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ASSESSMENT OF FEMALE INFERTILITY PROBLEMS BASED ON HORMONAL IMBALANCE IN RAMANATHAPURAM DISTRICT. TAMIL NADU, INDIA

L. Jeya Praba[1]*, G. Veera Rajeswari[2], D. Addline[3], Viji Margaret[4], Bindu Bennet[5]

[1*,2,3,4,5]Zoology Department and Research Centre, Sarah Tucker College (Autonomous), Affiliated to Manonmaniam Sundaranar University, Tirunelveli-627007, Tamil Nadu, India.

***Corresponding Author:** L. Jeya Praba
Email: jayaprabha2009@gmail.com

Abstract:
Women's health is greatly influenced by hormones. Women's hormonal imbalances can be brought on by a variety of factors, including stress, tension, rapid weight gain, etc. The understanding of the origins and diagnosis of female infertility has been viewed as being highly dependent on hormonal abnormalities. A specially designed data sheet was used for the collection and analysis of data for 510 infertile females. The present study aims to investigate the relationship between the age of infertile female with hormonal imbalance and ovulation disorder (PCOS) in association with Body mass index (BMI) and menstrual cycle leads to female infertility in the study area Ramanathapuram District.

Keyword: Hormones, infertility, hormonal imbalance, PCOS, BMI, menstrual cycle

1. Introduction

Infertility is a multi-dimensional health issue. It can also be brought on by ovulation disorder (PCOS), hormonal imbalance, tubal factors, cervical problems, age-related factors, uterine problems, and the choices imposed by the modern lifestyle for assisted reproduction etc (1). Despite the lack of recent data on infertility, it has been estimated that 48 million couples and 186 million people experience infertility globally (2,3). Women are more likely to experience hormonal imbalance, which typically starts while they are in their middle years. Despite the fact that this seems like just another biological problem, the woman's relationship with her loved ones is genuinely impacted (4).

Oestrogen and progesterone, which are both generated in same amounts, are the primary hormones in the bodies of women. However, when the balance is off, one hormone or another is produced more, which changes behaviour and other aspects of life. Infertility may be caused by increased or decreased production of any of the reproductive hormones that control a woman's reproductive cycle, including luteinizing hormone (LH), oestrogen (E2), follicle stimulating hormone (FSH), and luteinizing hormone-like (LH). Having thyroid issues may result in ovarian issues. High prolactin level can also prevent ovulation. Hypothyroidism may cause menstrual irregularities and affect female fertility and pregnancy potential. The Anti Mullerian Hormone (AMH) level falls continuously with increasing age, corresponding to the loss of ovarian function and thus leading to infertility. Hyperprolactinemia, or high levels of prolactin in females who are not pregnant or nursing, can lower gonadotropin levels and prevent ovulation, which results in amenorrhea. Both men and women's reproductive health are significantly impacted by prolactin.

"High levels of prolactin" and endocrine disorders, including "hyperthyroidism, hypothyroidism, Cushing disease and Addison's disease may also lead to anovulation" (5) Hyperprolactinemia is a disorder where there is an excess of prolactin, a hormone that stimulates the production of breast milk and may also interfere ovulation. The menstrual cycle is regulated by hormones. Either too much (hyperthyroidism) or not enough (hypothyroidism) thyroid hormone can cause interruption of the menstrual cycle or infertility. Other possible underlying causes may include excessive exercise, eating disorders, injury or tumours.

Polycystic ovary syndrome (PCOS) is characterized by infertility, menstrual disturbances and obesity. A woman with PCOS has an unbalanced level of the female sex hormones.

In view of the above stated information, the goal of the current investigation was to ascertain the relationship between hormonal imbalance and ovulation disorder (PCOS) and also study the PCOS in association with Body mass index (BMI) and menstrual cycle leads to female infertility in the study area Ramanathapuram

2. Materials and Methods

A random sampling method is used to collect the data related to different hormonal problems of infertile female between the age of 18-44 years. The study was conducted in a private hospital with fertility centre at Ramanathapuram. This study protocol was accepted by ethics committee of the private hospital. A specially designed data sheet was used for collection and analysis of data for 510 infertile females.

Hormonal imbalance leads to infertility (FSH, L H , E 2 , PRL, TSH and AMH) were analyzed among 510 infertile females. Data analysis was done by using statistical tool. Correlation and Regression were used to determine the relationship between age of infertile female and hormone (FSH, L H , E 2 , PRL, TSH and AMH) risk factors on infertility.

