Original Research

THE FREQUENCY OF ELEVATED PROLACTIN LEVEL IN POLYCYSTIC OVARY SYNDROME WOMEN (PCOS) AND ITS' EFFECT ON PREGNANCY RATE

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ABSTRACT

Introduction: Prolactin is a hormone secreted from anterior pituitary gland which has different functions throughout the body of the fertile females. Women with polycystic ovary syndrome (PCOS) may exhibit a mild elevation of serum prolactin level. High prolactin level can affect the fertility potential causing ovulatory dysfunction. Even those with normal ovulation, failure of producing a sufficient amount of progesterone after ovulation may occur which resulted in a deficient endometrium; less liable for embryo implantation(luteal phase defect). Thus, this research is aimed to study the frequency of elevated prolactin in women with PCOS and to evaluate its' effect on pregnancy rate. **Methods:** Fifty-three infertile females were included. They divided in to two major groups: Group I: females with PCOS and Group II: females with no PCOS. Both groups sub-divided in to two subgroups: Group A with serum prolactin more than 20 ng/dl and Group B with normal serum prolactin 2-20 ng/dl. All females were included in ICSI program followed by assessment of pregnancy rate in both groups. **Results:** The study was showed that 69.44% of women who suffered from PCOS had an elevated serum prolactin level with a mean of 31.17±10.24. Pregnancy rate was lower in the females with high serum prolactin level in both PCOS and non-PCOS women. **Conclusion:** Hyperprolactinemia is more frequent in the females with PCOS than normal ovulatory females. Elevated serum prolactin level negatively affects implantation and decreases the chance of getting a pregnancy following ICSI.

Keywords : Serum prolactin , PCOS, ICSI , Pregnancy rate.

Introduction

Polycystic ovary syndrome is a state of chronic anovulation affecting young women usually as a result of an imbalance of reproductive hormones (Adam, 2014). Women with PCOS exhibit abnormal high serum androgen which results in failure of ovulation and reducing the chance of conception (Al-Hindawi,2018) Elevated prolactin level had been reported in PCOS patients (Apostolos,2018). There is an argument whether PCOS and hyper prolactinemia share a common mechanism, coincidental, a cause-result relationship or both of them are distinct clinical entities(Kemal et al., 2009). PCOS usually result from improper steroidogenesis, hyper secretion of ovarian androgen, excess luteinizing hormone (LH) and hyper estrogenemia (Susie et al., 2018). Both hyper prolactinemia and PCOS cause androgen excess but the source of androgen excess in hyper prolactinemia of adrenal origin which resolved on dopamine agonist medications while in PCOS its mainly of ovarian source (Gonen et al., 1989). Some literatures documented an elevated prolactin level in females with polycystic ovaries (Amir et al., 2016). The possible mechanism is an altered dopaminergic and opiodergic tones which has been observed in both conditions (Perez et al., 2018).

However, some postulated that the elevated prolactin level which has been recorded in PCOS is transient and tends to be related to certain underlying factors most probably stress, drugs and associated hypothyroidism. So, any significant elevation of prolactin in PCOS patients must be fully investigated (Alpesh & Mohd, 2018) and measuring serum prolactin level in such patients usually done because both disorders share certain clinical presentations (Szosland et al., 2015).

High prolactin level can affect the reproductive potential of the females through its inhibitory effect on GnRH neurons to inhibit GnRH secretion or affect the pituitary gland and decrease the secretion of gonadotropins resulting in ovulatory dysfunction (Ursula, 2012). High serum prolactin also can interfere with the response of the uterine endometrium to the estrogen which is necessary for follicular growth and endometrial proliferation (Daly et al., 1981). Prolactin also may interfere with the luteal phase (Ahmed et al., 2018). However the role of prolactin in the implantation and successful pregnancy is still uncertain (Ioannidis et al., 2005). For successful embryo implantation, good quality embryo, adequately developed endometrium and a functional corpus luteum are essentials (Perez et al., 2018). So, any factor which may interfere with implantation and decrease the chance of getting pregnancy should be fully investigated.

Methods

This is a prospective cohort study in which the infertile couples were taken from the Fertility Center, Al- Sadr Medical City, Al- Najaf AL-Ashraf/Iraq.

An oral consent was taken from all couples to be involved in the study. Fifty three infertile females selected randomly were included and divided in to two major groups Group I with PCOS (n=36) and Group II without (normal ovulatory with or without tubal obstruction) (n=17) and all of them were subjected to intra cytoplasmic sperm injection(ICSI) as a fertility treatment measure. The age of all females was 35 years old and less, all of them were stimulated by GnRH (gonadotropin releasing hormone) antagonist protocol + gonadotropins; (Cetrorelix 0.25mg*1 + Follitrope 75 iu*2 for approximately 7-14 days). The partners of those females had either normal semen parameters or with moderate impairment of semen quality according to WHO,2010. Male partners with sever impairment of semen parameters and frozen sperms were excluded. Other possible causes of elevated serum prolactin were also excluded eg., pituitary adenoma, drugs-induced and hypothyroidism.

