SJIF Impact Factor: 5.464

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 5.
Issue: 4.
Page N. 222-228
Year: 2021

Original Article www.wjahr.com

HYPERPROLACTINEMIA AND ITS CORRELATION WITH HYPOTHYROIDISM IN INFERTILE WOMEN

[1]Dr. Wafaa Salah Abd-Alamieer, [2]*Dr. Sahar Abdul Baqi Sabti Al Dulaimi and [3]Dr. Mina Taha Al-Wassiti

[1]Senior Obstetrics & Gynecology, In Department Obstetrics &Gyecology, Al-Kadhymia Teaching Hospital, Baghdad – Iraq.
[2]Senior Obstetrics & Gynecology, Al-Yarmok Teaching Hospital, Baghdad-Iraq.
[3]C.A.B.O.G, Karkh Hospital For Child birth, Baghdad, Iraq.

Received date: 08 June 2021 **Revised date:** 28 June 2021 **Accepted date:** 18 July 2021

***Corresponding author: Dr. Sahar Abdul Baqi Sabti Al Dulaimi**
Senior Obstetrics & Gynecology, Al-Yarmok Teaching Hospital, Baghdad-Iraq.

ABSTRACT

Hyperprolactinemia is a common endocrine disorder of hypothalamic-pituitary ovarian axis affecting the reproductive functions. Despite the significant role of hyperprolactinemia in infertility. Aim of the study to find the prevalence of hypothyroidism in hyperprolactinemic infertile women and the prevalence of hypothyroidism in primary and secondary infertility and the prevalence of galactorrhea and menstrual disorder in hyperprolactinemic infertile women. **Methods:** Prospective case study 108 cases of primary and secondary infertility investigated for serum prolactin levels serum TSH levels at Al-Kadhimya Teaching Hospital, Baghdad-Iraq. **Results:** There were 64 (59%) of the 108 infertile women were primary infertility and 44 (40.7) were secondary infertility. Their ages ranged between (20-45) years with a mean ± SD (33.44 ± 7.29) years. Most of age group were (30-35) years, and most of women with duration of infertility above 4yearse. Prevalence of hyperprolactinemia was (46.9 %) in primary and (45.5 %) in secondary infertility. There were 50(53.7%) cases of hyperprolactinemia out of 108 cases of infertility. 6 (12.0%) cases of hyperprolactinemia had hypothyroidism. **Conclusion:** The high prevalence of hyperprolactinemia with infertility stresses the fact that all the cases of infertility subjected for serum prolactin estimation. Prolactin estimation done at early stages of infertility checkup rather than straight away going for more costly tests or invasive procedures. There is a prevalence of hypothyroidism in hyperprolactinemia. All the cases of hyperprolactinemia need to have TSH estimation.

KEYWARDS: Infertility, Hypothyroidism, Hyperprolactinemia, Galactorrhoea.

INTRODUCTION

Infertility defined as the inability to conceive after one year of unprotected intercourse of reasonable frequency is termed infertility. It can be subdivided into primary infertility that is there is no prior pregnancy and secondary infertility which follow at least one prior conception.[1] couple has achieved a pregnancy previously but are having difficulty currently with conception,[2,3] Infertility is a global health issue, affecting 12 to 14% of the couples worldwide and remains stable in recent years.[1] The World Health Organization (WHO) estimates that 60 to 80 million couples worldwide currently suffer from infertility.[4] According to the standard protocol, infertility evaluation usually identifies different causes, including male infertility (30%), female infertility (35%), the combination of both (20%), and finally unexplained or "idiopathic" infertility (15%).[5] Traditionally, measurement of Prolactin and thyroid hormones, especially (TSH) considered an important component infertility workup in women,[6] infertility represents a common condition with important medical, economic and psychological implications. Infertility has a serious impact on husband-wife relationship including their physical and mental health. In the society, childlessness is a challenging condition to the couple and has to face many social and family problem.[6] If there is a history of irregular period or amenorrhea especially if associated with galactorrhea, hirsutism or obesity then it need measurement of FSH,LH,TSH and prolactin, timing sample to coincide with the early follicular phase of the cycle if the woman is having period, we take women in age group between (20-45) years. Exclusion criteria are; male factor, disorder of ovulation, tubal factor, any congenital anomaly of urogenital tract and any obvious

