CHAPTER ONE

Introduction

1- Introduction :-

1-1- infertility:-

Reproductive health usually include four element fertility regulation ,safe pregnancy and child birth ,infant and child health and safe sex .one of indicator of lacking reproductive health is infertility .(Abdalla , 2011) Infertility remains a global health problem with an increasing incidence. It is estimated that worldwide, between 70 and 80 million couples suffer from infertility, and most of these are residents of developing countries, including the Middle East .(Omer etal, 2015).

Inferyility :- is The inability to conceive after one year of un protected intercourse (Abdulla , 2011) it is estimated that 25% of couples will experience an episode of infertility during their reproductive life. (Shannon etal ,2006) Primary Infertility refer to couple or patient who have had no previous successful pregnancy Secondary infertility encompasses patient who have previously conceived but are currently unable to conceive (Shannon etal ,2006) The World Health Organization (WHO) estimates that 60 to 80 million couples world wide currently suffer from infertility. (Agrawal etal ,2013).

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%)(Agrawal etal ,2013) Female infertility accounts for 37% of all infertile couples and among them most are due to ovulatory disorder and is often associated with dysregulation hormonal network(Nallusamy etal ,2016).

Presence of abnormally high values of prolactin <25ug/l is termed **hyperprolactinemia** which one of the most common endocrineological disorder of the hypothalamo –pituitary axis affecting fertility.(Nallusamy etal ,2016) It is present in as high as 9 to 17% in women with

reproductive disorders (Agrawal etal ,2013) Hyperprolactinemia affects the fertility potential by impairing pulsatile secretion of GnRH and interferes with the action of gonadotropins at the ovarian level so interfering with ovulation.(Nallusamy etal ,2016)

1-2- Rationale:-

Infertility a global health problem with an increasing incidence. In view of the increasing number of infertility among Sudanese women, that has an impact on ovulation and menstruation and other complications , In Sudan there is few published data concerning serum prolactin level in infertile Sudanese woman and it is correlation with TSH and to explain the relation between TSH,TRH and Prolactin.

1-3-objectives:-

1-3-1- General objective:-

To assess of hyperprolactinemia in infertile women and its correlation with TSH

1-3-2- Specific objectives :-

-to estimate serum TSH level in the infertile Sudanese women .

-to find out the correlation between prolactin and thyroid stimulating hormone.

-to find out the frequency of hyperprolactinemia in infertile women.

-to compare TSH level in infertile women with and without hyperprolactinemia

-to assess high TSH level in prolactin group of infertile women

CHAPTER TWO

Literature Review

2-literature review:-

2-1- infertility:-

The inability to conceive after one year of unprotected intercourse it is estimated that 25% of couples will experience an episode of infertility during their reproductive life.

Primary infertility :- refer to couple or patient who have had no previous successful pregnancy.

Secondary infertility :- encompasses patient who have previously conceived but are currently unable to conceive (Shannon etal ,2006)

The World Health Organization (WHO) estimates that 60 to 80 million couples worldwide currently suffer from infertility. 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%)(Agrawal etal ,2013)

Infertility problem often arise as result of hormonal dysfunction of hypothalamic-pituitary-gondal axis measurement of peptide and steroid hormones in serum is therefore an essential aspect of evaluation of Infertility . (Shannon etal ,2006)

2-1-1- male infertility :-

It has been reported that 50% of in fertility problem are male in origin however male infertility goes undetected because low sperm count or abnormal sperm motility combined with normal female reproductive function merely result in delayed conception .

80% of infertile men not have a definable cause (idiopathic impaired sperm function) (Shannon etal ,2006)

The rest 20% of infertile men are due to following causes :-

- Endocrine disorders:-

Thyroid disorder , Pituitary failure , Hyperprolactinemia , Adrenal hyperplasia , Testicular failure , Hypothalamic dysfunction   (kallamann's syndrome) Exogenous androgens

- Anatomic :-

Congenital absence of deferens , Obstructed vas deferens ,   Varicocele ,Retrograde ejaculation , Congenital abnormalities of ejaculatory system.