The female partners were evaluated by history, physical examination, anthropometric measure; weight, height and body mass index (BMI), hormonal profile and trans-vaginal ultrasound (TVUS) for diagnosis of polycystic ovaries, antral follicles counts and endometrial thickness(ET).

Blood was drawn at the morning of the day 2 of the menstrual cycle before 10.00 am. Serum was obtained by centrifugation and tested by ELISA using commercial kits(CAA38264.1-MyBioSource) to measure prolactin level. Normal serum value in non-pregnant, non-lactating fertile female is 2-20 ng/dl(Kathleen and Timothy, 2017). Cycle day 2(CD2) assessment of luteinizing hormone(LH), follicle stimulating hormone (FSH) and estrogen (E2) was also done. According to the level of serum prolactin, we sub-divided the females of both groups in to two sub-groups: group A with normal prolactin level 2-20 ng/dl (n=11) and group B with high prolactin level more than 20 ng/dl (n=24). Controlled ovarian stimulation by GnRH antagonist was done for all females. Following ovulation trigger; Pregnyl 10000 iu, Oocyte retrieval was done by the gynecologist under general anesthesia and TVUS when the woman had 8-14 follicles and their size more than 17 mm. At the same time the fresh ejaculated semen was prepared by sperm migration/direct swim-up from a pellet. ICSI was commenced and embryo transfer was done at day 3. Biochemical pregnancy was tested by human chorionic gonadotropin (hCG) assay 14 days following embryo transfer. Pregnancy rate was calculated by dividing the number of women with positive hCG / the number of women whom embryo transfer was done*100%. The result were compared between both groups to predict the effect

of elevated serum prolactin level on pregnancy rate and implantation. Analysis of the data was done by SPSS (version 24.0). The comparison for the mean ± SD was assessed by t-test and for the percentage by Chi-square and the variation considered significant when p-value ≤0.05.

Results

From all 53 sub-fertile females, 36 females had PCOS diagnosed according to Rotterdam criteria (Fauser et al., 2012) and 17 were normal ovulatory women whom attended the fertility clinic due to either tubal obstruction or mild-moderate male factor infertility. From 36 PCOS women 25 ones had a mean serum prolactin level 31.17±10.24 and only 11 women had a mean serum prolactin15.17±4.51, so the percentage of PCOS women with high serum prolactin (25/36) was 69.44%. The remaining 17 women were normal ovulatory women, nine had an elevated mean serum prolactin level 41.09±13.74 and 8 had a mean serum prolactin level 12.54±7.75. So, the percentage of normal ovulatory women having high serum prolactin (9/17) was 52.94%. So, the percentage women with high serum prolactin level was higher in PCOS group 69.44 VS 52.94%.

Table 1: Serum prolactin level in PCOS and non-PCOS groups.

Parameter	PCOS N (%)	Non-PCOS N (%)
Women with high serum prolactin	25(69.44%)	9(52.94%)
Women with normal serum prolactin	11(30.56%)	8(47.06%)

Table 2 shows the demographic data of the females of PCOS groups. There were no significant statistical differences regarding these parameters between both groups. p-value > 0.05.

Table2:Demographic data comparison between both sub-groups within PCOS group.

Parameter	Normal (n=11) Mean ±SD	High (n=25) Mean ±SD	P-value
Age (years)	28.36±3.64	27.16±4.46	0.43
BMI (Kg/m2)	28.88±2.12	29.96±4.80	0.48
Duration(years)	6.18±2.82	6.84±3.26	0.56

Table 3 compares CD2 hormonal profile and endometrial thickness (ET) in both groups. There was no significant statistical variation regarding cycle day 2 in E2, FSH levels and ET between females in both groups (p-value = 0.50, 0.55 and 0.68) respectively. The only exception was CD2 serum LH which showed a significantly higher level in women with normal prolactin level with a mean of 5.72±3.50 vs 3.84±1.92 in women with high prolactin level (p-value = 0.04).

Table 3: A comparison of cycle day 2 hormones and endometrial thickness within PCOS sub-group.

Parameter	Normal (n=11) Mean±SD	High (n=25) Mean±SD	P-value
E2 (pg/ml)	44.63±30.17	39.44±20.16	0.54
LH (IU/L)	5.72±3.50	3.84±1.92	0.04
FSH (IU/L)	4.93±1.47	4.98±1.64	0.92
ET (mm)	3.63±0.92	3.76±1.09	0.74

Regarding to pregnancy rate, its best estimated in table(4). It was higher in females with normal serum prolactin level 27.27% in comparison with females with high serum prolactin 24%.

