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Prevalence of hyperprolactinemia and clinical characteristics in Mexican women with infertility

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Abstract

Background: *Hyperprolactinemia is increased in women with infertility and recurrent pregnancy loss; the prevalence of hyperprolactinemia in Mexican women with infertility is unknown.* **Objective:** *To know the prevalence of hyperprolactinemia and the clinical-biochemical characteristics in Mexican women with infertility.* **Methods:** *This cross-sectional study included infertile women attending in a third-level hospital. All women had prolactin determination and a complete hormonal profile. Women with TSH > 2.5 mIU/L or those taking dopaminergic drugs were excluded. The prevalence of hyperprolactinemia was calculated with a 95% confidence interval (95% CI).* **Results:** *A total of 869 women were included in the study. The prevalence of hyperprolactinemia was 9.6% (95% CI 7.7-11.7%). Of the 83 women with hyperprolactinemia, 52 (62.2%) had serum prolactin values between 25 and 40, 17 (20.4%) between 41 and 60, and 14 (16.8%) > 60 ng/m. The prevalence of one or more miscarriages in women with hyperprolactinemia versus those without hyperprolactinemia among women with secondary infertility was 19/20 (95%) versus 116/197 (58.9%), respectively, p = 0.002. The prevalence of anovulation and clinical hyperandrogenism was significantly higher in women without hyperprolactinemia.* **Conclusion:** *Hyperprolactinemia affects one of ten Mexican women with infertility. Women with hyperprolactinemia and secondary infertility showed a higher frequency of a history of one or more miscarriage.*

Keywords: *Infertility. Hyperprolactinemia. Galactorrhea. Miscarriage. Prolactin.*

Prevalencia de hiperprolactinemia y características clínicas en mujeres mexicanas con infertilidad

Resumen

Antecedentes: *La hiperprolactinemia se incrementa en mujeres con infertilidad y pérdida gestacional recurrente. Se desconoce la prevalencia de hiperprolactinemia en mujeres mexicanas con infertilidad.* **Objetivo:** *Conocer la prevalencia de hiperprolactinemia y las características clínico-bioquímicas en mujeres mexicanas con infertilidad.* **Método:** *Estudio transversal que incluyó a mujeres con infertilidad en un hospital de tercer nivel. Todas las mujeres tenían determinación de*

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prolactina y perfil hormonal completo. Se excluyeron mujeres con hormona estimulante de la tiroides > 2.5 mUI/l o que tomaban medicamentos dopaminérgicos. Se calculó la prevalencia de hiperprolactinemia con intervalo de confianza al 95% (IC95%). **Resultados:** *En total se incluyeron 869 mujeres. La prevalencia de hiperprolactinemia fue 9.6% (IC95%: 7.7-11.7%). De 83 mujeres con hiperprolactinemia, 52 (62.2%) tenían valores de prolactina entre 25-40, 17 (20.4%) entre 41-60 y 14 (16.8%) > 60 ng/ml. La prevalencia de uno o más abortos espontáneos en mujeres con hiperprolactinemia vs. sin hiperprolactinemia entre mujeres con infertilidad secundaria fue: 19/20 (95%) versus 116/197 (58.9%), respectivamente (p = 0.002). La prevalencia de anovulación e hiperandrogenismo clínico fue significativamente mayor en mujeres sin hiperprolactinemia.* **Conclusiones:** *La hiperprolactinemia afecta a una de cada diez mujeres mexicanas con infertilidad. Las mujeres con infertilidad secundaria e hiperprolactinemia mostraron mayor frecuencia de antecedente de uno o más abortos.*

Palabras clave: *Infertilidad. Hiperprolactinemia. Galactorrea. Aborto espontáneo. Prolactina.*

Introduction

Infertility is defined as the inability of a couple to conceive after 12 months of sexual relations without using any family planning methods[1]. It is estimated that between 8 and 15% of all couples will experience primary or secondary infertility at some point in their reproductive lives[1,2].