Based on the data, female infertility associated with BMI, irregular menstrual cycle, PCOS, Hypothyroidism and Hyperprolactinemia are also analyzed.

3. Result

The distribution of cases according to the level of FSH, LH, PRL, E2, PRL, TSH and AMH hormones were shown in Table 1. Figure 1a and 1b depicts the distribution of cases for different age groups according to normal and abnormal level of hormones. Table 2 explains correlation between each hormone level (FSH, LH, E2, AMH AND TSH) of cases with different age group (yr.). According to the study's findings, frequencies and percentage of the clinical characteristics for the infertile females about Hypothyroidism, Hyperprolactinemia, PCOS with Hypothyroidism and PCOS with Hyperprolactinemia by age group(Yr.) were tabulated (Table 3).

The relationship between BMI and PCOS at various age groups (Yr) of infertile females is given in Table 4. PCOS was more prevalent (66.1%) in the 21–25 yr age group. According to the findings of this study, frequencies and percentage of the clinical characteristics menstrual cycle and PCOS according to age group (yr) of the infertile female were tabulated (Table 5).

Hormones Characteristics	**Level of Hormones**		**Age Group (yr)**						**Frequency**	**Percentage (%)**
			≤ 20	**21– 25**	**26 - 30**	**31 - 35**	**36 - 40**	**Above 40**		
			No of cases (Total 510)							
FSH (µIU/ml)	Normal	**3.50 - 12.50**	36	165	150	56	28	2	437	85.69
	Abnormal	Below and Above Normal level	8	24	20	9	9	3	73	14.31
LH (µIU/ml)	Normal	**2.4-12.6**	41	154	147	47	27	5	421	82.55
	Abnormal	Below and Above Normal level	3	35	23	18	10	0	89	17.45

E2 (pg/ml)	Normal	**27-123**	39	147	131	49	29	4	399	78.24
	Abnormal	Below and Above Normal level	5	42	39	16	8	1	111	21.76
PRL (ng/ml)	Normal	**5.18-26.53**	32	127	115	50	27	2	353	69.22
	Abnormal	Below and Above Normal level	12	62	55	15	10	3	157	30.78
TSH (µIU/ml)	Normal	**0.4-4.0**	35	146	129	52	29	4	395	77.45
	Abnormal	Below and Above Normal level	9	43	41	13	8	1	115	22.55
AMH (ng/ml)	Normal	**1.5- 4**	10	72	73	31	13	0	199	39.02
	Abnormal	Below and Above Normal level	34	117	97	34	24	5	311	60.98

Table 1: The observed frequencies and percentage of infertile female according to FSH, LH, E2, PRL, TSH and AMH hormones at different age group (yr).

Note: Table shows the percentages of infertility female had normal level of hormone (85.69%), (82.55%), (78.24%), (69.22), (77.45) and (39.02) and abnormal level (14.31), (17.41%), (21.76%), (30.78%), (22.55) and (60.98) for FSH, LH, E2, PRL, TSH and AMH hormones respectively. More (60.98) infertile female had abnormal AMH than other hormones. FSH - Follicle stimulating hormone, LH – Luteinizing hormone, E2 – Oestrogen, AMH – Anti Mullarian hormone, TSH – Thyroid stimulating hormone, PRL – Prolactin

HORMONES	**Cases (510)**						**Regression (R^2)**	**Mean Age** 26.87±5.05	**Correlation (r)**
	Age Group (Yr)								
	≤ 20	**21 - 25**	**26 - 30**	**31 - 35**	**36 – 40**	**Above 40**		Mean Hormone level	
FSH µIU/ml (5-7)	5.84 ± 2.71	7.16 ± 10.68	6.85 ± 4.52	8.01 ± 9.55	7.14 ± 4.27	11.32 ± 7.55	0.645	7.08 ± 7.95	0.803
LH µIU/ml (5-7)	5.53 ± 2.94	6.09 ± 5.54	5.42 ± 4.68	4.24 ± 3.69	4.24 ± 3.70	4.95 ± 2.86	0.479	5.43 ± 4.75	0.692
E2 pg/ml (50-80)	69.39± 54.97	54.20 ± 35.96	59.29 ± 43.80	49.08 ± 33.27	81.20 ± 79.79	44.64 ± 21.57	0.043	58.53 ± 45.04	0.208
AMH ng/ml (1.5-4)	5.39 ± 2.81	5.29 ± 4.91	5.03 ± 5.47	3.83 ± 3.16	1.89 ± 2.24	1.41 ± 1.34	0.896	4.72 ± 4.71	0.947
TSH µIU/ml 0.4-4	4.27 ± 6.08	4.61 ± 8.01	3.72 ± 6.17	3.30 ± 3.917	6.52 ± 17.14	3.61 ± 2.93	0.009	4.25 ± 7.93	0.092
PRL ng/ml 5.18-25.0	23.12± 10.77	25.44 ± 15.56	25.82 ± 23.75	21.09 ± 12.83	23.55 ± 8.92	28.75 ± 9.43	0.129	24.67 ± 17.79	0.359

