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Dose specification of Dopamine agonist, pergoline: Treatment in a cohort of subfertile Iraqi women with asymptomatic hyperprolactinemia: A prospective study

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ABSTRACT

Infertility is an important problem experienced by a significant proportion of couples in the population. Hyperprolactinemia is a key finding in a subset of women with primary and secondary infertility. Pergoline has been investigated by many authors to reduce serum prolactin and to increase ovarian follicle size; however, significant controversy is present in the available literature to justify conductance of the present study. This study was aimed to evaluate the role of pergoline treatment in a subset of subfertile Iraqi women on both ovarian follicle size and serum prolactin level. The current study involved 60 subfertile women who were treated with pergoline at a dose of 2.5 mg every 3 days for 8 weeks. Baseline estimation of serum prolactin and ovarian follicle size at luteal phase was performed and the second reading of these variables was conducted 8 weeks after treatment. The study was carried out in Al-Diwaniyah maternity and child teaching hospital in Al-Diwaniyah province, Iraq. The study was started at August 2016 and extended through January 2018. The results revealed that after 8 weeks from regular treatment with pergoline, serum prolactin was highly significantly reduced from 64 (45) ng/ml to 30.4 (24) ng/ml (P <0.001). In addition, it was found that the follicle size was highly significantly increased from 10 (2) mm to 17.5 (4.75) mm (P<0.001). It has been concluded that pergoline is an effective mode of treatment to treat subfertile women with asymptomatic hyperprolactinemia and to increase the size of growing ovarian follicles.

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INTRODUCTION

Anovulation disorders share a fraction of about 30 percent of infertility and usually manifest with irregular cycles ("oligomenorrhoea") or a lack of cycles ("amenorrhoea"). In a significant proportion of cases, treatments are routine and highly effective, for that reason couples may need only several visits to infertility specialists. This approach provides an easy and private marital relation when compared to the more complicated assisted reproductive technologies. Nevertheless, medical ovulation induction treatment modalities are not always successful in establishing pregnancy in subfertile couples. The type of approach for ovulation induction may be medical or surgical and this is often determined according to the cause of infertility (Katsikis et al., 2006). A pituitary microadenoma is a usual cause behind Hyperprolactinemia. This results in reduced production of a pituitary follicle stimulating hormone (FSH) and luteinizing hormone (LH). The common form of presentation is secondary

amenorrhoea; however, a number of ladies may give a history of galactorrhoea. In some patients, headache and disturbance of vision may be part of the clinical presentation and these cases macroadenoma are suspected and are in need of rapid intervention to prevent further catastrophic complications. Medical treatment is usually successful in managing the great majority of women with microadenoma with subsequent restoration of the menstrual cycle and fertility (Fairley and Taylor, 2003).

Prolactin (PRL) is the hormone that secreted by the anterior lobe of the pituitary gland that possesses its main biological function in starting and maintenance of the process of lactation. As a pathology in human, "hyperprolactinemia" most often manifests as a disorder of ovulatory and is usually accompanied by "secondary amenorrhea or oligomenorrhea" (Majumdar and Mangal, 2013).The principal physiological function of prolactin is initiation and maintenance of milk production. However, it also has metabolic actions, participates in reproductive breast maturation (Benker et al., 1990) and enhances immune reactions (Oner, 2013). Overall actions of prolactin are mediated via its binding to specific receptors in the lymphoid cells, gonads, and liver (Nilsson et al., 2009). The level of prolcatin in serum is a function of equilibrium between a group of stimuli and inhibitory factors both internal and external. Mediators that participate in the regulation of its secretion are of various origins, central nervous system, pituitary gland and some peripheral mediators (Sakamoto, 2016). Hypothalamic hormones exert dual control over prolactin secretion. The main signal is tonic inhibitory regulation of dopamine that is hypothalamic that passes through the "portal venous system" to function via pituitary "lactotroph D2 receptors". Other negative control factors of prolactin secretion include acetylcholine, norepinephrine, gamma-aminobutyric acid (GABA) and somatostatin (Majumdar and Mangal, 2013). The principal biologic hyperprolactinemia consequence is "hypogonadotropic hypogonadism (HH)" that results from the reduction of pulsatile gonadotropin-releasing hormone (GnRH). A raised concentration of prolactin leads to anovulation as it inhibits the pulsatility of LH and deregulates hypothalamic action via estrogen receptors blockage. Functions on the ovary might result from reduced LH receptors affinity in the "corpus luteum" and an accompanying reduction in the synthesis and release of progesterone, leading to not merely anovulation but also reduction of follicular development and insufficient "corpus luteum", usually known as termed as "short luteal phase." (Esmaeilzadeh et al., 2015).