- Abnormal spermatogensis

- Abnormal motility

- psychosocial   (Shannon etal ,2006)

2-1-2- female infertility:-

Menstrual cycle and conception depends up on complex physiological , anatomical and immunological factors .the essential requirement in the females is functionally intact hypothalamic-pituitary –ovarian axis to regulate normal folliculogenesis .pituitary hormones FSH , LH ,PRL and thyroid hormone are required for the normal development of ova . (Hardeep etal ,2014)

Female infertility accounts for 37% of all infertile couples and among them

most are due to ovulatory disorder and is often associated with dys regulation

hormonal network(Nallusamy etal ,2016)

factor that participate to female infertility include the followings:-

-Ovarian or hormonal factors

Metabolic disease , Thyroid , Obesity , Poly cystic ovary syndrome , Androgen   excess , Menopause , Gondal dysgenesis , Resistant ovarian syndrome , Premature ovarian failure ,

Hyperprolactinemia , Pituitary insufficiency , Hypothalamic insufficiency , Lutal phase deficiency , Hypogonadotropic hypogonadsim , hypergonadotropic hypogonadsim .

-tubal factors:-

-immunological factors

-psychological factors

-cervical factors

-latrogenic

-uterine factors (Shannon etal ,2006)

Evaluation of female infertility include :-

-detailed history and physical examination (papanicoleau cervical and vaginal smear)

-postcoital test

-evaluation of ovulation which include:-

-progesterone measuremenet,basal body temperature and measuremenet of luteinizing hormone surge

2-2 - Prolactin :-

Prolactin is a peptide hormone synthesized by lactotropes of the anterior pituitary gland.(Salah etal, 2013)Shortly after its discovery and partial characterization, PRL was prominently featured in *The New York Times* on December 3, 1937, indicating that it held the "key to peace in the world." The article, based on a lecture delivered by Prof. C. R. Stockard, proposed that "higher forms of life" were "governed by a 'glandocracy,' with the glands of internal secretion as the supreme rulers [in this instance PRL], exerting absolute control not only over the functioning of the individual from conception to death but also over the relationship of men and other vertebrate animals to each other. (Reed etal, 2003)

2-2-1- prolactin biochemistry :-

The human PRL gene, located on chromosome 6 apparently arose from a single common ancestral gene giving rise to the relatively homologous PRL, GH, and placental lactogen related proteins Several factors influence PRL gene expression, including estrogen, dopamine, TRH, and thyroid hormones PRL is a 199-amino-acid polypeptide containing three intramolecular disulfide bonds. It circulates in blood in various sizes: monomeric PRL ("little" PRL; 23 kd), dimeric PRL ("big" PRL; 48 to 56 kd), and polymeric forms (also known as "big, big" PRL; > 100 The monomeric form is the most bioactive PRL. In response to TRH, the proportion of the more active monomeric form increases(Reed etal, 2003)

Prolactin is structurally related to GH and human placental lactogen . Considered a stress hormone, it has vital functions in relationship to reproduction. Prolactin is classified as a direct effector hormone (as opposed to a tropic hormone) because it has diffuse target tissue and lacks a single endocrine end organ.(Robert etal ,2010)

2-2-2- prolactin regulation:-

Prolactin is unique among the anterior pituitary hormones because its major mode

of hypothalamic regulation is tonic inhibition rather than intermittent stimulation. Prolactin inhibitory factor (PIF) was once considered a polypeptide hormone capable of inhibiting prolactin secretion; dopamine, however ,is the only neuroendocrine signal that inhibits prolactin and is now considered to be the elusive PIF Any compound that affects dopaminergic activity in the median eminence of the hypothalamus will also alter prolactin secretion Examples of medications that cause hyperprolactinemia include phenothiazines, but yrophenones, metoclopramid and antipsychotics that antagonize the dopamine D2 receptor. (Robert etal ,2010)

The synthesis of prolactin is done by the lactotrophs in the anterior pituitary gland and gene for its synthesis is located on chromosome 6 The estrogen and TRH are positive modulators whereas dopamine is a negative modulator of prolactin secretion. Progesterone acts as an inhibitor of prolactin synthesis. A high level of TSH stimulates prolactin secretion and causes ovulatory dysfunction (.(Hardeep etal ,2014)

TRH stimulates PRL but probably does not play an important role in PRL secretion. Estrogen stimulates PRL gene transcription and secretion explaining why women have higher PRL levels and why cycling women have a higher PRL pulse frequency than postmenopausal women and men(Reed etal, 2003)

