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Hyperprolactinemia and Pregnancy Outcome in Females Undergoing *In vivo* Fertilization or Intracytoplasmic Sperm Injection: A Prospective Cohort Study

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Authors' contributions

This work was carried out in collaboration among all authors. Author ANS contributed to the conceptualization, methodology, formal analysis, investigation, resources, data curation, original draft writing, review and editing, visualization, supervision, project administration, and funding acquisition. Author HRE was involved in the methodology, validation, formal analysis, investigation, resources, data curation, original draft writing, and review and editing. Author MFA contributed to software, formal analysis, investigation, data curation, original draft writing, review and editing, visualization, and validation. Author RMEN participated in the conceptualization, methodology, validation, formal analysis, review and editing, supervision, and project administration. All authors contributed to the conceptualization, refinement of the study, analysis, and manuscript preparation. They actively participated in the cases included in this study, reviewed the final manuscript, and approved it for publication.

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Original Research Article

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ABSTRACT

Background: Since slight rises in prolactin levels are thought to interrupt ovulation and consequently impair fertility, it is unclear whether mild hyperprolactinemia should be treated before commencing IVF (*In Vivo* Fertilization) or ICSI (Intracytoplasmic Sperm Injection) cycles. The goal of this study was to explore cumulative pregnancy results of IVF/ICSI treatments for infertility caused by tubal or male factors in persons with normal baseline prolactin levels to those with minor elevations, especially values less than 50 ng/ml.
Methods: The Comparative Observational Prospective Cohort research comprised 260 women who had IVF/ICSI due to anovulatory causes. Participants were separated into two groups: Group A had normal baseline prolactin levels (less than 25 ng/ml), while Group B had slightly increased basal prolactin levels (25-50 ng/ml). The study looked at cumulative pregnancy outcomes such the number of oocytes harvested, mature oocytes, and the quantity and quality of embryos.
Results: The study revealed that the rates of clinical pregnancy were significantly higher in women with mildly high prolactin levels compared to those with normal levels. In addition, the group with modestly increased prolactin had more M2 oocytes and embryos. Prolactin levels did not correlate with the number of recovered oocytes, M2 oocytes, or embryos.
Conclusion: In women undergoing IVF/ICSI, somewhat raised blood prolactin levels were associated with higher clinical conception rates, overall live birth rates, and more M2 oocytes and embryos.

Keywords: Cumulative outcomes of pregnancy; disruption of ovulation patterns; intracytoplasmic sperm injection; serum prolactin levels.

1. INTRODUCTION

Prolactin (PRL), an anterior pituitary gland hormone, is required for reproductive function [1]. It is well known for its role in nursing, regulated by dopamine signaling pathways [2]. Hyperprolactinemia, or exceptionally elevated prolactin levels, may interfere with endometrial receptivity, impede corpus luteum function, impact the growth of embryos, and impair the processes of reproduction by preventing gonadotropin-releasing hormone, or GnRH, production, causing hypogonadotropic hypogonadism [3]. Dopamine agonists are commonly used to treat hyperprolactinemia in infertile women, while their effectiveness in IVF cycles is debatable [4]. Although hyperprolactinemia is typically associated with infertility, growing data suggests that prolactin is involved in a variety of reproductive processes [5]. Elevated prolactin levels in follicular fluid have been linked to improved oocyte quality and outcomes such as corpus luteum development, endometrial receptivity, and blastocyst implantation [4]. Transient hyperprolactinemia has been observed during IVF cycles, with inconsistent results regarding its influence on outcomes; nonetheless, some studies suggest possible advantages for fertility and conception rates [5,6]. Measuring prolactin levels before starting IVF or ICSI treatment is crucial for identifying and addressing potential hormonal imbalances that may affect reproductive outcomes [4,5]. This manuscript emphasizes the impact of hyperprolactinemia on IVF and pregnancy outcomes, offering valuable insights to improve the success of assisted reproductive techniques. These findings can help guide clinicians in tailoring treatments to individual patients, thereby enhancing the likelihood of achieving live births. This study sought to explore variations in blood prolactin levels after ICSI and their impact on clinical pregnancy rates.