Pergolin is A "methanesulfonate" salt prepared (from pergolide) via combining molary equal quantities of methanesulfonic acid and pergolide. This drug is used in the treatment of Parkinson's disease since it has both D1 and D2 dopamine receptors agonist actions (Tysnes and Storstein, 2017). The short and long-term actions of "oral pergolide mesylate" were evaluated and following a pergolide mesylate single dose (50 μgram) of, serum prolactin levels got less step wisely to come to a minimum level of 20% 6 hours following at baseline readings (Prabhakar and Davis, 2008). The lactotroph is one of the special endocrine cells that are unique as its basal secretory phase is relatively high. Tonic negative control by dopamine, that keeps low circulating prolactin concentration, needs a steady large dopamine input. Prolactin is controlled by the hypothalamus is unique since dopamine production by the hypothalamic tuberoinfundibular region (TIDA) is an inhibitory rather than stimulatory signal in contradiction to the situation of other pituitary hormones in which case hypothalamic signals are stimulatory. Dopamine regulated prolactin production via a direct action on anterior pituitary gland by inhibiting the basal secretory activity of these cells. It performs this action through binding to D2 receptors that are present on lactotrophs cell membrane. The activation of these receptors leads to reduced prolactin gene expression and exocytosis via a number of cellular signaling pathways (Fitzgerald and Dinan, 2008). "Luteinizing hormone (LH)" has an essential contribution in gonadal biologic activity. LH assisted by FSH initiates growth of follicles and the process of ovulation. For that reason, the natural growth of follicles is the product of synergistic contribution of LH and FSH (Raju et al., 2013). The present study was conducted to investigate the role of pergoline in treating subfertile women with asymptomatic hyperprolactinemia.

PATIENTS AND METHODS

The current study involved 60 subfertile a symptomatic hyperprolactinemic woman who was treated with pergoline at a dose of 2.5 mg every 3 days for 8 weeks. Baseline estimation of serum prolactin and ovarian follicle size at luteal phase was performed and the second reading of these variables was conducted 8 weeks after treatment. The study was carried out in Al-Diwaniyah Maternity and Child Teaching hospital in Al-Diwaniyah province, Iraq. The study was started at August 2016 and extended through January 2018.

Statistical analysis

Statistical analysis was carried out using statistical package of social sciences (SPSS) version 23.0. Numeric data were expressed as median and interquartile range (IQR). Wilcoxon test was used to evaluate the level of significance in changes of both serum prolactin and ovarian follicle size before and

after treatment with pergoline. The level of significance was considered at $P \leq 0.05$.

RESULTS

After 8 weeks from regular treatment with pergoline, serum prolactin was highly significantly reduced from 64 (45) ng/ml to 30.4 (24) ng/ml (P <0.001), as shown in figure 1. In addition, it was found that the follicle size was highly significantly increased from 10 (2) mm to 17.5 (4.75) mm (P<0.001), as shown in figure 2.