2-2-3- prolactin function:-

PRL is essential for human survival because of its role in milk production during pregnancy and lactation. Additional biologic functions ascribed to PRL include reproductive and metabolic effects, mammary development .pigeon crop sac activity, fresh water survival, melanin synthesis, water-seeking behavior of newts, molting, and parental behavior Although PRL and its receptor are clearly crucial in lower animals the impact of PRL on maternal

behavior in humans has not been fully delinated . Several lines of evidence indicate that PRL is a lymphocyte growth factor and stimulates immune responsiveness. PRL levels change in concert with immune disease, as seen in patients with lupus erythematosus (Reed etal, 2003)

2-2-4- prolactin production :-

The calculated production rate of PRL ranges from 200 to 536 μg/day/m 2 , and the metabolic clearance rate ranges from 40 to 71 mL/min/m2 PRL is cleared rapidly with a calculated disappearance half-life ranging from 26 to 47 minutes. PRL secretion occurs episodically in 4 to 14 secretory pulses, each lasting 67 to 76 minutes, over 24 hours PRL is secreted episodically during the day, with the highest levels achieved during sleep and the lowest occurring between 10 AM and noon (Reed etal, 2003)

2-2-5 Hyperprolactinemia:-

Hyperprolactinemia is one of the most common endocrine disorder of the hypothalamic-pituitary ovarian axis affecting the reproductive functions.4 It is present in as high as 9 to 17% in women with reproductive disorders It is defined as the Presence of abnormally high values of prolactin,>25μg/L Hyperprolactinemia affects the fertility potential by impairing pulsatile secretion of GnRH and interferes with the action of gonadotropins at the ovarian level so interfering with ovulation (Nallusamy etal ,2016)

Hyperprolactinemia is usually associated with menstrual and ovulatory disorders like amenorrhea, oligomenorrhea, an ovulation , ovulatory cycles with short or inadequate luteal phase, and galactorrhea Approximately two thirds of women having both galactorrhea and amenorrhea will have hyperprolactinemia.(Avasthi etal ,2006)

There are many physiologic, pharmacologic, and pathologic causes of hyperprolactinemia, and a common error by clinicians is to ascribe any elevation in prolactin to prolactinoma." (Robert etal ,2010)

Causes of hyperprolactinemia :-

Idiopathic Hyperprolactinemia

An elevated circulating PRL level in patients in whom no cause is identified is considered idiopathic, and these patients are relatively resistant to dopamine

Macroprolactinemia :-

PRL is a 23-kd single-chain polypeptide but may also be produced in higher molecular mass forms (50 and 150 kd). Macroprolactinemia reflects a predominant larger circulating PRL molecule (particularly the 150-kd variety) with markedly reduced bioactivity

Prolactinoma :-

A prolactinoma is a pituitary tumor that directly secretes prolactin, and it represents the most common type of functional pituitary tumor. The clinical presentation of a patient with a prolactinoma depends on the age and Gender of the patient and the size of the tumor (Robert etal ,2010)

Other Causes of hyperprolactinemia :-

-Physiologic :- (Pregnancy , Lactation , Stress , Sleep , Coitus , Exercise)

-Pathologic:-

-Hypothalamic-Pituitary Stalk Damage such as (Tumors , Craniopharyngioma , Suprasellar pituitary mass extension , Meningioma , Dysgerminoma , Hypothalamic metastases , Granulomas , Infiltrations , Rathke's cyst , Irradiation , Trauma , Pituitary stalk section , Suprasellar surgery)

-Pituitary Disorder such as (Prolactinoma , Acromegaly , Macroadenoma (compressive) , Idiopathic , Plurihormonal adenoma , Lymphocytic hypophysitis or parasellar)

-*Systemic Disorders* *such like (* Chronic renal failure , Polycystic ovarian disease , Cirrhosis , Pseudocyesis , Epileptic seizures , Cranial radiation , Chestneurogenic chest wall trauma, surgery, herpes zoster)

-Pharmacologic

-*Neuropeptides* as

Thyrotropin-releasing hormone , PRL-releasing peptide

-*Drug-Induced Hyper secretion* as *(* Dopamine receptor blockers , *Cholinergic Agonists ,* Physostigmine , *Antihypertensives ,* Labetolol , Reserpine , Verapamil)

-*H2 Antihistamines* as *(* Cimetidine , Ranitidine)

*-**Estrogens***

-*Oral Contraceptives*(Reed etal, 2003*)*

2-3- Thyroid stimulating hormone:-

Thyrotropin is glycoprotein hormone synthesized in the adenohypophysis that promotes the growth of ,sustains ,and stimulate the hormonal secretion of thyroid gland .(Demers etal ,2006)