2. MATERIALS AND METHODS

From April 2023 to April 2024, an observational, prospective cohort study was conducted on all women who had IVF/ICSI treatment for tubal or male infertility using the gonadotropin-secreting hormone agonist (GnRHa) long protocol. These

patients were selected from the reproductive health clinic at Kafr El-Sheikh University Hospital. The study adhered to the ethical standards specified in the Declaration of Helsinki. It was authorized by the Scientific and Ethics Committee of Kafr El-Sheikh University's OBGYN department on March 25, 2023, under protocol number [KFSIRB200-87]. A total of 260 women between the ages of 20 and 45 with infertility caused by anovulatory causes (excluding PCOS and hyperandrogenism), tubal factors, or male factors and basal serum prolactin levels less than 50 ng/ml were included. The participants were divided into two groups: Group A (130 women with normal basal prolactin levels less than 25 ng) and Group B (130 women with slightly increased basal prolactin levels between 25 and 50 ng). Women aged 20 to 45 years with primary or secondary infertility caused by anovulation (excluding PCOS or hyperandrogenism), tubal factors, or male factors who were having ICSI and had basal prolactin levels that were normal or moderately increased below 50 ng/ml were eligible. Exclusion criteria included hyperprolactinemia, uterine malformations, many unsuccessful ICSI efforts, embryo transfer beyond day 3, frozen-thawed cycles, and pregnancy contraindications such as uncontrolled medical disorders (diabetes, heart disease, hypertension, or ovarian tumors). Patients who were taking prolactin-lowering drugs (e.g., antipsychotics, risperidone), had thyroid dysfunction, or had medical disorders that affected blood prolactin levels (e.g., acromegaly, chronic renal failure) were also excluded. The ICSI cycles began in the Kafr El-Sheikh assisted reproduction unit. All patients provided written informed consent before blood samples were collected. The spouses' tests included follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), prolactin, and semen analysis. Serum prolactin levels were tested four times, beginning with a baseline measurement on the second day of the menstrual cycle, prior to GnRHa-induced pituitary downregulation. All oocyte pick-ups (OPUs) and embryo transfers (ETs) were set for 9:00 a.m., following an eight-hour fast. Blood samples were immediately submitted to Kafr El-Sheikh University Hospital's central laboratory for immunoassay analysis with the ADVIA Centaur Immunoassay System (CP Immunoassay System®, SIEMENS AG, Munich, Germany). All patients followed the typical long GnRH agonist regimen, beginning on the 21st day of the cycle (mid-luteal phase) with 0.1 mg of Triptorelin administered subcutaneously (Decapeptyl ®FERRING PHARMACEUTICALS, Switzerland). Folliculometry was carried out until mature ova (18 to 22 mm) were detected, at which point 10,000 IU of recombinant human chorionic gonadotropin (HCG; Choriomon, American Remedies Healthcare Pvt. Ltd.) was injected intramuscularly to stimulate final oocyte maturation. Gonadotropins in the form of highly purified human follicle-stimulating hormone (UroFollitropin) (FOSTIMON®, IBSA, Institute Biochimique SA, Lugano, Switzerland) were administered intramuscularly beginning on the second day of menstruation, with doses adjusted according to the patient's age, basal FSH level, antral follicular count (AFC), and body mass index (BMI). Stimulation was monitored by transvaginal ultrasonography and serial E2 measures beginning on the seventh day of the cycle, with individual HMG dosage modifications depending on follicular response. When three or more follicles ≥18 mm formed, 10,000 units of HCG (Choriomon, American Remedies Healthcare Pvt. Ltd.) were given intramuscularly. Oocytes were extracted using ultrasound-guided transvaginal aspiration around 36 hours following the HCG trigger. ICSI was performed in accordance with [7]. Embryo growth was monitored daily using a standardized scoring method until the transfer of cleavage stage embryos (Day 3). The remaining embryos were grown to blastocysts (days 5 or 6) for vitrification. Frozen-thawed embryo transfers were possible in both artificial and natural cycles. Luteal support was administered with daily intramuscular injections of 100 mg progesterone (Prontogest ® IBSA, Institute Biochimique SA, Lugano, Switzerland) beginning on the day of ET and continuing for 16 days. Pregnancy was verified using β-HCG > 10 IU on day 11 post-ET, followed by a second, higher value 48 hours later, and ultrasound at 7 weeks gestation to confirm fetal pole and heart activity. Clinical pregnancy was defined as an intrauterine pregnancy in which at least one baby had a heartbeat at 6 weeks gestation. The cumulative outcome, known as the clinical pregnancy rate (CPR), included healthy intrauterine pregnancies at 6 weeks' gestation after transferring all embryos from the examined stimulation cycle. Secondary outcomes were the number of retrieved oocytes, mature oocytes, embryos, embryos transplanted, and total live birth rate. The cumulative pregnancy outcomes for women with baseline prolactin levels < 25 ng were compared to those with levels between 25 and 50 ng who were not given dopaminergic medications.