Table 2: Correlation between FSH, LH, E2, PRL, TSH and AMH hormones level of cases and different age group (yr)

Note: The data are presented as group means (± SD). Table shows AMH has higher correlation around 0.9465 against female aged between 18-44 yr. In FSH the value of correlation 0.803 slightly less than AMH and more than LH 0.6920. FSH hormone increases with increasing age and AMH decreases with increasing age. There is no any significant correlation between the E2 level, TSH and PRL hormones and age

(FSH - Follicle stimulating hormone, LH – Luteinizing hormone, E2 – Oestrogen, AMH – Anti Mullarian hormone, TSH – Thyroid stimulating hormone, PRL – Prolactin).

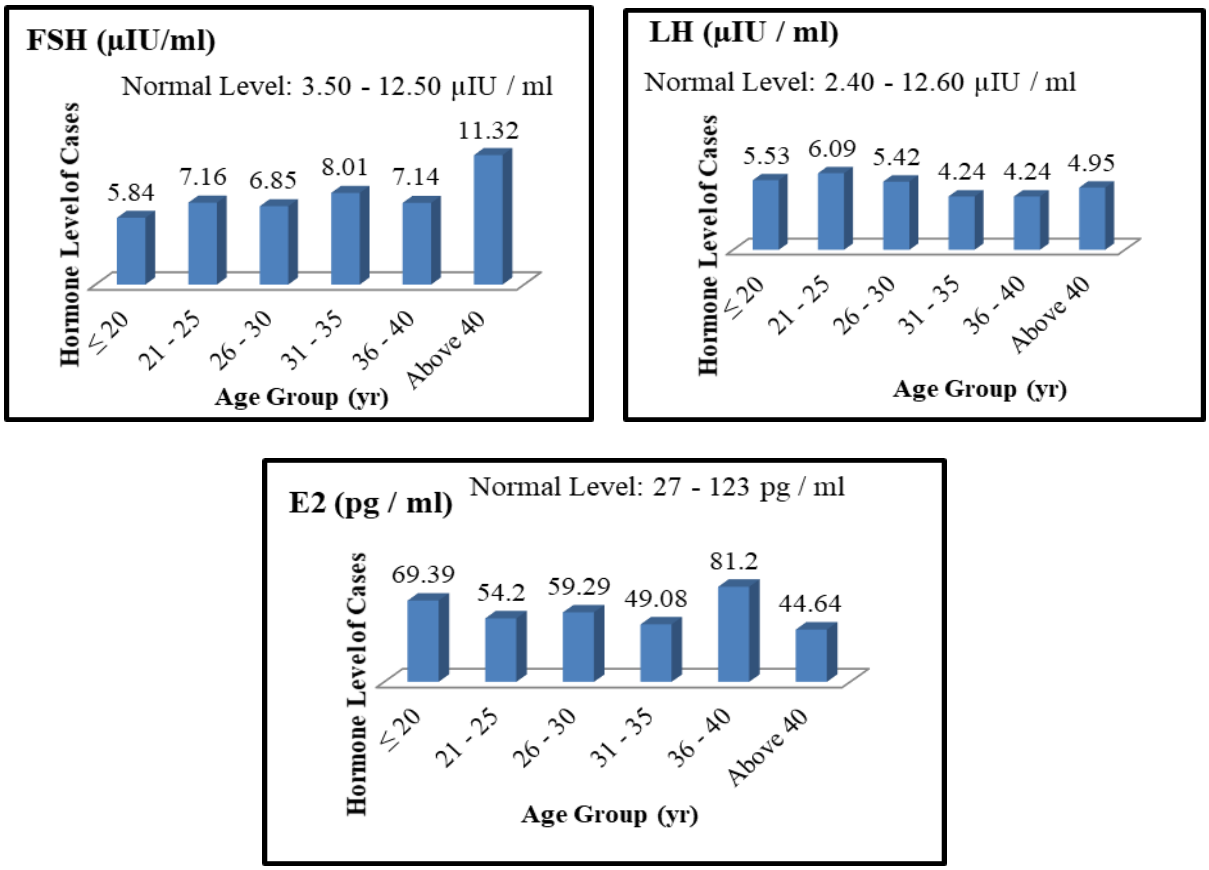

Figure 1a: The distribution of cases according to normal and abnormal level of gonadotropin hormones FSH, LH and E2

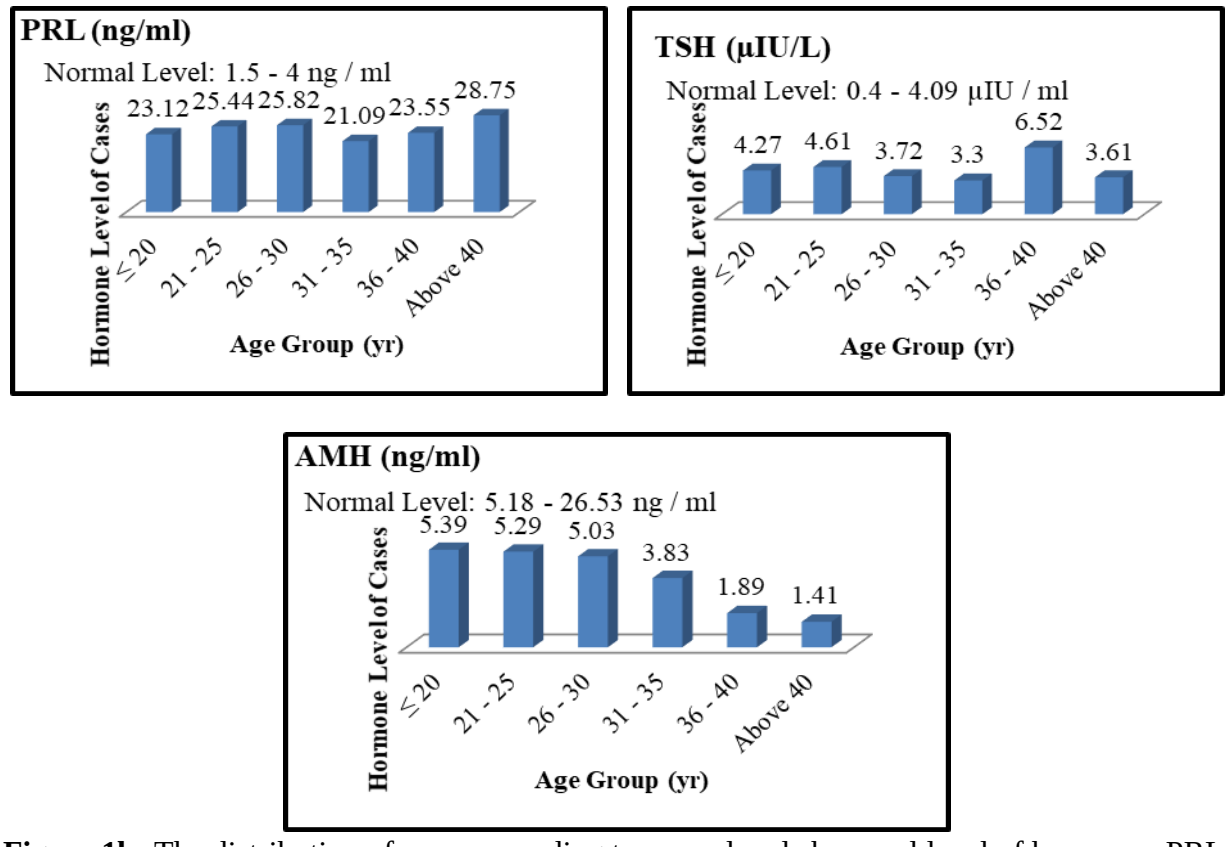

Figure 1b: The distribution of cases according to normal and abnormal level of hormones PRL, TSH, AMH