2-3-1- Thyrotropin biochemistry:-

TSH is a glycoprotein hormone that is a hetero dimer of two non covalently linked and subunits. The subunit is common to TSH, LH, FSH, and hCG, but the subunit is unique and confers specificity of action The subunit is the earliest hormone gene expressed embryonically; activation of the subunit gene occurs later under the influence of GATA-2 and Pit-1The 13.5-kb subunit gene is located on chromosome 6 and comprises four exons and three introns Although the subunit gene is expressed in thyrotroph, gonadotroph, and placental cells, its regulation is uniquely cell-specific.(Reed etal, 2003)

With molecular weight of 26.6KDa TSH is secreted by thyrotrophs cell of anterior lobe of pituitary gland .(Demers etal ,2006)

2-3-2- TSH production :-

The TSH production rate is normally 100 to 400 mU/day, with a calculated circulating half-life of about 50 minutes. Secretion rates are enhanced up to 15-fold in hypothyroid subjects and are suppressed in states of hyperthyroidism. The degree of TSH glycosylation determines the metabolic clearance rate as well as bioactivity, and in hypothyroidism the molecule appears highly sialylated. Immune reactive fetal pituitary TSH is detectable by 12 weeks. Immediately after full-term birth, there is a brisk rise in TSH ,which remains elevated for up to 5 days before stabilizing at adult levels Although TSH secretion is pulsatile, the low pulse amplitudes and long TSH half-life result in modest circulating variances. Secretory pulses every 2 to 3 hours are interspersed with periods of tonic non pulsatile TSH secretion Circadian TSH secretion peaks between 11 PM and 5 AM (Reed etal, 2003)

2-3-3- TSH regulation :-

Thyrotropin releasing hormone a tripeptide is produced in hypothalamus . TRH act on the pituitary thyrotropes to stimulate both synthesis and release of TSH .TSH in turn control the thyroid gland and the synthesis and release of the thyroid hormone .TSH also control size and number of thyroid follicular cells . arise in thyroid hormone concentration elicit an inhibitory effect on the pituitary response to TRH conversely a fall in thyroid hormones concentration cause an increase in both TRH and TSH secretion.(Demers etal ,2006)

2-3-4- TSH function :-

TSH acts on the thyroid gland to induce thyroid hormone synthesis and release and to maintain trophic thyroid cell integrity The TSH G protein-coupled (GPC) receptor is located on the thyrocyte plasma membrane and is encoded by a gene on chromosome 11q31(Reed etal, 2003)

CHAPTER THREE

Material and Method

3- Material and Method :-

3-1-study Design :-

This study designed as analytical cross-sectional study .

3-2- Study Area :-

This study was carried in Khartoum state

3-3- Study Population :-

80 cases of Infertile women in Khartoum state

3-4- Study Period:-

The study was carried between Mars- July . 2016

3-5- Sampling :-

3-5-1- Inclusion Criteria:-

Infertile women in Khartoum state

3-5-2-Exclusion Criteria :-

- Male factor infertility, female factors-tubal factor, urogenital tract anomalies and obvious organic lesion in pelvis

- History of thyroid disease/thyroid surgery/thyroid medication.

- Women unwilling to participate or sign the informed consent.

3-6- Collection:-

5ml venous blood collected from each participant women and placed in plain tube centrifuged for 10 min at 3500 rpm. The serum which obtained used in determination of TSH and PRL level .

3-7- Method:-

3-7-1 prolactin assay:-

The essential reagents required for an immunoenzymometric assay include high affinity and specificity antibodies (enzyme labeled and immobilized), with different and distinct epitope recognition, in excess, and native antigen. In this procedure, the immobilization takes place during the assay at the surface of a microplate well through the interaction of streptavidin coated on the well and exogenously added biotinylated monoclonal anti-PRL antibody. Upon mixing monoclonal biotinylated antibody, the enzyme-labeled antibody and a serum containing the native antigen, reaction results between the native antigen and the antibodies, without competition or steric hindrance, to form a soluble sandwich complex. Simultaneously, the complex is deposited to the well through the high affinity reaction of streptavidin and biotinylated antibody. This Immobilized complex = sandwich complex bound to the well After equilibrium is attained, the antibody-bound fraction is separated from unbound antigen by decantation or aspiration. The enzyme activity in the antibody-bound fraction is directly proportional to the native antigen concentration. By utilizing several different serum references of known antigen values, a dose response curve can be generated from which the antigen concentration of an unknown can be ascertained.