Sample size: The calculation for the sample size was based on clinical pregnancy rates. According to previous research [8], the pregnancy rate was 25% for women with serum prolactin levels below 30 ng/ml, and 42.7% for women with serum prolactin levels between 30 and 60 ng/ml. Based on these figures, it was determined that a minimum of 112 participants per group would be required to achieve an 80% power to reject the null hypothesis at a significance level of α = 0.05, using a t-test for independent samples. Allowing for a 15% dropout rate, the final sample size was set at 130 participants per group. This calculation was performed using MedCalc® Statistical Software version 19.5.3 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020).

Statistical analysis: Numerical data following a normal distribution were described using mean ± standard deviation (± SD), while non-normally distributed data were summarized as median and range or interquartile range (IQR). Categorical data were expressed as frequencies and percentages. The Kolmogorov-Smirnov test was employed to assess the normality of numerical data. Comparisons between groups for normally distributed numerical variables were made using the Student's t-test for independent samples, whereas the Mann-Whitney U test was used for non-normally distributed data. For categorical data, the Chi-square ($\chi 2$) test was used, and the exact test was applied when the expected frequency was below 5. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and IBM SPSS Statistics version 22 for Windows (IBM Corp, Armonk, NY, USA).

3. RESULTS

A total of 260 women were split into two groups of 130 each: those with PRL less than 25 ng/mL and those with PRL greater than 25 ng/mL.

Table 1 shows that there were no significant variations in demographic factors such as age, BMI, length of infertility, or type of infertility across the groups.

Table 1. Demographic characteristic between both groups

Variable	Group A PRL <25 N=130	Group B PRL >25 N=130	95% CI	P value
Age (years)	31.46±4.62	31.49±4.88	-1.13 to 1.19	.958
BMI (kg/m2)	27.92±3.16	28.26±3.08	-0.42 to 1.1	.384
Duration of infertility (years)	52.41±25.2	53.22±26.13	-5.45 to 7.0	.799
type of infertility				
• Primary	66 (50.77%)	62 (47.70%)	-	.709
• Secondary	64 (49.23%)	68 (52.30%)		

[1,2, and 3] Values (continuous quantitative data) are given as the means±SDs, [4] values (categorical) are given as numbers (percentages). The Kolmogorov–Smirnov test was used to analyze the normality of the data distribution characteristics namely, age, BMI, and duration of infertility, or all the study patients.

** T test was used for normally distributed continuous quantitative data.*

#Fisher exact test was used for qualitative (categorical) data

A P value <0.05 was considered to indicate statistical significance, so the P value of the study group was not significant.

Table 2. Hormonal profile on D2

Variable	Group A PRL <25 N=130	Group B PRL >25 N=130	95% CI	P value
FSH (IU/L)	6.54±1.45	6.42±1.52	-0.24 to 0.48	.50
LH (IU/L)	4.18±1.48	3.99±1.36	-0.15 to 0.53	.26
E2 (pg/mL)	49.63±14.85	51.87±15.49	-1.46 to 5.94	.23
TSH (mIU/L)	3.17±1.11	3.08±1.12	-0.18 to 0.36	.51
AMH (ng/ml)	2.31±1.06	2.15±1.16	-0.11 to 0.43	.27
Basal PRL level (ng/ml)	10.65±5.85	33.75±4.66	21.80 to 24.39	< .01
AFC (follicles)	13.03±4.78	14.08±5.65	-0.22 to 2.32	.10

[1,2,3,4,5,6, and 7] Values (continuous quantitative data) are presented as the means±SDs. The Kolmogorov–Smirnov test was used to evaluate the normality of the data distribution in all the study patients.

