Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 1476 - 1486
Received 05 March 2021; Accepted 01 April 2021.

# Effectiveness of Cabergoline in prevention of Ovarian hyperstimulation syndrome in hyperprolactinaemic patients with polycystic ovary syndrome

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## ABSTRACT

polycystic ovary syndrome (PCOS) associated with abnormal secretion of gonadotrophin, (high concentration of LH serum, depressed FSH level, also an LH/FSH ratio≥2).Hyperprolactinaemia is generally PCOS-associated (about 30 percent of female).Viewed also in both normal and stimulated cycles,throughout the late phases of follicular and luteal. It is proposed that both prolactin (PRL) and LH may be increased bya drop in the inhibitory dopamine effect.The aim of the study is to evaluate the effect of cabergoline on fertility parameters in females with controlled ovarian stimulation of PCOS. Patients and method: Ovarian stimulation was compared between two groups of females with hyperprolactinaemic-PCOS; cabergoline was given to the first group, decreasing plasma PRL concentrations that typically seen with the induction of ovulation. This paper found out a decreased total number of FSH recombinants ($P<0.04$) was observed, ampoulesin the untreated group of hyperprolactinaemiPCOS. Fewer days for HCG administration to meet ($P < 0.044$), A significantly higher peak plasma concentration of oestrogen ($P < 0.03$) in comparison with the group that were treated. This group demonstrated substantially greater ovarian volume and improved total follicle numbers of all sizes by ultrasound inspection.Due to a mild syndrome of ovarian hyperstimulation that occurred during induction of ovulation, five cycles of 58 were cancelled regarding untreated hyperPRL-PCOS females. two out of 42 cycles was cancelled in patients treated with cabergoline. No major variations were found in the pregnancy rate or multiple pregnancies.In generalthe data indicate dopaminergic regulation of release of LH and encourage cabergoline usage in these patients' treatment, To maintain better monitoring of the response of the ovaries and, therefore, To reduce the OHSS, without reducingpregnancy chances

**Keywords:** hyperprolactinaemic (PCOS), hyperprolactinaemic polycystic ovary syndrome**,** Cabergoline, ovarian stimulation

## INTRODUCTION

PCOS, or Stein-Leventhal syndrome (Evans &Riley, 1958), or hyperandrogenic anovulation (HA), among the most popular disorders of the endocrine system affecting femalesduring age of reproduction (Azziz, 2004). It is a condition described by Stein and Leventhal in 1935, in which an average of 10 small cysts with a diameter ranging from 2 to 9 mm grow on either or both ovaries and/or the volume of ovaries exceeds 10 ml in at least one ovary (Balen & Rajkowha, 2003).According to diagnostic criteria from the National Institutes of Health,systematic screening of womenPCOSS is believed to affect 4-10% of females. (Azziz e , 2004). Recent research indicates that PCOS is a chronic condition, manifesting from prenatal age, although it was historically regarded as a disease of adult women. Actually, Under the Rotterdam Diagnostic Guidelines, In teenagers, the prevalence of PCOS ranges from At least 3 percent (Hashemipour, 2004) Up to a 26

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percent max(Driscoll, 2003). However, in young ages, the prevalence of the disease is still considered uncertain (Kamangar , 2015).
PCOS'seffect on the economy. In the United States, around $4 billion is spent annually on screeningthe illnessand treating its multiple morbidity, like morbidity infertility,diabetes mellitus and hirsutism. In order to pay for the condition, More than $800 million a year are spending by the Australian Health System. For this condition, More than $800 million in expensesannually by the Australian Health System (Azziz , 2005). In contrast to patients without it, females with PCOS are twice as likely to be hospitalized. (Hart & Doherty, 2015). Accurate and early identification of PCOS is therefore required not only to avoid potential comorbidities in health, but also to decrease financial costs and burdens (Kamangar, 2015).