organic lesion. Hyperprolactinemia is one of the most common endocrine disorder of the hypothalamic-pituitary ovarian axis affecting the reproductive functions. It is present in as high as 9 to 17% in women with reproductive disorders.[7] There is also a higher crude prevalence of hypothyroidism in hyperprolactinemia in infertile women. TRH in addition to increasing TSH causes rise in prolactin level.[8] Hypothyroidism is commonly associated with hyperprolactinemia and such patients exhibit ovulatory failure. Hence, assessment of serum TSH and prolactin levels are mandatory in the work up of all infertile women.[9] It observed that the prevalence of hyperprolactinemia associated hypothyroidism that is high in infertile women as compared to normal fertile female.[10] Aim of the study to find the prevalence of hypothyroidism in hyperprolactinemic infertile women and the prevalence of hypothyroidism in primary and secondary infertility and the prevalence of galactorrhea and menstrual disorder in hyperprolactinemic infertile women.

METHOD

Prospective case study conducted in the outpatient department of fertility center ,Al-Kadhymia Teaching Hospital, Um Al Banein Center ,Iraq, Baghdad, from first of January 2014 till thirty of July 2014, one hundred and eight (108) female patients with infertility were included of age group (20-45) years old, all patients were instructed about the research, related history and physical examination data were recorded(including duration of infertility, type of infertility, drug history, presence of galactorrhea ,menstruation disorder ,hypothyroidism symptoms, symptoms were dry skin, cold weather intolerance, constipation, hirsutism, alopecia, weight gain, muscle cramp). The exclusion criteria that adopted during case selection were male factor infertility and amongst the female factors were tubal factor, any congenital anomaly of the urogenital tract, or any obvious organic lesion. All history of thyroid disease or previous thyroid surgery or being on thyroid medications were also amounted to exclusion for the study, patient on treatment for hyperprolactinemia were excluded from the study. Workup done which included semen analysis, hysterosalpingography, ultrasonography, serum prolactin levels, diagnostic ultrasound, and serum TSH levels. For prolactin estimation, a fasting midmorning venous sample in follicular phase taken. Blood allowed centrifuging for 10 mints directly after aspiration by using gelatin tube (gel and clot activator) that allows separation of the serum above the gelatin layer then will use the cobas analyser. Roche Diagnostics introduces the cobas brand as the umbrella for products used to complete or expand the screening, diagnostic and monitoring applications of the professional laboratory. The Electro-Chemi-Luminescence -Immuno-Assay intended for use on Elecsys and cobas e immunoassay analyzers. We use cobas analyser to add special reagent to find the prolactin hormone in the serum during 20 mints, then machine analyse the sample automatically and digitally, level determined by using a kit provided by roche. The specimen was stored at 2-8 o C for short time (maximum two days) if i need to store more than 2 days, I have to freeze them under -18 o C after that I have to incubate it at 2-8 o C before analysing. The prolactin concentration in the sample calculated based on a series of standards. The color intensity is proportional to the prolactin concentration in the sample. The normal range taken was 4.79-23.3 ng/dl. Serum TSH levels were measured when prolactin levels were >24.0 ng/dl using auto analyzer from Roche (Cobas). Co. Women with serum prolactin levels > 100 ng/dl were advised CT scan or MRI. Statistical analysis done by used SPSS 22, categorical data used frequency, percentage. Continuous data used mean and standard deviation. Chi-square test used for association between categorical variables while t depended test and ANOVA used for different between continuous variables. Statistical significance considered whenever the P-value was equal or less than 0.05.

RESULTS

One hundred and eight patients were included in the study, 64 (59%) had primary infertility and 44 (40.7%) secondary infertility, high percentage (28.7%)of women where in age group between (30-35) years in both groups, and most of duration of infertility of more than 4 years (43.5%), their mean was 3.75±2.13 (Table 1).

Table 1: The distribution of age and duration of patients included in the study.

