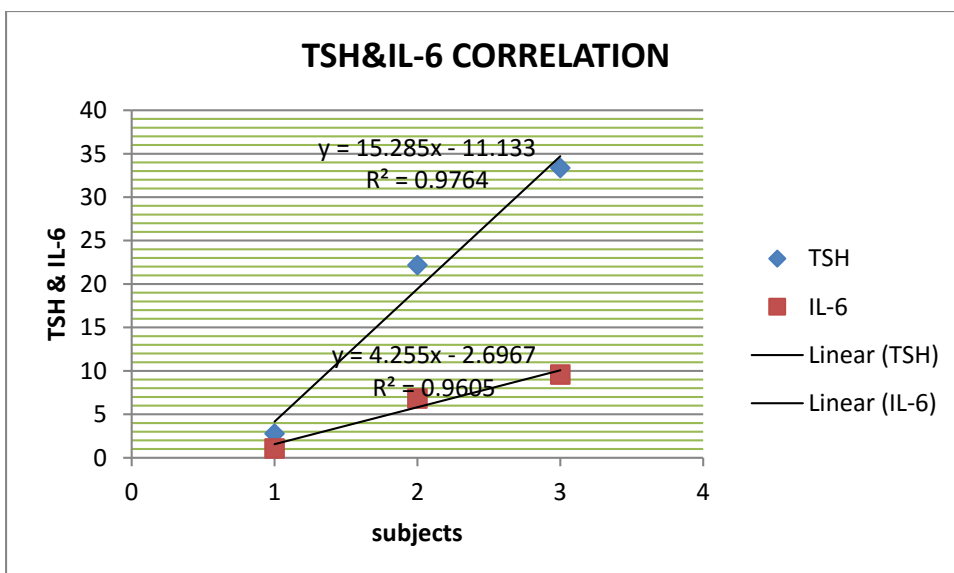


Fig. 4: Showed a positive linear correlation between Hypothyroid and depressed infertile subjects