** T test was used for normally distributed continuous quantitative data.*

A P value <0.05 considered to indicate statistical significance, so the P value of the study group was not significant.

Table 3. ART and COH outcomes

Variable	Group A PRL <25 N=130	Group B PRL >25 N=130	95% CI	P value
Gonadotropins dose (IU)	275.77±62.10	273.46±57.46	-12.3 to 16.92	.75
Number of oocytes retrieved in OPU	10.43±4.24	11.88±5.33	0.27 to 2.62	.01
Number of M II oocytes	6.58±3.52	8.23±4.49	0.66 to 2.63	.001
Number of embryos	4.18±2.93	6.45±3.98	1.41 to 3.12	<.001
Number of women				
Yes	118 (90.7%)	127 (97.7%)	RR=4	.03
No	12 (9.3%)	3 (2.3%)		
Fertilization rate (%)	61.60±11.90	66.92±11.77	2.43 to 8.21	.0003
Number of embryos transferred	1.98±0.94	2.53±1.01	0.31 to 0.78	.0001
Cumulative pregnancy rate	70 (53.85%)	89 (68.46%)	1.46	.02
Cumulative birth rate	43 (33%)	85 (65.4%)	1.93	<.001

[1,2,3,4,6, and 7] Values (continuous quantitative data) are given as the means±SDs, [5,8,and 9] values (categorical) are given as numbers (percentages). The Kolmogorov–Smirnov test was used to analyze the normality of the data distribution characteristics of all the study patients.

** T test was used for normally distributed continuous quantitative data.*

#Fisher exact test was used for qualitative (categorical) data

A P value <0.05 was considered to indicate statistical significance.

Table 4. Correlation between prolactin and different parameters in group A and B

Variable	Group A PRL <25. N=130	Group B PRL >25 N=130
Number of oocytes retrieved in OPU	R = 0.0309 P value = .727	R = 0.018 P value = .847
Number of metaphase II oocytes	R = 0.0812 P value = .359	R = -0.007 P value = .936
Embryo	R = 0.0896. P value = .310	R = 0.002 P value = .981
Number of embryos transferred	R= -0.0567 P value = .526	R = -0.0835 P value = .347

Across both groups (PRL < 25 and PRL > 25), there appears to be no statistically significant correlation between prolactin levels and the number of oocytes retrieved in OPU, the number of metaphase II oocytes, the number of embryos, or the number of embryos transferred. All the p-values are well above the commonly accepted threshold for statistical significance (0.05), and the correlation coefficients are all very low, indicating weak or no relationships between prolactin levels and these parameters

Table 2 shows that the hormonal profiles and antral follicle count (AFC), which include FSH, LH, E2, TSH, prolactin, AMH, and AFC, were similar between the groups.

Table 3 reveals that, with the exception of gonadotropin dosages, there were substantial variations in ART and controlled ovarian hyperstimulation (COH) results.

Table 4 shows that there was no significant correlation between prolactin levels and the number of oocytes recovered, metaphase II oocytes, embryos, or embryos transplanted in either group.

4. DISCUSSION

A substantial body of research highlights the multifaceted role of prolactin in various physiological functions, including reproduction, growth, metabolism, electrolyte transport, behavior, immunity, and cancer development [9]. While prolactin is well-recognized for its role in lactation, it is also implicated in reproduction, contributing to oocyte development [10], corpus luteum formation and maintenance, implantation, steroid production, and immune modulation [4]. Maintaining appropriate prolactin levels is considered essential for optimal reproductive outcomes, with fluctuations during the menstrual cycle further underscoring its role in reproduction. Transient hyperprolactinemia is prevalent during controlled ovarian stimulation (COS) for assisted reproductive technology, but its impact on fertility outcomes is unknown [11]. The purpose of this study was to look at how moderately increased prolactin levels (25-50 ng/ml) affected clinical pregnancy rates as well