		No	%
Age (years)	20---	13	12.0
	25---	20	18.5
	30---	31	28.7
	35---	19	17.6
	40-45	25	23.1
	Mean ± SD (Range)	33.44±7.29	(20-45)
Duration (years)	1	10	9.3
	2	40	37.0
	3	11	10.2
	=>4years	47	43.5
	Mean ± SD (Range)	3.75±2.13	(1-7)

Regular menstrual cycle were present in 51 patients, 26 (44.8%) in patients with normal prolactin level and 25 (50%) of high prolactin level, 57 patients showed some menstrual abnormalities (amenorrhea 6, irregular menstruation 49, menorrhagia 2), there was no significant difference regarding menstrual abnormality (P=0.205) between cases of normal prolactin level and hyperprolactinemia, we found that 92 (85.7%) did not have galactorrhea and 16 (14.8) have galactorrhea, 3 (5.2%) of patients with galactorrhea with normal prolactin level and 13 (26.0%) of high prolactin level, galactorrhea was either the chief complaint or was detected in clinical examination, there is high significant differences between hyperprolactinemia and galactorrhes (P=0.002), 5.17% was the prevalence of galactorrhea in in normal prolactin level, while 26.0% was the prevalence of galactorrhea in hyperprolactinemia (Table 2).

Table 2: The prolactin level in relation to menstrual cycle.

		Serum prolactin (ng/ml)				P-value
		Normal		High		
		No	%	no	%	
M.C.	Amenorrhea	2	3.4	4	8.0	0.205
	Irregular	30	51.7	19	38.0	
	Menorrhagia	-	-	2	4.0	
	Regular	26	44.8	25	50.0	
Galactorrhea	Yes#	3	5.17	13	26.0	**0.002**
	No	55	94.8	37	74.0	
***Significant using Pearson Chi-square test for difference between proportions at 0.05 level**						

#represents the prevalence of galactorrhea

Concerning hystrosalpangiograph, all patients had patent Fallopian tubes, as none with tubal factor infertility was included in the study. Ultrasound was done to all patients it showed no abnormality in 94 (87.0%). Table 3 shows various pathologies found on ultrasound (seven with PCOS, two with adenxial cyst, two with chocolate cyst, two with fibroid, and one with endomaterial hyperplasia).

Table 3: The type of infertility and the ultrasound findings.

		No	%
Type of infertility	Primary	64	59.3
	Secondary	44	40.7
US findings	PCOS	7	6.5
	Adenexial cyst	2	1.9
	Chocolate cyst	2	1.9
	Fibroid	2	1.9
	Endo hyperplasia	1	0.9
	Normal	94	87.0

Primary infertility was found in 34 (58.6%) women of normal prolactin level and in 30 (60%) of women with hyperprolactinemia while secondary infertility was found in 24 (41.4%) in infertile women with normal prolactin level and in 20 (40%) in women with secondary infertility with hyperprolactinemia, there is no significant differences between type of infertility and prolactin level (P=0.884). The prevalence of hyperprolactinemia in primary infertility was 46.9% (30 out of 64), while the prevalence of hyperprolactinemia in secondary infertility was 45.5% (20 out of 44). Normal ultrasound found in 51 (87.9%) infertile women with normal prolactin level and in 43 (86.0%) infertile women with hyperprolactinemia, also pathological findings using ultrasound in relation to serum prolactin level showed a non- significant differences (P=0.121) (Table 4).

Table 4: The serum prolactin level according to type of infertility and to ultrasound finding.

		Serum prolactin (ng/ml)				P value
		Normal		High		
		No	%	No	%	
Type of infertility	Primary	34	58.6	30	60.0	0.884
	Secondary	24	41.4	20	40.0	
US findings	PCOS	6	10.3	1	2.0	0.121
	Adenexial cyst	-	-	2	4.0	
	Chocolate cyst	-	-	2	4.0	
	Fibroid	1	1.7	1	2.0	
	Endo hyperplasia	-	-	1	2.0	
	Normal	51	87.9	43	86.0	
***Significant using Pearson Chi-square test for difference between proportions at 0.05 level**						

The infertile women included in the study were further subdivided into 2 subgroups

- Group I; includes 50 infertile women with hyperprolactinemia (53.7%).
- Group II; includes 58 infertile women with normal serum prolactin level (46.3%).