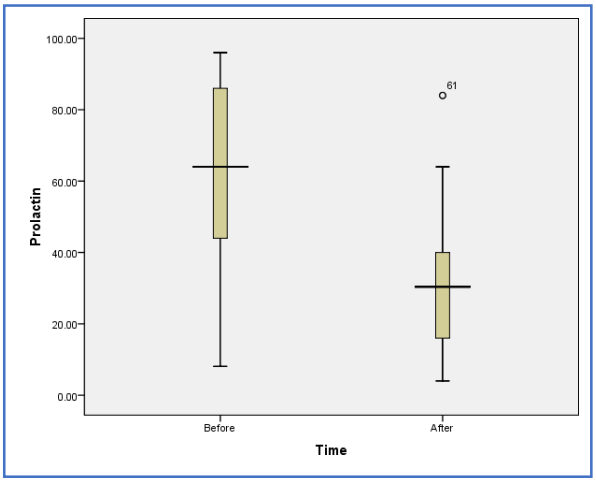

Figure 1: Prolactin level (median and interquartile range) before and after treatment

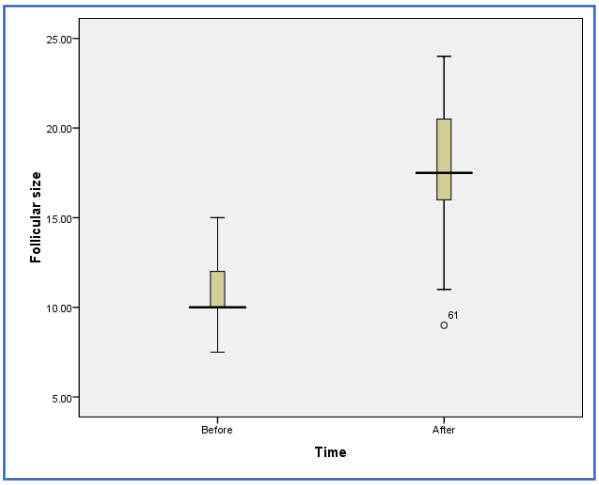

Figure 2: Follicle size (Median and interquartile range) before and after treatment

DISCUSSION

The present study showed that pergolin was significantly able to reduce the serum level of prolactin in subfertile women in addition to the finding that ovarian follicle size was significantly increased with the different rate of response to pergoline. We believe that pergolin, as dopamine agonist drug resulted in inhibition of the high baseline prolactin secretion in subfertile women enrolled in the present study. This action is supposed to happen by the action of pergolin on D-2 receptors present on the cell membrane of lactotrophs in the anterior pituitary gland.

The dopamine receptors in the pituitary gland are associated with G proteins coupled receptor (Cronin et al., 1983). Two intracellular messengers in pituitary cells, Ca^{2+}, and cAMP have major effects in regulating secretory vesicles fusion with the plasma membrane to liberate hormones (Gregerson, 2006). Electrophysiological studies showed that spontaneous fluctuations of calcium concentration are action potential-dependent and these are responsible for the high basal prolactin production (Rankin et al., 2009). When extracellular Ca^{2+} is removed, the spontaneous firing of action potentials is abolished resulting in reduced basal prolactin release to a concentration that is nearly similar to that when dopamine agonists are applied (Lledo et al., 1992; Rankin et al., 2009). In normal pituitary cells, application of dopamine also inhibits adenylyl cyclase (AC) activity(Gonzalez-Iglesias et al., 2006; Martin, 2003), which may have a role in prolactin release inhibition (Martin, 2003; Van Goor et al., 2001). This effect could be attributed to the actions of cAMP and its kinase on the exocytotic events (Munoz, 1988) and/or abolishing of Ca^{2+} signaling route (Obadiah et al., 1999).

CONCLUSION

We believe that the use of pergoline in the present study caused reduction in the level of basal prolactine secretion through its action as a dopamine agonist by the mechanism that has just explained and by this way the reduction of prolactine resulted in the release of inhibition submitted by prolactine of gonadotrophine leading to improvement in ovulation and ovarian follicle size but as this response differs from woman to other, thus the dose of pergoline should be adjusted individually, in which every woman have its required dose and course of treatment because many of this woman achieved normal follicular size after one month ultrasound examination. This may improve fertility in women who are subfertile and have asymptomatic hyperprolactinemia.

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