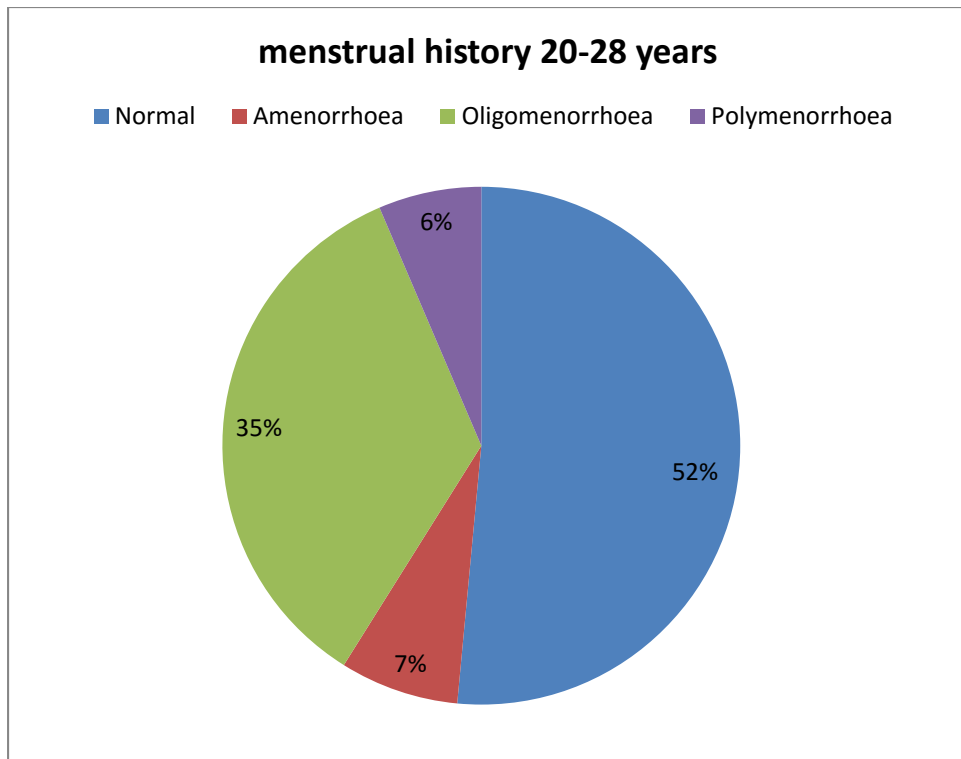


Fig. 5: Showed menstrual history between 20-28 years of subjects

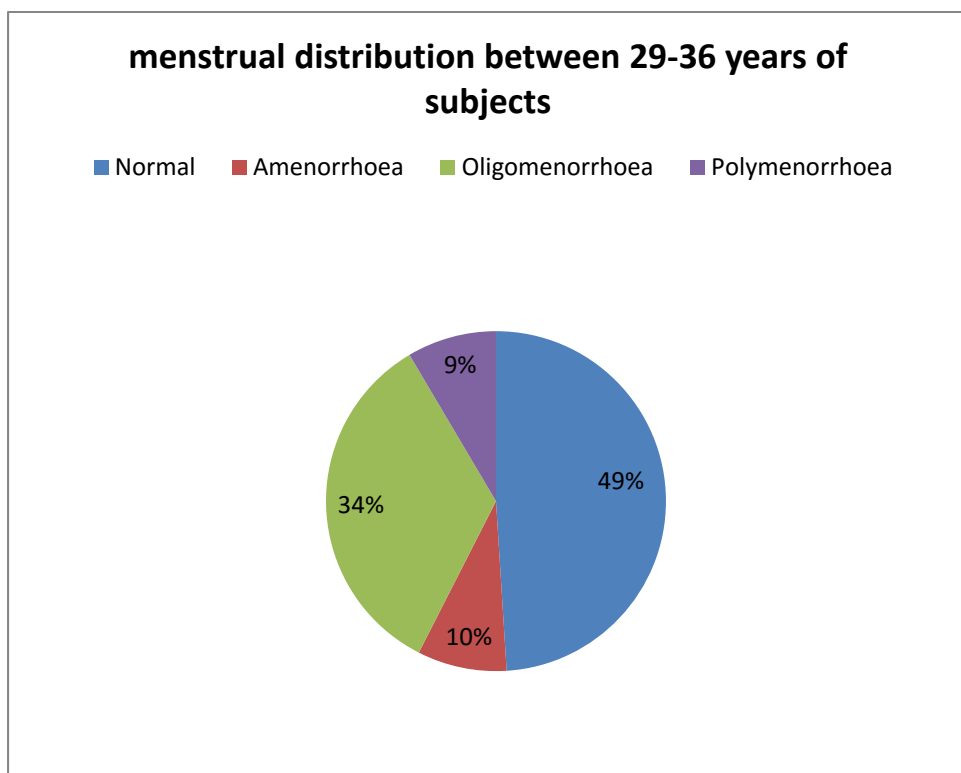


Fig. 6: Showed menstrual distribution between 29-36 years of subjects.

Table 1: Thyroid profile in age group 20-28 (n=102) and control (n=50)

Parameters	Control Mean \pm SD (n=50)	NPH Mean \pm SD (n=61)	PIH Mean \pm SD (n=30)	SIH Mean \pm SD (n=11)	CON and NPH p-value	CON And PIH p-value	CON and SIH p-value	PIH and SIH p-value	NPH and PIH p-value	NPH and SIH p-value
T₃	1.25 \pm 0.36	0.45 \pm 0.42	0.38 \pm 0.04	0.27 \pm 0.04	0.0001 * hs	0.0001 * hs	0.0001 * hs	0.0001 * hs	0.366NS	0.1624NS
T₄	10.07 \pm 2.53	3.42 \pm 1.23	3.14 \pm 0.87	2.16 \pm 1.18	0.0001 * hs	0.0001 * hs	0.0001 * hs	0.0061S	0.2676NS	0.0024S
TSH	2.78 \pm 1.07	7.10 \pm 1.12	9.76 \pm 3.56	13.42 \pm 5.85	0.0001 * hs	0.0001 * hs	0.0001 * hs	0.0196S	0.0001 * hs	0.0001 * hs