After the obtaining the TSH level measurement the sample group of 108 infertile women revealed that 96 (88.9%) had normal TSH level and 12 (11.1%) had high level of TSH. The prevalence of hypothyroidism (TSH level >5uIu/ml) in normal prolactin women was 10.3% (6 out of 58) while the prevalence of hypothyroidism in hyperprolactinemic women was 12.0% (6 out of 50) with a P=0.464 in measuring TSH level between women with normal prolactin level and women of hyperprolactinemia (Table 5).

Table 5: The percentage of prolactin level and TSH level in hyperprolactinemia.

TSH in hyperprolactinemia(ulu/ml)	Serum prolactin (ng/ml)				P value
	Normal		High		
	No	%	No	%	
<5	52	89.7	44	88.0	0.464
5—9	1	1.7	2	4.0	
10—14	-	-	-	-	
15—19	2	3.4	-	-	
>20	3	5.2	4	8.0	
***Significant using Pearson Chi-square test for difference between proportions at 0.05 level**					

Table 6 shows the incidence of hyperprolactinemia was (50/108) hence it was seen that 30 of them had primary infertility and 20 of them had secondary infertility, 8 of infertile women with serum prolactin>100 ng/ml (5 of them with primary infertility and 3 with secondary infertility), all the 8 infertile women were advised to have MRI or CT scan. The table also shows the serum TSH level in hyperprolactinemia, which revealed that there was hypothyroidism in 3 patients of primary infertility and 3 of patients of secondary infertility, the relation between the type of infertility and hypothyroidism is also shown in the table. The result indicate that there is no significant difference between primary and secondary infertility on prevalence of hypothyroidism, there is no significant different between serum prolactin and type of infertility (P=0.996), no significant difference between TSH level in general and type of infertility (P=0.267), also no significant difference between TSH level in hyperprolactinemic women and type of infertility (P=0.868) (Table 6).

Table 6: The TSH level in hyperprolactinemia in primary and secondaryinfertility.

	Type of infertility					
	Primary		Secondary		Total	
	No	%	No	%	No	%
Serum prolactin (ng/ml)						
<=25	34	53.1	24	54.5	58	53.7
26—50	15	23.4	11	25.0	26	24.1
51—100	10	15.6	6	13.6	16	14.8
101--150	3	4.7	2	4.5	5	4.6
151---200	-	-	-	-	-	-
>200	2	3.1	1	2.3	3	2.8
P value	0.996					
TSH level (ulu/ml)						
<5	59	92.2	37	84.1	96	88.9
5—9	2	3.1	1	2.3	3	2.8
10—14	-	-	-	-	-	-
15—19	-	-	2	4.5	2	1.9
>20	3	4.7	4	9.1	7	6.5
P value	0.267					
TSH level (ulu/ml) in hyperprolactinemia						
<5	27	90.0	17	85.0	44	88.0
5—9	1	3.3	1	5.0	2	4.0
10--14	-	-	-	-	-	-
15--19	-	-	-	-	-	-
>20	2	6.7	2	10.0	4	8.0
P value	0.868					