Parameters	Group	Age Group (yr) (Cases 510)						Frequency	Percentage (%)
		≤ 20	21 - 25	26 - 30	31 - 35	36 - 40	Above 40		
Hypothyroidism	Present	5	30	36	15	8	1	95	18.4
	Absent	39	160	134	50	29	3	415	81.37
Hyper prolactinemia	Present	1	7	11	2	1	0	22	4.3
	Absent	43	183	159	63	36	4	488	95.69
PCOS with Hypothyroidism	Present	4	24	28	8	2	2	68	12.9
	Absent	40	166	142	57	35	2	442	86.67
PCOS with Hyperprolactinemia	Present	1	5	9	1	0	0	16	3.1
	Absent	43	185	161	64	37	4	494	96.86

Table 3: Percentage of individuals with various parameters hypothyroidism, hyperprolactinemia and hypothyroidism, hyper prolactinemia with PCOS based on age group (yr)

Note: Table reveals the observed frequencies and percentage of the clinical characteristics for the studied women including, Hypothyroidism, Hyperprolactinemia, PCOS with Hypothyroidism, PCOS with Hyperprolactinemia. It shows a relatively high percentage (18.4) of PCOS with Hypothyroidism among the studied women while most of them were 21-25, 26-30 age group. (PCOS - Poly cystic ovarian syndrome).

Age Group (yr)	BMI														
	≤ 18.5 Below normal		% of PCOS	18.6 - 24.9 Normal		% of PCOS	25 - 29.9 Over weight		% of PCOS	≥ 30 Obesity		% of PCOS	Total		
	Total No. Of Cases (N)	PCOS Cases (N)		Total No. Of Cases (N)	PCOS Cases (N)		Total No. Of Cases (N)	PCOS Cases (N)		Total No. Of Cases (N)	PCOS Cases (N)		Total No of Cases (N)	Total PCOS Cases (N)	PCOS %
≤ 20	4	2	50	27	18	66.7	12	7	58.3	1	1	100	44	28	63.6
21 - 25	10	9	90	116	72	62.07	57	41	71.9	6	4	66.7	189	126	66.7
26 - 30	6	2	33.3	99	61	61.62	56	35	62.5	9	5	55.6	170	103	60.6
31 - 35	1	1	100	32	14	43.8	26	13	50	6	2	33.3	65	30	46.2
36 - 40	0	0	0	24	6	25	12	4	33.3	1	0	0	37	10	27.0
>40	0	0	0	2	0	0	3	0	0	0	0	0	5	0	0
Total	21	14	66.7	300	171	57	166	100	60.2	23	12	52.2	510	297	58.24

Table 4: Association of BMI with PCOS at different age group (yr) of infertile female in the study area Ramanathapuram.

Note: PCOS was higher (72) in the age group 21-25 and 61 at normal level of BMI. Next higher (61) in the age group 26-30 at normal BMI. 126 of infertile female had PCOS in the 21-25 age group. (PCOS - Poly cystic ovarian syndrome)

Age group (yr)	Risk factor - Menstrual cycle		PCOS with Irregular menstrual cycle	
	Regular Menstrual Cycle (N)	Irregular Menstrual Cycle (N)	PCOS Cases (N)	Irregular Menstrual Cycle with PCOS (%)
≤ 20	1	27	28	96.43
21 - 25	0	126	126	100
26 - 30	5	98	103	95.15
31 - 35	9	21	30	70
36 - 40	7	3	10	30
Above 40	0	0	0	0
Total	22	275	297	92.6

Table 5: Association of PCOS with menstrual cycle at different age group (yr) of infertile female in the study area Ramanathapuram.

Note: Table shows 92.6% of infertile female had PCOS and irregular menstrual cycle. Irregular menstrual cycle was higher (126) in the age group of 26-30 yr. Next higher (98) in the age group of 26-30 yr. 126 individuals had both PCOS and irregular menstrual cycle. (PCOS - Poly cystic ovarian syndrome).

4. Discussion

Hormonal imbalance is caused by improper diet, stressful or depressed life styles and use of drugs. Normal female fertility is interfered due to the dysfunctioning of the FSH, LH, E2, PRL, TSH and AMH hormone levels. The primary and secondary infertile individuals in this investigation demonstrated a range of changes in their serum concentrations of FSH, LH, E2, TSH, AMH, and PRL. Chioma and Emine (6) found elevated levels of serum PRL, PG, and E2. According to Evers (7), hyperprolactinemia has a number of effects that can prevent ovulation and cause infertility, including a decrease in GnRH (Gonadotropin Releasing Hormone), an inhibition of LH and FSH release, and an inhibition of both oestrogen and progesterone secretion in the ovary. The increased levels of serum PRL concentration are consistent with this report.