3-7-2 TSH assay :-

The essential reagents required for an immunoenzymometric assay include high affinity and specificity antibodies (enzyme conjugated and immobilized), with different and distinct epitope recognition, in excess, and native antigen. In this procedure, the immobilization takes place during the assay at the surface of a microplate well through the interaction of streptavidin coated on the well and exogenously added biotinylated monoclonal anti-TSH antibody. Upon mixing monoclonal biotinylated antibody, the enzyme-labeled antibody and a serum containing the native antigen, reaction results between the native antigen and the antibodies, without competition or steric hindrance, to form a soluble sandwich complex.
Simultaneously, the complex is deposited to the well through the high affinity reaction of streptavidin and biotinylated antibody.
After equilibrium is attained, the antibody-bound fraction is separated from unbound antigen by decantation or aspiration. The enzyme activity in the antibody-bound fraction is directly proportional to the native antigen concentration. By utilizing several different serum references of known antigen values, a dose response curve can be generated from which the antigen concentration of an unknown can be ascertained

3-8- Ethical considerations :-

Oral Informed consent was obtained from all the participants at the start of the study.

3-9- *Statistical analysis :-*

Data were analyzed by computer program (SPSS) Pearson correlation test ,

T. test were used for the calculation. $P \leq 0.05$ was considered significant

3-10-Quality Control :-

Each assay includes control sample with each calibration curve   and is estimated as same as sample

CHAPTER FOUR

RESULTs

4- Results :-

-Among the 80 infertile females, 20 has elevated serum prolactin level (>25 µg/L) . The assessment of hyperprolactinemia was 25% (20/80) in infertile women and the mean value of serum prolactin in infertile women was (13 ± 5.9 µg/L) and the mean value of serum prolactin in hyperprolactinemaic infertile women was (35.9 ± 10 µg/L) as explained in table 1

.-The mean serum TSH level in infertile women with hyperprolactinemia was (3.35 ± 1.39) and The mean serum TSH level in infertile women without hyperprolactinemia was (1.92 ± 1.18) the TSH level was higher in infertile women with hyperprolactinemia and was statistically highly significant (p=0.000) as it cleared in.(table 2)

-There was moderate positive correlation between TSH and prolactin level . TSH and prolactin values when there were correlated in infertile Sudanese women .The mean value of TSH was 2.3± 1.4 mIU/ml in infertile patients . Mean prolactin levels in infertile group was 18.7±12.3 ng/ml and Pearson correlation (R=0.614) As in figure 1

- The assessment of high TSH level in infertile Sudanese women was (7.5 %)(6/80) The assessment of high TSH level in infertile Sudanese women with hyperprolactinemia was (25%)(5/20) (table 4)

Table4- 1- assessment of hyperprolactinemia in infertile women in Khartoum state

Prolactin Group	Prolactin level mean $\pm$ SD	No of cases	Frequency
0—25 µ g/L	13 $\pm$ 5.9 µ g/z	60	75%
>25 µ g/L	35.9 $\pm$ 10 µ g/L	20	25%
Total		80	100%

Among the 80 infertile females, 20 has elevated serum prolactin level (>25 µg/L) . The frequency of hyperprolactinemia in infertile women was 25% (20/80)

Table 4-2- Comparison of TSH level in prolactin group of Infertile women

Prolactin Group	TSH level	P .value
0—25 µ g/L	1.9 +/- 1.18	0.00
>25 µ g/L	3.53 +/- 1.39	

The TSH level was higher in infertile women with hyperprolactinemia compared to infertile women with normal prolactin level and was statistically highly significant (p=0.000)