## Pathophysiology of PCOS

### Previous hypotheses

Several theories have arisen to describe the pathophysiology of PCOS. At first, it was assumed that excess intrauterine androgen was a primary culprit in the disease 's growth. However, medical studies have recently shown neither a Correlation between excessive exposure to Prenatal androgen and the development of PCOS Youth(Hickey, 2009). Nor is there an increase in cord blood androgen levels in femaleborn tomothers with PCOS (Anderson, 2010).“The expandability theory of adipose tissue, another hypothesis, found that infants with intra-uterine growth restriction (IUGR) and spontaneous catch-up growth can develop decreased expandability of tissue, meaning they do not store lipids in their fat tissues properly.Insulin resistance can, therefore, cause PCOS and hyperandrogenemia”. (2009 by de Zegher). This does not extend to patients with PCOS, however. Those that do not have IUGR but do not have random catch-up growth (Ibáñez, 1998, 2009).

### A multifaceted disease

“The best explanation of PCOS pathophysiology deals with it as a multi-faceted disease involving unregulated ovarian steroidogenesis, aberrant insulin signaling, severe oxidative stress, and hyperandrogenemia in patients with PCOS can be partly explained by an intrinsic defect of theca cells.In the absence of trophic factors, women with PCOS have theca cells, which often secrete elevated levels of androgens due to intrinsic stimulation of steroidogenesis” (Nelson, 1999). In contrast to healthy controls, this intrinsic dysregulation often affects granulosa cells that produce up to 4 times higher levels of anti-mulleric hormone in females with PCOS (Azziz , 2009; Pellatt, 2007; 2009; Villarroel, 2011). In females with PCOSStudies also suggest a highfollicles number. The preantralalso limited antral follicles, usually (Webber, 2003). In certain maturing follicles, a defect in apoptotic processes further raises their count in females with PCOS (Das, 2008).Reduced insulin sensitivity has been established as an intrinsic portion of PCOS, independent of obesity, because of a post receptor binding defect in the insulin signaling pathways (Dunaif, 1997).An alteration in gene expression through microarray gene analysis of some actors in insulin signaling pathways was also reported (Cortón , 2007, 2008). Furthermore, Increased glycooxidative stress associated with PCOS (González e, 2006),Secondary to failure of mitochondria (Victor, 2009). In patients with PCOS, oxidative stress itself may cause insulin resistance and hyperandrogenism(Victor et al . , 2009).
PCOS genomic identification-susceptibility loci (Chen, 2011) and PCOS family aggregation (Azziz, 2004,2011) Support for the role of genetics in this disease's etiology. In patients with PCOS, a few reports revealed an inherited portion of androgen excess (Yildiz, Legro, 1998; 2006; Escobar-Morreale, 2005). In addition, a PCOS-associated polymorphic marker in the fibrillin 3 gene, D19S884, has been identified in various sets of families carrying the disease (Urbanek, 2007; Segars &Decherney, 2010).

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 1476 - 1486
Received 05 March 2021; Accepted 01 April 2021.

**Infertility**

"PCOS may have reduced fertility in females (Hart & Norman, 2006; Hart & Doherty, 2015). Due to the related endocrine and gynecological disorders that affect ovarian function and performance" (Hart and Norman, 2006). ). Up to 90% of ovulatory diseases (Hull, 1987) are correlated positively with infertility by PCOS-associated recurrent anovulation cycles (Imani, 1998). In 1995, in a PCOS population with primary and secondary infertility, up to 50 and 25 per cent of women were identified in a study (Balen, 1995). In 2015, a study by Hart and Doherty found that infertility is 10 times more prevalent in women with PCOS compared to healthy controls (Hart & Doherty, 2015).

On the other hand, some results have shown that femaleswith PCOS who conceive may have complications related to pregnancy, like gestational diabetes (Bruyneel, 2014) pregnancy-related hypertension (Hu, 2007;Sir-Petermann., 2012; Bruyneel, 2014), and preeclampsia (Katulski, 2015) to a greater degree compared to matched controls. Different study results also mentioned an increase of miscarriage in PCOS females (Balen, 1993; Homburg, 1993; Wang, 2001; Winter, 2002).

The PCOS phenotype, classical or not, on womenfertility isnot totallyunderstood. Based on small studies documenting the impact of PCOS on pregnancy outcomes, there is also minimal evidence. Detailed studies are necessary in order to estimate the level of infertility in different PCOS phenotypes and to know the reasons for this group of women's increased negative pregnancy outcomes.