Normally FSH and LH hormones levels are in the ratio of 1:1. If the ratio is 1: 2 or 2:1 it leads to irregular menstrual cycle. In the present investigation the mean value of FSH mIU/ml hormone is 7.08 ±7.95 and LH mIU/ml is 5.43± 4.75 and leads to 72.16% of female had irregular menstrual problems. FSH, LH, E2, AMH, TSH and PRL hormonal imbalance were just a minor suspected etiologic factor in causing infertility for women. The current study shows that low percentage of infertile female had abnormal level of all hormones and the increased percentage of female infertility 60.98% (311) was caused by AMH hormone only. According to the standard value, several investigations also showed that infertile women had normal hormone levels (8). This support Sudha and Reddy's (9) findings that only (3.31%) of the investigated women experienced hormonal abnormalities.

FSH, LH, E2, AMH, TSH and PRL hormone level showed various variations in infertility women. This agrees with the similar findings of Chioma and Emine (10), which indicated that LH, FSH, PRL, and E2 in showed variation in primary infertility. In the present study different age group between18-44 (yr) were correlated with mean value of FSH, LH, E2, AMH, TSH and PRL hormones. This statistical results showed that there was a correlation between different age group of infertile women and AMH (0.947), FSH (0.803) and LH (0.692) hormone level.

AMH is essential for normal oocyte production. Normally when the age is increased, AMH hormone level is gradually declined. In the present study also AMH hormone was decreased with increasing age. The results indicated that AMH level was higher in below 30 yr and lower in above 35 yr age group than the normal value. This can be supported by related similar studies that reveal ageing causes infertility and results in significantly decreased levels of AMH (11,12) Normal value of AMH is about 1.5 to 4 ng/ml. The mean value of AMH in infertile female is 4.72 ± 4.71. The rate of pregnancy chances is reduced due to low level of AMH in women and cause infertility. Low levels of AMH have poor ovarian reserve.

In the present study FSH level was increased with age. The mean value of FSH in infertile female is 7.08 ± 7.95. The levels of FSH and the age group of infertile females showed a strong positive correlation. This finding confirms that ageing significantly raises FSH levels, which disrupt ovarian function and are linked to infertility (13) (Liu *et al.*, 2015). Abnormal level of FSH was also noted in different age group and cause infertility in all the age group.

Slight variation occurred in the level of LH, TSH and PRL hormone with different age group of infertile female. It is necessary to have normal TSH levels in order to fertilize. The present data also indicate that variations in TSH levels in the narrower range or borderline cases, i.e. 4–5, 5–6, and >6.0 μIU/ml, should not be uncared for infertile women. The hypothyroidism in this group of infertile women is carefully identified and treated. According to research on thyroid dysfunction, treatment for hypothyroidism should begin when both TSH and PRL levels are elevated. Only then could the causes of hyperprolactinemia be determined. TSH and PRL levels were assessed for infertility during the initial consultation in the USA (14). The treatment for hypothyroidism involves thyroxine-based

hormone therapy. It restores normalcy to the menstrual cycle, levels of PRL, and increases the fertility rate.

Irregular menstrual cycles, hypothyroidism, polycystic ovarian syndrome (also known as Stein-Leventhal syndrome), and hyperprolactinemia are among the hormonal abnormalities that affect ovulation (15). Hypothyroidism was a significant risk factor to cause infertility and observed in 18.4% (95) of cases compared to 11.4% of control. Majority (36) were between 26-30 and (35) 21-25. Hivre (16) proved that the predominance of hypothyroidism was slightly higher in the infertile female. These disorder leads to menstrual irregularities in the result of infertility. Thyroid problem was found to be a risk factor for primary infertility in the present study which consistent the findings of Goswami *et al.,* (17), stated that a relatively higher occurrence of hypo thyroidism in primary infertile females, when compared to the control group, reflects infertility in female towards thyroid insufficiency or the vice versa. Thyroid dysfunction is one of the reproductive disorder, ranging from aberrant sexual development to menstrual irregularities and infertility, according to Bercovici (18) and Vaquero *et al.* (19). Hypothyroidism is commonly related with hyper prolactinemia and such patients exhibit ovulatory failure and menstrual irregularity, luteal phase defect.