Increased reproductive age is a significant factor in reduced fertility. For women, fertility peaks in the early to mid-20s, declines slightly in the early 30s, and declines significantly in the middle to late 30 s[2]. The fertility decline in females typically begins around 25-30 years, and the median age of last birth is 40-41 years[1].

In Mexico, Vite et al. reported that the endocrine-ovarian factor was the most frequent factor that influence infertility (82.7%), followed by the cervical factor (80%), the male factor (38%), and the tube-peritoneal factor (29%)[3].

Infertility is a common reproductive health issue with an incidence ranging from 20 to 46% worldwide, representing between 45 and 65% of gynecological consultations[4].

Prolactin is a hormone produced in the lactotrophs of the anterior pituitary gland as the predominant source[5], also being synthesized in the genital tract, especially in the myometrium, and its main function is for the induction and maintenance of lactation in the peripartum and postpartum periods[6].

Hyperprolactinemia is a common endocrinological disorder that can stem from physiological, pathological, or idiopathic causes; the predominant physiological consequence of hyperprolactinemia is suppression of pulsatile GnRH[7,8].

The prevalence of hyperprolactinemia in an unselected normal adult population was 9-17% in women with reproductive disorders[3,9]. A prevalence of 4% was reported in Spanish women[9]. In asymptomatic women with infertility, a prevalence of hyperprolactinemia of 23.9/100,000 person-years has been reported[10]. The prevalence of hyperprolactinemia in the general adult population ranges from 0.1 to 0.4%[11,12]. Between 20 and 25% of women with secondary amenorrhea present hyperprolactinemia, and 30-90% of hyperprolactinemic women experience galactorrhea[13]. In at least 50% of cases of chronic hyperprolactinemia, it may be caused by a pituitary tumor[7,11].

Hyperprolactinemia can disrupt follicular development and luteal body function by inhibiting progesterone production[6]. In addition, there is an increase in dopamine in response to hyperprolactinemia, leading to the inhibition of GnRH production or subsequent ovarian failure[6]. It is the most common cause of chronic hypophyseal anovulation. Depending on its severity, it can lead to luteal phase defects, oligo-ovulation, anovulation, and amenorrhea, thus causing infertility[6].

The most common clinical symptoms reported by women with hyperprolactinemia are infertility, headaches, galactorrhea, oligomenorrhea, and visual changes[14]. In the Latin American population, publications on the prevalence of hyperprolactinemia in women with infertility are limited.

The etiology of polycystic ovary syndrome (PCOS) is multifaceted, involving genetic and epigenetic predispositions, hypothalamic and ovarian dysfunction, excessive androgen exposure, insulin resistance, and mechanisms associated with adiposity[15-18]. The hyperprolactinemia linked with PCOS is believed to stem from an imbalance in androgen production, potential changes in dopamine release, and/or persistent hyperestrogenism[19]. The management may be individualized based on clinical findings[20-21].

The aim of this study was to determine the prevalence of hyperprolactinemia and clinical-biochemical characteristics in Mexican women with infertility.

Methods

Study design

This observational cross-sectional study was conducted at the National Institute of Perinatology Isidro Espinosa de los Reyes; women attending the infertility clinic from 2006 to 2012, with serum prolactin measurement and basic infertility examinations, were included. All women had a hormonal profile on days 3-5 of the menstrual cycle, including LH, FSH, estradiol, prolactin, TSH, total T3, and free T4. Progesterone was determined between days 21 and 23 of the natural or progestogen-induced cycle. Hormonal determinations were carried out in the institute's endocrinology laboratory chemiluminescence with the IMMULITE 2000 Immunoassay System. In addition, all women had a gynecological ultrasound.

The exclusion criteria were women with pregnancy, clinical and subclinical hypothyroidism (TSH ≥ 2.5 mIU/L), history of bromocriptine or cabergoline treatment on admission, and those without a second prolactin determination to confirm the diagnosis of hyperprolactinemia.