With regard to the effect on the fetus, relative to healthy women, Women with PCOS are 2.5 times more likely to give birth to little children of gestational age than healthy women (Katulski, 2015) and offspring display an increased morbidity and mortality relative to control (Fauser, 2012).

**Hyperprolactinemia and controlled ovarian stimulation in PCOS**

An endocrine disorder most often associated with anovulation of unknown etiology is polycystic ovary syndrome (PCOS). With a well-known ovarian ultrasound pattern, the syndrome classification is based on both clinical and endocrine characteristics. Chronic anovulation, obesity, hirsutism, and hyperandrogenaemia of oligomenorrhoea are variably associated with irregular secretion of gonadotrophin, elevated serum LH concentration, depressed FSH, and? 2 (Erickson, 1992 ; Adams,1986; Jacobs, 1996; Doldi, 1999).

30 percent of PCOS patients have moderate hyperprolactinaemia. (Duignam, 1976; Isik, 1997; Falaschi , 1977; Isik, 1997; Coremblum &Taylor, 1982).

In addition, A temporary increase in plasma prolactin (PRL) concentrations in both normal and stimulated cycles can be observed during the late follicular and luteal phases (Doldi, 2000). Hypothalamic dopamine is known to be the primary PRL secretion inhibitor in humans. (Webster, 1999), and central dopaminergic pathways can play a possible, albeit controversial role in the release of LH. (Falaschi, 1986; Prelevic, 1987). Separate investigators dopaminergic control on the secretion of gonadotrophin was also indicated and suggested that, in females with hyperPRL-PCOS, a decrease in the inhibitory effect of dopamine may cause abnormal release of PRL and LH. A few studies have examined the impact of treatment with dopamine agonists on ovarian response in patients with polycystic ovarian alterations and moderate, elevated serum PRL levels.

"In view of the significance of dopaminergic regulation in PCOS, we retrospectively examined the clinical effect of cabergoline, Effective dopamine agonist and PRL secretion inhibitor, ovarian reaction (ovarian size, number of follicles developed), peak estradiol in HCG administration in such patients during recombinant FSH (rFSH) stimulation protocols"...

## METHODS

At our Reproductive Endocrinology Clinic, 50 couples undergoing medical assisted procreation (PMA) attempts were enrolled in the study. Female patients underwent hysterosalpingography, and laparoscopy and hysteroscopy were performed on some of them as well. According to World Health Organization (WHO) requirements, all of the male partners had normal semen consistency (World

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Health Organization, 1992). In the past two years, every couple has struggled to conceive. At least three cycles of clomiphene citrate, with no further infertility therapy, were given.
For the diagnosis of PCOS, all women met our requirements: a history of anovulatory infertility and/or oligomenorrhea or amenorrhea, a Ferriman-Gallwey score >7 for hirsutism, hyperandrogenemia, elevated LH, Increased Volume of the Ovarian, and 10 follicles with a 2-8 mm diameter ultrasound test. All had medium, elevated serum concentrations of PRL (mean 31.5 ± 3.1 ng/ml).
Measured prior to ovarian stimulation in the middle and/or late follicle process and mid luteal phase of the menstrual cycle. Elevated PRL levels are not responsible for any organic lesions (serum PRL levels > 50 ng / ml) or treatment.
Previous ovarian stimulation (Group A: mean PRL concentration = 32.8 ± 3.6 ng/ml) to a decrease in plasma PRL concentrations (12.5 ± 2.8 ng/ml) was treated in 21 patients with cabergoline (Dostinex®, 0.5 mg, half tablet per week). During the lengthy treatment for ovarian stimulation, therapy was continued.
Without medication for hyperprolactinemia, 29 patients (group B: mean PRL concentration = 31,1 ± 3,2 ng/ml) completed an ovarian stimulation program.

**Stimulationprotocol**
Prolong protocol was done for all women. This consisted of an s.c. of 0.1 mg/day Gonadotropin-releasing hormone (GnRH) agonist (Triptorelin, Decapeptyl ®, IPSEN) doses administered on day 21 following withdrawal bleeding or spontaneous menstruation caused by progestin.