Table 4: Pregnancy rate comparison between the PCOS sub-groups

Parameter	Normal	High	P-value
Pregnant	3 (27.27%)	6 (24%)	**0.2**
Not pregnant	8(72.73%)	19(76%)	

Table 5 shows the demographic data of the females within non-PCOS groups. There were no significant statistical differences regarding to these parameters between both sub-groups at p-value > 0.05 except BMI which is higher in women with normal serum prolactin at p-value=0.03.

Table5:Demographic data comparison between both sub-groups within non-PCOS group.

Parameter	Normal (n=8) Mean ±SD	High (n=9) Mean ±SD	P-value
Age (years)	28.50±3.81	27.77±4.71	0.73
BMI (Kg/m2)	28.16±4.34	24.17±2.39	0.03
Duration(years)	5.50±4.89	7.77±3.23	0.27

Table 6 compares CD2 hormonal profile and endometrial thickness (ET) in both groups within non-PCOS group. There was no significant statistical variation regarding cycle day 2 in E2, LH, FSH levels and ET between females in both groups (p-value = 0.84, 0.42, 0.73 and 0.93) respectively.

Table 6:A comparison of cycle day 2 hormones and endometrial thickness within non-PCOS group.

Parameter	Normal (n=9) Mean±SD	High (n=8) Mean±SD	P-value
E2 (pg/ml)	33.71±15.21	35.46±19.69	0.84
LH (IU/L)	9.75±19..62	4.32±2.17	0.42
FSH (IU/L)	8.39±12.25	6.94±2.69	0.73
ET (mm)	3.25±0.46	3.22±0.83	0.93

Regarding to pregnancy rate in non-PCOS group, its best estimated in table 7. It was higher in females with normal serum prolactin level 62.5% in comparison with females with high serum prolactin 55.55%.

Table 7: Pregnancy rate comparison between the non- PCOS sub-group:

Parameter	High	Normal	P-value
Pregnant	5(55.55%)	5(62.5%)	**0.06**
Not pregnant	4(44.45%)	3(37.5%)	

Discussion

There is a controversy about the relation between polycystic ovary syndrome and hyper prolactinemia and weather PCOS associated with hyper prolactinemia, hyper prolactinemia is a part of PCOS pathophysiology or the abnormal hormonal environment of PCOS lead to hyper prolactinemia is a matter of debate and a subject of a wide research (Amir et al., 2016). The exact mechanism is still unknown, the theory of persistent hyper estrogenemia in polycystic ovary syndrome stimulates prolactin secretion is sometimes considered to be responsible (Swathi and Sujaya, 2015). About 5-30% of PCOS exhibited a mild elevation in serum prolactin level (20-40 ng/dl) (Baskind and Balen, 2016)

It has been reported that this mild elevation is transient and persistent elevation should be investigated by brain MRI to exclude associated pituitary prolactinoma (Sheehan, 2004).

The study was showed that 69.44% of sub-fertile PCOS patients had an elevated prolactin level (more than 20 ng/dl) in comparison with 52.94% in the normal ovulatory women.

Some was in agreement with this result and showed that serum prolactin level is higher than normal in PCOS patients (Sedighe et al., 2014). This could be explained by the hypothesis that some points of the PCOS pathogenesis related to deficient hypothalamic dopaminergic activity which also responsible for elevated LH/FSH ratio and thyroid stimulating hormone (TSH) (Anthony et al., 1984). Many disagreed with this and states that serum prolactin level in PCOS patients are normal and the association between PCOS and high serum prolactin level is just an accidental finding (Szosland et al., 2015).

High serum prolactin (hyper prolactinemia) has been proven to negatively affect the outcome of ICSI. Studies had concluded that infertile females with normal serum prolactin showed a higher fertilization rate and pregnancy rate (Del Pozo, 1985) (Reinthaller et al., 1987) (Huang et al., 1991). Other researches had found that the effect of an elevated serum prolactin on ICSI tends to be insignificant (Pattinson et al., 1990)(Chang et al., 1993). Meanwhile, subsequent studies had found a positive correlation between high serum prolactin and ICSI outcomes (Mendoz et al., 1997) (Mendoz et al., 1999).

The current study showed that the pregnancy rate was less in the females who had high serum prolactin level. Similar results were obtained from different studies which was reported that hyperprolactinemia decrease cleavage and pregnancy rate (Ahmed et al., 2018). Some researches tried to prove this by studying the ICSI outcomes in infertile females with hyperprolactinemia after lowering serum prolactin by bromocriptine in the preceding cycle. They found a higher pregnancy rate and higher rate of developing good quality embryos which might responsible for the increased pregnancy rate(Gonen et al., 1989). So, further studies about the possible factors which might be responsible for lowering pregnancy rate in hyper prolactinemic patients are suggested and studying the effect of high serum prolactin on embryo quality and further embryonic development is recommended

Conclusion:

Hyper prolactinemia is more frequent in the females with PCOS than normal ovulatory females. Elevated serum prolactin level negatively affects implantation and decreases the chance of getting a pregnancy following ICSI.

Conflicts of Interest

The author declare no conflicts of interest.

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