The primary objective was to know the prevalence of hyperprolactinemia, defined by a serum prolactin concentration > 25 ng/mL[22], confirmed by a second determination. As a secondary objective, the following clinical-biochemical characteristics were compared between women with hyperprolactinemia and women without hyperprolactinemia: age (years at the admission), weight in kg, height in meters, body mass index (BMI) calculated according to the formula weight in kg/height in m^2. Oligo-anovulation was defined by periods of interval between menstrual cycles > 35 days or intervals between menstrual cycles < 21 days and/or serum progesterone in the mid-luteal phase less than 4 ng/mL. Frequency of galactorrhea, PCOS according with the Rotterdam criteria, and hormonal profile determinations were also compared.

Sample size

To find a prevalence of hyperprolactinemia of 10%, considering a confidence level of 95% and precision or margin error of 2% was necessary to study 864 women with infertility. We included all women who fulfilled the inclusion criteria during the study period.

Statistical analysis

Descriptive statistics were performed using frequencies and percentages for qualitative variables and mean with standard deviation for continuous quantitative variables. Prevalence of hyperprolactinemia was calculated with a 95% confidence interval (95% CI). To compare variables, the Chi-square test or Fisher's exact test was used for differences in proportions, and the Student's t-test or Mann-Whitney U test for differences in means, according to the distribution of each continuous variable. The SPSS Version 20 software, Chicago, IL, was used for the analysis.

Results

A total of 869 women with infertility who met the inclusion criteria were studied; three women with hyperprolactinemia who entered the infertility clinic already pregnant were excluded. The prevalence of hyperprolactinemia was 9.6% (95% CI 7.7-11.7%). Figure 1 shows the distribution of the 83 women with hyperprolactinemia according to prolactin levels; of them, 52 (62.2%) had serum prolactin levels between 25 and 40 ng/mL, 17 (20.4%) between 41 and 60 ng/mL, and 14 (16.8%) > 60 ng/mL.

The clinical characteristics of women with and without hyperprolactinemia are shown in table 1. There were no differences in age, BMI, duration of infertility, type of infertility, biochemical hyperandrogenism, and acanthosis nigricans. A higher frequency of women PCOS was observed in women without hyperprolactinemia, although it was not statistically significant. In women with hyperprolactinemia, there was a high frequency of galactorrhea and a lower frequency of anovulation and clinical hyperandrogenism, both with statistical significance $p < 0.05$.

Out of the total women studied, 25% (217) had secondary infertility, 20 in the hyperprolactinemia group, and 197 in the group without hyperprolactinemia. Among women with secondary infertility, a higher number of women with hyperprolactinemia compared to those without hyperprolactinemia had one or more miscarriages, 19 (95%) versus 116 (58.9%), respectively, $p = 0.002$, in women with two or more miscarriages, there were 5 (25%) versus 25 (12.7%) $p = 0.12$ in the groups with and without hyperprolactinemia, respectively.

In the analysis of biochemical characteristics, a significantly higher difference was observed in prolactin levels ($p = 0.0001$) and progesterone levels ($p = 0.0001$) in the group of women with hyperprolactinemia. There were no other biochemical differences between the study groups (Table 2).

Table 1. Clinical characteristics of infertile women with and without hyperprolactinemia

Characteristic	Total n = 869	Women with hyperprolactinemia n = 83	Women without hyperprolactinemia n = 786	p*-value
Age (years)	29.8 ± 3.9	30.4 ± 3.8	29.8 ± 4.0	0.19
Weight (Kg)	66.2 ± 12.0	66.4 ± 10.5	66.2 ± 12.1	0.84
Height (m)	1.50 ± 0.7	1.53 ± 0.18	1.55 ± 0.6	0.06
BMI (kg/m^2)	27.4	27.4 ± 4.3	27.3 ± 4.5	0.77
Years of infertility	5.1 ± 2.9	5.5 ± 3.0	5.1 ± 2.9	0.19
Primary infertility	652 (75)	63 (75.9)	589 (74.9)	0.92
Galactorrhea	4 (0.5)	4 (4.8)	0 (0)	0.01
Oligo-anovulation	467 (53.7)	33 (39.8)	434 (55.2)	0.01
Polycystic Ovary Syndrome+	291 (33.4)	23 (27.7)	268 (34.1)	0.29
Clinical hyperandrogenism&	109 (12.5)	4 (4.8)	105 (13.5)	0.03
Biochemical hyperandrogenism	257 (29.5)	24 (28.9)	233 (29.6)	0.89
Acanthosis nigricans	114 (13.1)	9 (10.8)	105 (13.4)	0.57

Values expressed as mean ± standard deviation and/or frequency with (percentage).
*Student's t-test or Chi-square test. +Defined by the Rotterdam criteria[16], &Score on the Ferriman-Gallwey scale > 8[16].