as the quality and quantity of retrieved oocytes, mature oocytes, and embryos. We studied 260 infertile women having IVF/ICSI therapy due to anovulatory causes. Participants were separated into two groups: Group A (130 women with baseline prolactin levels < 25 ng/ml, 12 excluded owing to fertilization failure) and Group B (130 women with basal prolactin levels between 25-50 ng/ml, 3 eliminated for the same reason). Kamel et al. [11] and others previously reported transitory hyperprolactinemia after ovum extraction, peaking at 93.2 ng/ml and returning to normal before embryo transfer [11,12]. Our data revealed that clinical pregnancy rates were considerably higher in women with modestly raised prolactin levels than those with normal levels (68.46% vs. 53.85%; P = 0.02). Consistent with this, Zhang et al. [13] found a positive relationship between greater prolactin levels and cumulative clinical pregnancy rates, with significant differences in prolactin levels between individuals with positive and negative pregnancy outcomes at all measurement points. Furthermore, women with modestly raised prolactin levels produced considerably more mature oocytes (M2) and embryos (P = 0.001 and 0.0001, respectively). Zhang et al. [13] found comparable results, with more embryos and oocytes in patients with prolactin levels more than 16.05 ng/ml. In a study of 544 individuals, Iancu et al. [14] discovered no link between serum prolactin levels and the number of oocytes or embryos. Our findings also demonstrated a substantial difference in the cumulative live birth rates between the two groups. Zhang et al. [13] found that raising prolactin levels during ovarian stimulation increased pregnancy outcomes. In contrast, our study observed no significant association between prolactin levels and the number of recovered oocytes, metaphase II oocytes, embryos, or transplanted embryos. In contrast, Kamel et al. [11] found a link between blood prolactin levels and better quality embryos prior to ovum pick-up. Mendoza et al. [15] found that greater baseline prolactin levels were related with more developed oocytes and high-quality embryos, indicating that prolactin plays a function in oocyte maturation and embryonic development. Zhang et al. [13] suggested that prolactin's positive impacts on pregnancy outcomes might be attributed to its participation in oogenesis, embryonic development, and luteal function. The presence of prolactin receptors or mRNA in mature oocytes and cumulus cells supports its role in oocyte development and maturation [16]. Women with somewhat higher baseline prolactin levels had a considerably greater rate of positive pregnancy tests than those with normal prolactin levels (68.46% vs. 53.85%; P = 0.02). Similarly, Kamel et al. [11] discovered that women who conceived had considerably greater levels of prolactin than those who did not. In contrast, Trikoilis et al. [17] reported no difference in blood prolactin levels between pregnancy-test negative and positive groups when evaluating stress indicators in infertile nulliparous women undertaking their first IVF/ICSI treatment cycle. In addition, Duan et al. [18] found that hyperprolactinemia treatment has no effect on cumulative live birth rate and perinatal outcomes in IVF-ET. While Maiter [19] stated that mild to moderate hyperprolactinemia is commonly observed in young women experiencing infertility. It is essential to conduct a prolactin test for these individuals, regardless of the presence of additional symptoms that may indicate elevated prolactin levels, such as galactorrhea or irregular menstrual cycles. Once macroprolactinemia is ruled out, it is important to investigate and eliminate the possibility of prolactinoma and other non-tumorous causes of hyperprolactinemia. For young women who are confirmed to have hyperprolactinemia and are planning to conceive, appropriate treatment should be initiated [19].

5. CONCLUSION

Our findings show that a modest rise in serum prolactin levels is associated with an increased clinical pregnancy rate, a higher cumulative live birth rate, and a higher proportion of M2 oocytes, embryos, and embryos transplanted in women pursuing IVF/ICSI.

CONSENT

All patients provided written informed consent before blood samples were collected.

ETHICAL APPROVAL

The study adhered to the ethical standards specified in the Declaration of Helsinki. It was authorized by the Scientific and Ethics Committee of Kafr El-Sheikh University's OBGYN department on March 25, 2023, under protocol number [KFSIRB200-87].

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image

generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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