Con- control, NPH- normal pregnant hypothyroid women, PIH--primary infertile hypothyroid women, SIH- secondary infertile hypothyroid women, Hs: *highly significant, s: significant, NS: non significant

Table 2: Thyroid profile in age group 29-36(n=66) and control(n=50)

Parameters	Control Mean \pm SD (n=50)	NPH Mean \pm SD(n=8)	PIH Mean \pm SD (n=18)	SIH Mean \pm SD (n=40)	CON and NPH p-value	CON and PIH p-value	CON and SIH p-value	PIH and SIH p-value	NPH and PIH p-value	NPH and SIH p-value
T₃	1.25 \pm 0.36	0.47 \pm 0.13	0.27 \pm 0.04	0.19 \pm 0.10	0.0001 * hs	0.0001 * hs	0.0001 * hs	0.0019S	0.0001 * hs	0.0001 * hs
T₄	10.07 \pm 2.53	3.28 \pm 0.16	3.11 \pm 0.67	1.76 \pm 1.23	0.0001 * hs	0.0001 * hs	0.0001 * hs	0.0001 * hs	0.4899NS	0.0001 * hs
TSH	2.78 \pm 1.07	6.12 \pm 1.34	15.13 \pm 3.12	18.22 \pm 1.34	0.0001 * hs	0.0001 * hs	0.0001 * hs	0.0001 * hs	0.0001 * hs	0.0001 * hs

Con- control, NPH- normal pregnant hypothyroid women, PIH-- primary infertile hypothyroid women, SIH- secondary infertile hypothyroid women, Hs: *highly significant, s: significant, NS: non significant

Table 3: Thyroid profile in total infertile subjects (n=99) and control n=50

Parameters	Control (A) Mean \pm SD n=50	Total 20-28 years(B) Mean \pm SD (PIH+SIH) n=41	Total 29-36 years(C) Mean \pm SD (PIH+SIH) n=58	p-value Aand B	p-value A and C	p-value B and C
T₃	1.25 \pm 0.36	0.55 \pm 0.08	0.46 \pm 0.14	0.0001 * hs	0.0001 * hs	0.00035S
T₄	10.07 \pm 2.53	5.3 \pm 2.05	4.87 \pm 1.34	0.0001 * hs	0.0001 * hs	0.0001 * hs
TSH	2.78 \pm 1.07	22.18 \pm 9.41	33.35 \pm 4.46	0.0001*	0.0001*	0.0001*

TSH WAS *highly significant Hs: *highly significant, s: significant, NS: non significant

Table 4: Infertility profile and IL-6 in 20-28 years subjects (n=102) and control n=50

Parameters	Control Mean \pm SD (n=50)	NPH Mean \pm SD (n=61)	PIH Mean \pm SD (n=30)	SIH Mean \pm SD (n=11)	CON and NPH p-value	CON and PIH p-value	CON and SIH p-value	PIH and SIH p-value	NPH And PIH p-value	NPH and SIH p-value
FSH	10.47 \pm 5.42	0.64 \pm 0.09	1.22 \pm 4.18	2.98 \pm 0.16	0.0001 * hs	0.0001 * hs	0.0001 * hs	0.1739NS	0.2789NS	0.0001 * hs
LH	16.19 \pm 5.004	4.76 \pm 2.01	1.92 \pm 1.12	3.94 \pm 1.10	0.0001 * hs	0.0001 * hs	0.0001 * hs	0.0001 * hs	0.0001 * hs	0.1935NS
PRL	14.74 \pm 10.42	16.45 \pm 3.98	41.12 \pm 11.22	75.24 \pm 28.16	0.2399NS	0.0001 * hs	0.0001 * hs	0.0001 * hs	0.0001 * hs	0.0001 * hs
IL-6	1.16 \pm 1.56	1.25 \pm 0.24	2.85 \pm 1.72	3.96 \pm 1.96	0.6575NS	0.0001 * hs	0.0001 * hs	0.0855NS	0.0001 * hs	0.0001 * hs