Y= TSH level

Figure 1: Correlation of TSH With prolactin in infertile women

There were positive correlation between TSH and prolactin level in infertile women . Pearson correlation was (0.607) and p value is highly significant (0.00)
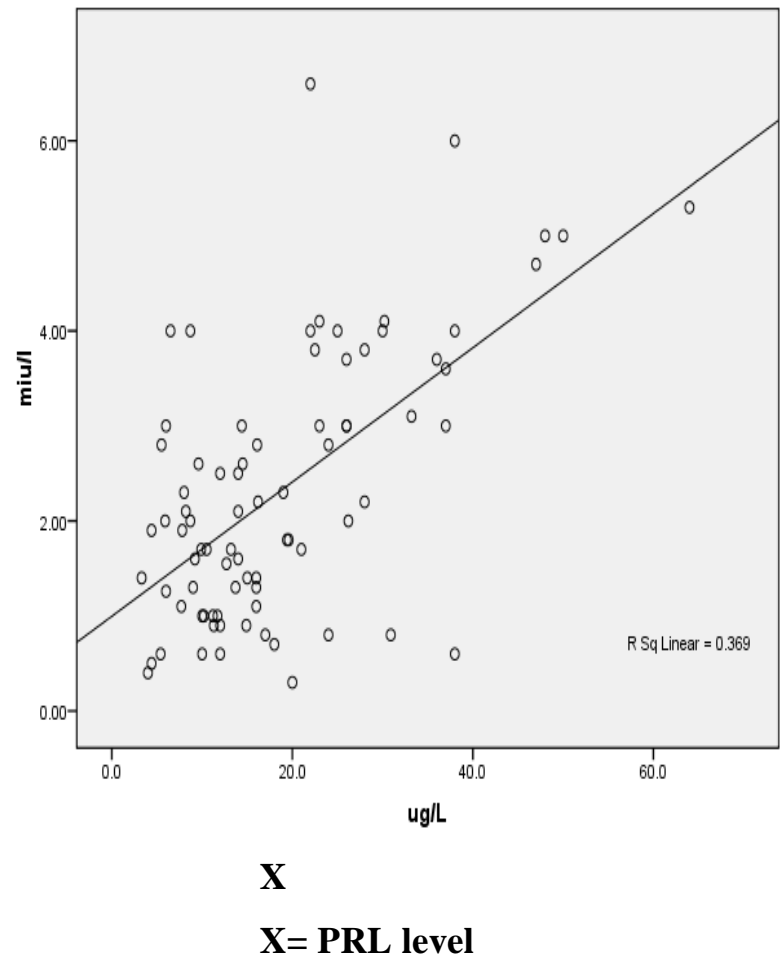

X

X= PRL level

Table 4-3 Assessment of high TSH level in prolactin group

Prolactin group	No of cases	No of cases with high TSH level	freqenecy
0—25	60	1	1.6%
>25	20	5	25%
Total	80	6	7.5%

The assessment of high TSH level in infertile Sudanese women was (7.5 %) The   assessment of high TSH level in infertile Sudanese women with hyperprolactinemia was (25%)

CHAPTER FIVE

Discussion

Conclusion

Recommendation

5-1- DISCUSSION :-

 Hyperprolactinemia is one of the most common endocrinological disorders affecting fertility. The understanding that hyperprolactinemia not only manifests as galactorrhea and amenorrhea but also causes gonadal dysfunction and infertility led to the estimation of prolactin in infertile females*(Nallusamy etal,2016)*

in this study assessment of hyperprolactinemia in infertile women Is 25% (80) which is similar to *Nallusamy et al ,2016)* in (Avasthi etal ,2006) 46% (Salah etal ,2013) 33.3% the prevalence is higher because hyperprolactinemia may result from stress may be due to the different stress levels of infertile women in different areas .

The present study has shown that amongst the hyperprolactinemic cases maximum cases have serum prolactin values between 25-50 ng/ml. Only 2 case had serum prolactin value more than 50 ng/ml (Table 1)

Out of 20 cases of hyperprolactinemia 5 cases had high TSH.. There is a positive correlation between prolactin level and TSH level as reported by *(Nallusamy etl,2016)*,(Avasthi etal,2006),(Salah etal ,2013).

- Out of 20 cases of hyperprolactinemia 5 cases had high TSH level with frequency about 25% of all cases of hyperprolactinemia s similar to(Avasthi etal, 2006),(*Nallusamy etal , 2016)* (*Hardeep etal,2014)*

- The ratio of proportions between hyperprolactinemia and high TSH level was 4:1 i.e. in every four hyperprolactinemic patients one has high TSH level similar to(*Nallusamy etal ,2016) (Hardeep etal,2014)* (Avasthi etal , 2006)

5-2- CONCLUSION:-

The present study revealed that in different groups of infertile women, an increase in serum Prolactin level and variation in TSH level were observed.

The main etiology of infertility was an ovulatory cycle due to Hyperprolactinemia which represent a common problem in reproductive dysfunction affecting about one-fourth of infertile women. There is moderate a positive correlation between increased prolactin level and TSH level in infertile women.