"The oestradiol serum concentration was measured during the next menstrual cycle and ultrasound scanning of the ovaries was performed. Gonadotrophin therapy was initiated if oestradiol plasma concentration was < 60 pg / ml and no follicles or cysts were > 10 mm in diameter. If ovarian quiescence was not reached, a further test 1 week later was carried out.The stimulation of gonadotrophin for the first five to seven days consisted of one FSH ampoule per day" (rFSH, Gonal-F 75 UI®, Serono, Rome, Italy).The dose adjustment (rFSH increases by 37.5-75 UI) was focused on the person response. With 5000 UI of human chorionic gonadotrophin, final maturation of the oocyte was achieved. (HCG, Profasi®, Serono, Rome, Italy) when there are at least 2 >16 mm follicles. After HCG administration, intrauterine insemination was conducted between 32-36 H.

**Statistical analysis**
The figures are classified as the mean ± standard deviation. Using variance and the t-test of the two-tailed study, variations in mean values were analyzed for individual hormone measurements.

## RESULTS

In both groups of patients, as shown in Table I. No major variations in age, androstenedione values, FSH and LH concentrations or testosterone were observed. Until GnRH analogue/rFSH treatment, the two groups displayed similar elevated serum PRL levels. PRL values in group A (11.9 ± 2.7 ng/ml) after cabergoline therapy were within the normal range. (A group: 42 cycles, mean = 2.33 per patient; B group: 58 cycles, mean = 2.50 per patient) Study of 100 ovulatory GnRH analog/rFSH/HCG cycles. The total number of rFSH ampoules per cycle was marginally lower in group B (without treatment with cabergoline) ($P < 0.05$) (Table II).
With fewer stimulation days prior to administration of HCG ($P < 0.05$), estradiol and peak serum concentrations were much higher at $P < 0.05$ compared to group A (treatment with cabergoline). On the day of HCG administration, progesterone serum concentrations were not significantly different between the two groups. In addition, through ultrasound tests, hyper PRL-PCOS patients developed

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Received 05 March 2021; Accepted 01 April 2021.

more follicles of all sizes (<10 mm: 4.4 ± 0.9 versus 4.7 ± 1.2; 10-15 mm: 5.7 ± 1.8 versus 7.6 ± 1.6; >15 mm: 4.6 ± 0.7 versus 5.3 ± 1.1) compared with treated hyperPRL- patients with PCOS on the day of HCG administration. Those differences ($P < 0.05$; $P < 0.05$; $P < 0.05$) were statistically significant.

Moderate ovarian hyperstimulation syndrome (OHSS) in group B produced 5 cycles out of 58 (8.6) percent compared to two cycles out of 42 (2.7 percent) in group A, the seven cycles were cancelled. Compared to 11 pregnancies in group B (five multiple pregnancies), there were a total of eight pregnancies in group A (three multiple pregnancies).

**Table 1:** Hyperprolactinemic femaleswith PCOS with clinical and hormonal data

| **Characteristics** | **Group A** | **Group B** | ***P*** |
|---|---|---|---|
| Number of females | 21 | 29 | - |
| Age (years) | 31.7 ± 3.4 | 32.7 ± 2.4 | NS |
| Body mass index | 22.8 ± 2.8 | 22.7 ± 2.3 | NS |
| FSH concentration (mUI/ml) | 6.1 ± 2.7 | 5.8 ± 2.2 | NS |
| LH concentration (mUI/ml) | 8.9 ± 1.7 | 8.8 ± 0.7 | NS |
| Testosterone concentration (nmol/l) | 5.1 ± 1.8 | 5.2 ± 0.3 | NS |
| Androstenedione concentration (nmol/l) | 12.3 ± 1.6 | 12.8 ± 2.7 | NS |
| PRL concentration (ng/ml) | 35.1 ± 2.5 | 33.3 ± 2.3 | NS |
| PRL conc. (ng/ml) after-treatment | 11.9 ± 2.7 | - | - |

Standard deviation±Values are mean
A Group with treatment
B group without treatment
PRL=prolactin
NS = not significant.