***Significant using Pearson Chi-square test for difference between proportions at 0.05 level**

DISCUSSION

Thyroid hormones have profound effects on reproduction and pregnancy. Thyroid dysfunction implicated in a broad spectrum of reproductive disorders, ranging from abnormal sexual development to menstrual irregularities and infertility .Primary hypothyroidism is associated with increased production of thyrotropin – releasing hormone (TRH), which known to stimulate pituitary TSH and PRL release. Hyperprolactinemia adversely affects infertility potential by impairing GnRH pulsatility and thereby ovarian functions.[3] It was observed that there is a difference in prolactine level in different types of infertility, Prevalence of hyperprolactinemia was 46.9 % in primary and 45.5 % in secondary infertility, this result is in agreement with the study by Nasima Akhter et al.[5] In addition, our study is in agreement with the findings of Kumkum et al.[11] who had depicted a prevalence of hyperprolactinemia in primary infertility was 46% in their study. The reason for that result may be due to fact that as hyperprolactinemia may cause or result from infertility. The higher prevalence in primary infertility found in our study explained by this phenomenon. The result of this study shows the effect of prolactin level on menstruation. Statistical analysis indicates changes in menstruation in women with hyperprolactinemia and in women with normal prolactin; this result is in agreement with the study by Caspian et al.[12] who found that menstrual disorder was 45.2% in his study, 23.5% in hyperprolactinemic patients and 21.8% in normal prolactin groups. These findings were similar to the report by Raber et al. that menstrual disorder was seen in 26% of the hyperprolactinemia patients.[13] Menstrual abnormalities were detected in about 60% of the infertile hyperprolactinemic cases in study by Goswami and Binita et al[9] Saxena et al.[14] and this study, which is nearly similar to that observed by Kumkum et al.[11] who had reported the abnormality to be 57.6% in their study, in the study done by Krasses et al.[15] the prevalence of menstrual irregularities reached 23% while being only 8% in those with normal prolactin level ($p<0.05$), our results disagree with Meier et al., study that was performed on 66 female patients with hyperprolactinemia, no cases of menstruation disorders was reported.[16] The cause of any type of menstrual disorder (amenorrhea, oligomenorrhea) occurs due to hyperprolactinemia resulting from a defect in the positive feedback of estrogen on LH, and due to LH and FSH suppression. (Hyperprolactinemia induces suppression of hypothalamic- pituitary- gonadal axis and resistance of the ovary to gonadotropin action, which result in amenorrhea and lack of ovulation). In this study, it observed that there is incidence of hypothyroidism in infertile women with hyperprolactinemia, so there is difference between women with hyperprolactinemia and women with normal prolactin level in development of hypothyroidism. The prevalence of hypothyroidism in women with hyperprolactinemia in our study was 12 %, while the prevalence in women with normal prolactin was 30.1% This result agrees with the study by Nasima Akhter et al.[5] The prevalence of hypothyroidism in infertile women with normal prolactin level in their study was 12.3% and prevalence of subclinical hypothyroidism

in women with hyperprolactinemia was 37.5%, while the result in other study in USA by Olivar,et al.[17] revealed lower prevalence rate, The most likely cause of development of hypothyroidism in hyperprolactinemic women is that prolactin secretion is controlled by prolactin inhibitor factor that is secreted from hypothalamus. Other factors like vaso active inhibitory peptide (VIP) and thyroid releasing hormone (TRH) cause to increase prolactin secretion fact, TRH in addition to increasing TSH causes rise in the prolactin level, in patients with primary hypothyroidism, increased levels of TRH can rise prolactin levels. The high prevalence rate of hypothyroidism in our study related to the lower level of TSH that we depend on.[8] Our results indicate that there is asignificant increase in the development of galactorrhea in women with high prolactin level while there is no significant increase in those with normal prolactin level, the prevalence of galactorrhea in our study was 26 % in hyperprolactinemic infertile women while prevalence of galactorrhea in women with normal prolactine level was 5.17 %,this result is in agreement with the finding in India by Prathibha ,et, al.[18] the finding in Iraq by Razzak et al.[19] observed a higher prevalence rate of hyperprolactinema and galactorrhea than that found in India, our results disagree with other result which found no significantrelation between the hyperprolactinemia and galactorrhea such as Raber et al.[13] They found galactorrhea in hyperprolactinemic group was 5.1% and it was 1.8% in normoprolactinemic patients. This difference was not statistically significant.Also, our results disagree with Meier et al.[16] study that performed on 66 female patients with hyperprolactinemia no cases of galactorrhea was reported (Meier, et al.[16] As hyperprolactinemia may result from stress, the variable prevalence may be due to the different stress levels of infertility patients in different areas Raber et al [(13)]. Obtaining results show that there are no significant difference ($p > 0.05$) between primary and secondary infertility on development of hypothyroidism, the results disagree by the result of Akhter et al. [(5)] who found that the prevalence of subclinical hypothyroidism is more in secondary infertility than in primary infertility. The higher prevalence of hypothyroidism in secondary infertility patients considered the sequel of previous autoimmune thyroid diseases that caused the thyroid function to worsen after the first conception.[20]

CONCLUSION

The high prevalence of hyperprolactinemia with infertility stresses the fact that all the cases of infertility subjected for serum prolactin estimation. Prolactin estimation done at early stages of infertility checkup rather than straight away going for more costly tests or invasive procedures. There is a prevalence of hypothyroidism in hyperprolactinemia. All the cases of hyperprolactinemia need to have TSH estimation.