5-3- Recommendation :-

-Other studies recommended to investigate various causes of hyperprolactinemia in Sudanese infertile women

- recommended to include a larger number of participant .

- recommended to investigate other causes of infertility in Sudanese women

- recommended to be conducted as prospective study.

- recommended to investigate Prevalence of hyperprolactinemia and its correlation with TSH in Sudanese infertile woman with primary and secondary infertility

- Based on these observations *recommended to* all patients of infertility serum prolactin should be estimated. serum TSH should be estimated in cases with raised prolactin to find out cases of primary hypothyroidism which is to be managed differently.

CHAPTER SEX

Appendix and References

6-1- Reference:-

- **Abdullah N M** (2011), *Epidemiology of Infertility in Gezira Region central of sudan*, research Journal of medical sciences, 5 (1): 56-60, doi=rjmsci.2011.56.60

- *Agrawal M , Samal S , Hariharan C and Agrawal S (2013). Prevalence of hyperprolactinemia in infertile cases and its correlation with TSH in a rural set up hospital. International Journal of Reproduction, Contraception, Obstetrics and Gynecology ;2:626-30. DOI: 10.5455/2320-1770.ijrcog20131227*

- **Avasthi *K*** , Kaur *J* , Gupta *S* and Narang *P A, (2006) Hyperprolactinema and its correlation with hypothyroidism in infertile women*, The Journal of Obstetrics and Gynecology of India *Vol. 56, No. 1 : January/February 68-71*

- *Haedeep S h G , Gurmanpreet **,** Gurdeep K B and Amarjit K , (2014) Correlation of TSH and Prolactin Levels in Patients with Primary Infertility ,* Scholars Journal of Applied Medical Sciences ; 2(4B):1267-1269

-**Laurence M D** and Mary V (2006) , Pituitary Function in : Carl A B , Edwared *R A and David E B , ed , Tietz Texetbook of Clinical Chemistry and Molecular Diagnostics ,4*[th] *ed ,USA ,Elsevier* SAUNDERS *: 1976-81*

- *Nallusamy S and Gracelyn L J (2016) . Prevalence of hyperprolactinemia in infertile women and its association with hypothyroidism. International Journal of Advances in Medicine;3:33-8.*

- **Omer M S** . (2015), *A Prospective Study of Hormonal Changes among Sudanese Women With Infertility. International Journal of Recent Scientific Research.* 6(10), 6956-6959

- **Reed L p** , Henry M K , Shlomo M and Kenneth S P , ed (2003) , *Williams Textbook of Endocrinology*, Tenth Edition ,USA, SAUNDERS:201-253

- **Robert E. J**, (2010) Introduction to Hormones and Pituitary Function in : Michael L B, Edward P F and Larry E S, ed , *Clinical Chemistry Techniques , Principles , Corelations* , Sixth Edition , 351 West Camden Street 530 Walnut Street Baltimore: Lippincott Williams & Wilkins, a Wolters K luwer Business:451-53 .

- **Salah Eldin A. A**, Abdelgadir A. E and Mohammed E M (2013), *Hyperprolactinemia as a cause of female primary infertility and its prevalence in Gezira State, Central Sudan*, Egypt. Acad. J. Biolog. Sci; 5(1): 31 -36

-*Shannon H and Ann M G (2006) ,Reproductive Related Disorder in : Carl A B , Edwared R A, David E B, ed , Tietz Texetbook of Clinical Chemistry and Molecular Diagnostics ,4th ed ,USA ,Elsevier* SAUNDERS *:2120-27.*

6-2- APPENDEX :-

6-2-1- QUESTIONNARE:-

Sudan University of Science and Technology

FACULTY OF MEDICAL LABORATORY SCINCE

DEPARTMENT OF CLINICAL CHEMISTRY

QUESTIONNAIRE

Prevalence of hyperprolactinemia and its correlation with TSH in   Sudanese infertile woman

Name:……………………………………………………NO:(………)

Age :(……………)years

Include criteria ;--

Infertile sudanase woman

Exclude criteria;--

Male infertility factors are investigated and excluded .

hormonal therapy(dopamine-thyroxin)(…)

hypothalamus pituitary axis disease (…..)

reproductive system defect (…….)

thyroid disease (………)

Infertile woman un willing to participate (………..)

Result ………………………………………………………………….