Table 2: Ovarian response features for both treated and untreated females with rFSH/HCG receiving theStimulation of the ovaries program.

| **Characteristics** | **Group A** | **Group B** | ***P*** |
|---|---|---|---|
| Number of females | 21 | 29 | - |
| Number of cycles | 42 | 58 | - |
| Number of FSH ampoules | 21.7± 7.8 | 15.1 ± 5.6 | S |
| HCG administration day | 11.3±3.6 | 11.3±2.2 | S |
| Concentration of Oestradiol (pg/ml) at HCGG | 1134±665 | 1438±641 | S |
| Progesterone (pg/ml) concentration in HCGG | 1.1 ±0.4 | 1.1 ±0.5 | NS |
| Total <10 mm follicles | 4.4±0.9 | 4.7± 1.2 | S |
| follicles number 10-15mm | 5.7±1.8 | 7.6± 1.6 | S |

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| | | | |
|---|---|---|---|
| follicles number>15mm | 4.6±0.7 | 5.3 ± 1.1 | S |
| OHSS. | 2 | 5 | - |
| Pregnancy cumulative | 8 | 11 | NS |
| Pregnancy multiples | 2 | 4 | - |

Valuesmeans±standard deviation
S meanssignificant
NS means not significant
OHSS means ovarian hyperstimulation syndrome

## DISCUSSION

The concept that moderate, temporaryPCOS and hyperprolactinaemia are not distinctive entities has been endorsed by several investigators (Falaschi, 1977; Coremblum and Taylor, 1982; Prelevic, 1987; Isik , 1997). In patients with PCOS, A moderatedeficit of dopamine may result in a boost in both PRL and LH,The inhibitory impact of hypothalamic dopamine and dopamine agonists on PRL is well established..

For six years anew Long-acting Cabergoline analog of the ergoline agonist D2in usage, has been.Cabergoline seems to be well tolerated and have a comparable Efficacy in the reduction of PRL and gonadal function restoration compared with other dopamine agonists. (Paoletti , 1994; Ciccarelli, 1997; Webster, 1999). In additionNo increase in rates of miscarriages, congenital birth defects, birthweight,the distribution of sex ratios within the predicted range was observed (Robert, 1996). Clinical data on the effect of dopamine on the release of gonadotrophin, especially LH, also are controversial.

Even if it is not clear about the mechanism(Klibanski, 1984; Falaschi , 1986; Chapman, 1987; Matsuzaki, 1994; Paoletti, 1996) Dopamine and its agonists have shown an inhibitory role in the secretionofLH and androgen levels innormal and hyperprolactinemic females. Dopamine agonists have been suggested as a beneficial in the management of PCOSS, based on their ability to reduce LH secretion (Falaschi, 1986; Isik, 1997).

The goal of our research was to assess.The clinical effects of cabergoline on stimulation of the ovaries in females with PCOS,Moderately elevated serum PRL that involved in an ovulation induction program.Moderate dopamine agonist cabergoline-treatedhyperprolactinemic,PCOS (group A) patients were compared with untreated hyperPRL-PCOS (group B) females during rFSH/HCG administration.

We noticed that:

Peak oestrogen plasma was much higher in untreated patients with hyperPRL-PCOS, with a reduced total amount of rFSH ampoules and less days of HCG administration.

A slightly higher volume of ovaries and an extended total number of follicles of all sizes were recorded in Group B by ultrasound.These results were in agreement with ( Enreco papaleo et al, 2001).

group B suspension of therapy in 5 cases due to ovarian hyperstimulation syndrome in comparison with twofemales in group A.

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Received 05 March 2021; Accepted 01 April 2021.

There were no major variations in either the overall pregnancy rate or the rate of multiple pregnancies.This is due to cabergoline inhibits VEGFR2 phosphorylation and signalling, thus reduced the incidence of OHSS and cycle cancelling without adverse effect on pregnancy and this is in agreement with Ata B, Seyhan A, et al, 2009.

Our data support the evidence of a dopaminergic component in regulating the release of LH in PCOS patients and indicate that pretreatment with cabergoline reduces the ovarian response to rFSH without affecting pregnancy rates or increasing the risk of multiple pregnancies. While these results are not statistically significant, in order to limit the risk of OHSS as a potentially important alternative in the clinical management of such patients, this approach should be explored further.



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Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 1476 - 1486
Received 05 March 2021; Accepted 01 April 2021.

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