ACKNOWLEDGMENTS

I thank great Allah for granting me the will and strength with which this research accomplished. I would like to express my deepest gratitude to my supervisor **Dr. Wafaa Salah Abd Al-Amieer** for her kind supervision, scientific guidance, valuable advices and continued encouragement throughout the course of my research.

REFERENCES

1. Sadhana Gupta.Infertility.In:Acomperhensive textbook of obstetrics and gynecology.1st edition. india. Jaypee brother, 2011; 222.
2. Frey KA, Patel KS. Initial evaluation and management of infertility by the primary care physicians. Mayo ClinProceeding J., 2004; 79(11): 1439- 43.
3. Poppe K,Velkeniers B.thyroid and infertility.Verh K AcadGeneeskd BelgJ, 2002; 64(6): 389-99.
4. WHO. Infecundity, infertility, and childlessness in developing countries: DHS Comparative Reports No 9. Geneva: World Health Organization, 2004; 1-74.
5. Sub-clinical hypothyroidism and hyperprolactinemia in infertile women: Bangladesh perspective after universal salt iodination. *The Internet Journal of Endocrinology*, 2012; 5.
6. Sharma Priyanka,Prasad Suvarna & Tangri Nitin.Serum infertility and itscorrolation with serum prolactin and TSH concentration-An unmatched case control study. *J Pharm Biomed Sci., 2013, May; 30(30): 902-907.*
7. Biller.BM, Luciano.A, Crosignani PGet al.guidelines for the diagnosis and treatment of hyperprolactinemia. J Reprod Med, 1999; 44(12 Suppl): 1075-84.
8. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J ClinEndocrinol Metab., 2002; 87: 489-99.
9. Goswami B, Patel S, Chatterjee M , et al. Correlation of Prolactin and Thyroid Hormone Concentration with Menstrual Patterns in Infertile Women. J Reprod Infertil, 2009; 10(3): 207-212.
10. Tasneem A, Fatima I, Ali A,et al. The incidence of hyperprolactinemiaand associated hypothyroidism: local experience from Lahore. Pak J Nucl Med, 2011; 1: 49-55.
11. Kumkum A, Jasmine K, Shweta G,et al. Hyperprolactinemia and its coorelation with hypothyroidism in Infertile women . J Obstet Gynecol India, 2006; 56(1): 68-7.
12. Adele Bahar,Ozra Akha,Zahraa Kashi,et al. Hyperprolactinemia in association with subclinical hypothyroidism .Caspian J. Intern Med, 2011; 2(2): 229-233.
13. Raber W, Gessl A, Nowotny P,et al. Hyperprolactinaemia in hypothyroidism: clinical significance and impact of TSH normalization. Clin

Endocrinol (Oxf)J, 2003; 58(2): 185-91.
14. Saxena, Alpana. Correlation of Prolactin and Thyroid Hormone Concentration with Menstrual Patterns in Infertile Women. J Reprod Infertil., 2009; 10(3): 207-12.
15. KrassasGE.Thyroid disease and female reproduction. Fertility and sterlility J., 2000; 74(60): 1063-70.
16. MeierC,Christ-CrainM, GuglielmettiM.Prolactin dysregulation in women with subclinical hypothyroidism: effect of levothyroxine replacement therapy.Thyroid J.october, 2003; 13(10): 979-8.
17. OlivarAC,ChaffkinLM,KatesRJ,et al.Is it necessary to obtain serum level of thyroid stimulating hormon and prolactin in asymptomatic women with infertility?.connecticut medicine, 2003Aug; 67(7): 393-5.
18. PrathibhaD,GovardhaniM,KrishnaPT.Prolactine levels in infertility and bromocriptine therapy in hyperprolactinemia.Journal of indian medical association, 1994; 92: 397-9.
19. Razzak AH,Wais SA.The infertile couple: a cohort study inDuhok, Iraq.East Mediterr Health J., 2002; 8: 234-8.
20. Mahmood S,Islam MM,Siddiqui NI, Hossian GA,et al. Prevalence of antithyroid microsomal antibody in thyroid patients of endemic goiter area.Mymensingh Med J., 2004; 13: 4-10.