IL-6; interleukin -6, FSH; follicular stimulating hormone, LH; luteinizing hormone, PRL; prolactin
Hs: *highly significant, s: significant, NS: non significant

Table 5: Infertility profile and IL-6 in 29-36 years subjects (n=66) and control n=50

Parameters	Control Mean \pm SD (n=50)	NPH Mean \pm SD (n=8)	PIH Mean \pm SD (n=18)	SIH Mean \pm SD (n=40)	CON and NPH p-value	CON and PIH p-value	CON and SIH p-value	PIH and SIH p-value	NPH and PIH p-value	NPH and SIH p-value
FSH	10.47 \pm 5.42	0.72 \pm 0.14	0.86 \pm 2.15	1.26 \pm 4.19	0.0001 * hs	0.0001 * hs	0.0001 * hs	0.741NS	0.8572NS	0.7195NS
LH	16.19 \pm 5.004	8.12 \pm 1.24	2.12 \pm 5.12	3.13 \pm 1.34	0.0001 * hs	0.0001 * hs	0.0001 * hs	NS0.2459NS	0.0035 * S	0.0001 * hs
PRL	14.74 \pm 10.42	15.12 \pm 2.14	48.27 \pm 11.17	87.18 \pm 32.63	0.9191NS	0.0001 * hs	0.0001 * hs	0.0001 * hs	0.0001 * hs	0.0001 * hs
IL-6	1.16 \pm 1.56	1.63 \pm 1.21	2.94 \pm 1.68	6.32 \pm 1.86	0.4204NS	0.0001*hs	0.0001 * hs	0.0001*hs	0.0594NS	0.0001 * hs

Hs: *highly significant, s: significant, NS: non significant

Table 6: Infertility profile and IL-6 in total infertile subjects (n=99) and control n=50

Parameters	Control(A) Mean \pm SD n=50	Total 20-28 years(B) Mean \pm SD(PIH+SIH) n=41	Total 29-36 years(C) (PIH+SIH) Mean \pm SD n=58	p-value A and B	p-value A and C	p-value BandC
IL-6	1.06 \pm 0.56	6.81 \pm 3.68	9.57 \pm 3.54	0.0001 * hs	0.0001 * hs	0.0003 S
FSH	10.47 \pm 5.42	4.20 \pm 4.34	2.12 \pm 6.34	0.0001 * hs	0.0001 * hs	0.0719 NS
LH	16.19 \pm 5.004	5.86 \pm 2.22	5.25 \pm 6.46	0.0001 * hs	0.0001 * hs	0.5632NS
PRL	14.74 \pm 10.42	116.36 \pm 39.38	135 \pm 43.80	0.0001 * hs	0.0001 * hs	0.0001 * hs

Hs: *highly significant, s: significant, NS: non significant

Table 7: Distribution according to menstrual

Age (Years)	Number (n)	Menstrual pattern	Number (n)	Percentage (%)
20-28	102	Normal	53	52%
		Amenorrhea	7	7.5%
		Oligomenorrhoea	36	35%
		Polymenorrhoea	6	6.5%
29-36	66	Normal	32	49%
		Amenorrhea	6	8.5%
		Oligomenorrhoea	22	34%
		Polymenorrhoea	6	8.5%

Discussion

In this study low levels of gonadotrophins (LH and FSH) were observed in both groups (20-28 years and 29-36 years) of infertile women. In the present study we were found the high level of prolactin hormone which were correlated with the study of Avasthi Kumkum [13] and Mishra.[14] The incidence of high prolactin levels (hyperprolactinemia) as the cause of female infertility was reported to be 18% by Avasthi kumkum, and 25% by Mishra [13,14].