Poppe and Velkeniers, (20); Olivar, (14) revealed that hyperprolactinemia can be caused by stress in a variety of settings. The varying occurrence may be related to the various stress levels, which also negatively affect reproductive potential by disrupting GnRH pulsatility and ovarian function. In the present study, among 510 samples the prevalence of hyperprolactinemia was 22 (4.3%) of cases compared to (13) 2.5% of control. Majority (11) were between 26-30 age group. Chioma and Emine (6) reported that PRL concentration is higher in infertile female. The increased levels of serum PRL concentration in the primary infertile are consistent with the study of Evers, (7) that hyperprolactinemia has a number of effects that can obstruct with ovulation leading to infertility, this includes decrease of GnRH (Gonadotropin Releasing Hormone), inhibition of LH and FSH release and inhibition of both Ooestrogen and Progesterone secretion in the ovary. The present results disagree with Unuane *et al.,* (21) which indicated that among 540 hyper prolactinemic patients, 64 % had infertility problems.

Among (510) infertile women, 58.2% of infertile female had higher percentage of PCOS, when compared to the control normal (7%). According to the present study PCOS was higher (66.7%) in the age group of 21-25 and also below 20 yr (63.6%). Similar to this, Miller (22) observed that younger women are more likely than older women to experience ovulatory dysfunction. Because the modern way of living plays a significant factor to cause the infertility. Rajashekar *et al.,* (23) reported that, among (2270) infertility females 46.50% (1057) were PCOS patients.

Weight reduction or significant weight gain with a body mass index (BMI) of more than 27 kg/m2 might result in ovarian dysfunction (24) Obesity, which causes infertility in 90% of PCOS-afflicted infertile women, is a separate cause of infertility (21). Most of the studied women were overweight (32.35%) mainly between 21-25 age group. Having a high body fat percentage reduces the likelihood of becoming pregnant by increasing oestrogen production, which the body perceives as birth control (25) Age factor plays an important role in female infertility, the longer the period of infertility the more the number of overweight or obese individuals. The results show that BMI greater than 29.5 is equally associated with an increased risk of infertility. These results are in line with those of other research showing that being overweight or having a high body fat percentage reduces the efficiency of ART, increases the risk of miscarriage, and impairs the ability to conceive (26) These negative consequences are also caused by coexisting factors including age and PCOS status (27) Infertile female with irregular menstrual cycle had PCOS.

The present study shows high percentage (92.6) of infertile female had PCOS with irregular menstrual cycle, more percentage of (100) infertile female had PCOS with irregular menstrual cycle in the age

group of 21-25 yr. At 21 -25 age group, all (126) infertile female with PCOS had irregular menstrual cycle. The menstrual cycle is regulated by hormones.

5. Conclusion

The current study on the hormones FSH, LH, and prolactin in infertile women assess the hormonal profile and validate the etiological significance of infertility caused by hyperprolactinemia. Hyperprolactinemia can cause an ovulation, irregular ovulation, galactorrhea, oligomenorrhea or amenorrhea in non-pregnant women. Follicle formation and oestrogen production require both luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Issues with FSH and LH is attributable to higher prolactin levels in infertile women compared to controls, which may be the cause of the infertility seen in this group of women. In this study female with have high risk of pregnancy due to the disorder of hormone AMH levels, and that the severity of AMH deficiency is related to the large number of female infertility. Women with PCOS have three characteristic symptoms such as irregular menstrual cycle, excess androgen and polycystic ovaries and exhibit a clinically significant increased risk of infertility.

Female fertility is maintained by hormones, which are essential for the body's proper operation. Our reproductive system is heavily influenced by hormones; even the smallest imbalance can result in a variety of infertility problems. Because lifestyle and eating habits have a significant impact on the body's hormonal balance, it is quite possible to treat it naturally by making certain lifestyle adjustments.

ETHICAL APPROVAL AND CONSENT

The study was carried out in collaboration with a private fertility hospital at Ramanathapuram. This study protocol was approved by ethical committee of the hospital. Before conducting the interview, the investigator explained the purposes of this study, the risks and the benefits, and the voluntary nature of participation to the couple and their informed consent was obtained in a questioner. Privacy and confidentiality was ensured and conducted face to face interview in the fertility hospital to collect the data.

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Competing interests

The authors have declared that no competing interests exist.

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