Our results of high prevalence of hypothyroidism in infertile women are also compatible with study conducted in our neighborhood countries.[15] In our study we were found that 35% and 34 % subjects were suffered by oligomenorrhoea, respectively in age group 20-28 years and 29-36 years, this is correlated with the other study.[16,17] In our study we were found that in hypothyroid reproductive age group of women having higher number of complain of oligomenorrhoea in both (20-28, 29-36 years) age groups. While 52 % and 49 % women were having normal menstrual pattern in both age group, when these were all hypothyroid women. After that hypothyroid reproductive age group women having history of amenorrhoea and poly menorrhoea 7.5 %, 6.5 %, 8.5 %, respectively.

The menstrual pattern was abnormal in the majority of infertile women. Prolactin is a polypeptide hormone and its main function is the stimulation of lactation in the postpartum period. Hyperprolactinemia induces suppression of the hypothalamic-pituitary gonadal axis and resistance of the ovary to gonadotrophin action, which results in amenorrhea and lack of ovulation, causing infertility. Infertility associated with hyperprolactinemia is reversible with treatment. Lowering the prolactin level to normal or near normal is often necessary to allow ovulation. [13]

Stress has been the source of much conceptual mental confusion and has been specified several ways. Tension has been conceptualized been as an event (a distressing circumstances external to the person) and as a response (the disturbance of a person's normal state). Stress is a kind of pain which affects the body and mind. Pregnancy loss can be a devastating experience regardless of the gestational age of the fetus or baby.

The biomarkers of the stress response include cortisol and HPA axis dysregulation, and inflammation, with potential markers including C-reactive protein (CRP) and interleukin 6 [18]. IL-6 is a protein that is encoded by IL-6 gene; IL-6 is an interleukin that acts as a both pro-inflammatory and anti-inflammatory cytokine. IL-6 is secreted by T cells and macrophages to stimulate immune response, e.g. during infection and after trauma, especially burns or other tissue damage leading to inflammation. Interleukin-6 is an upstream pro-inflammatory cytokine that induces both C-reactive protein and fibrinogen expression. Studies investigating the effects of psychological influences over reproduction have

prominently dealt with the negative influence of psychological "stress", which is popularly believed to have a central affect in infertility[19,20].

In our study we were found a significant change in level of Interleukin -6 (IL-6) in hypothyroid infertile and reproductive age group of women, when compare them with control. In our study the level of IL-6 was higher in those infertile women who were having complained of stress from a long period.

According to our study, Women who were having hypothyroidism and stress in their day today life because of their social and working environment are at heavy risk of complications in fertility. American Psychiatric Association (2004) survey reported that two thirds of Americans were likely to seek help for stress and 50% were concerned about the level of stress in their everyday lives; 44% of them were between 18 and 29 year old, and 46% of them were 30 to 49 year old; 40% were women and 35% were men. [21]

Several findings suggest that IL-6 may mediate the exacerbation of autoimmune disorder in the CNS.[22]. IL-6 has been shown to have immunoregulatory functions including the control of local and systemic inflammation [23]. IL-6 measurements can be influenced by the presence of serum proteins that from complex with IL-6, at least with conventional assays.[24]

Cytokines as the modulators of the immune system, also take part in the regulating of the ovarian cycle by endorsing follicular growth apart from guiding the infiltration and energizing of leucocytes essential for ovulation and tissue reconstructing throughout follicular rupture, luteinization and luteolysis [25, 26] IL-6 may contribute to oocyte maturation, since lower levels of IL-6 in the preovulatory follicular fluid were associated with IVF pregnancy failure[27]. On the other hand, higher levels of IL-6 have been detected in women with ovarian hyperstimulation syndrome and endometriosis. [28,29]

Both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are compulsory for follicle development and oestrogen production hence depleted degrees of these hormones may mean that fewer numbers of follicles will develop and there will be no Graffian follicle formation. Normally as follicles develop, estrogen levels rise which helps to stimulate the endometrium.

In the end by the present study we were showed that not only hypothyroidism but also its association with stress was more harmful to the reproductive age group of women, who were planned for a baby in near future. So in near future we can aware the reproductive age group of women that stress is also a big cause of infertility.

Conclusions

Thus the present study authenticated that an increase in interleukin -6 (depression/stress) was associated with moderate increase in infertility and abnormal menstrual cycle in hypothyroid reproductive age group women.

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