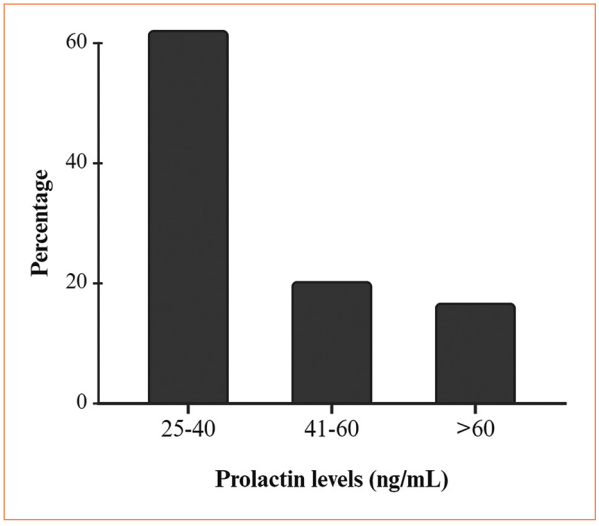

Figure 1. Frequency of women with different ranges of serum prolactin at the diagnosis of hyperprolactinemia.

Discussion

The prevalence of hyperprolactinemia in Mexican women with infertility was 9.6%. To the best of our knowledge, this is the first study reporting the prevalence of hyperprolactinemia in Mexican women with infertility. The group of women with secondary infertility and hyperprolactinemia more frequently had a history of one or more miscarriages.

Slightly elevated levels of prolactin can lead to luteal insufficiency in women during the menstrual cycle and are associated with recurrent miscarriages[23]. Any truly confirmed hyperprolactinemia should be treated in young women seeking to become pregnant. Preference should be given to cabergoline at the lowest dose that normalizes prolactin levels, and fertility could be restored in most women[23].

Hyperprolactinemia occurs in < 1% of the general population and in 5-14% of women with secondary amenorrhea[8]. Souter et al. reported a prevalence of hyperprolactinemia in women with infertility of 12.1%, of which 60.9% had pituitary magnetic resonance imaging without alterations[24]; this prevalence of hyperprolactinemia was similar to the findings in the present study; however, most women did not have magnetic resonance in this study.

Varaldo et al. demonstrated that prolactin levels can predict the presence of a pituitary lesion with modest accuracy but cannot predict a macroadenoma[25].

In the study conducted by van der Ham et al., it was found a similar prevalence of hyperprolactinemia in women with PCOS (n = 15, 1.1%) compared to controls (n = 9, 3.0%); the controls were women with regular

Table 2. Biochemical characteristics of infertile Mexican women with and without hyperprolactinemia

Characteristic	Women with hyperprolactinemia (n = 83)	Women without hyperprolactinemia (n = 786)	p*-value
Prolactin (ng/mL)	44.3 ± 24.7	12.4 ± 4.7	0.0001
TSH (mUI/L)	1.5 ± 0.51	1.5 ± 0.53	0.53
Total T3 (ng/mL)	123.9 ± 25.5	121.6 ± 29.6	0.5
Free T4 (ng/mL)	1.3 ± 0.25	1.3 ± 0.32	0.84
Estradiol (pg/mL)	47.0 ± 42.5	47.3 ± 40.7	0.94
Progesterone (ng/mL)	11.5 ± 18.0	6.7 ± 7.4	0.0001
FSH (mUI/mL)	5.6 ± 2.3	6.0 ± 5.4	0.57
LH (mUI/mL)	4.7 ± 8.9	4.5 ± 3.5	0.64
Insulin (µU/mL)	11.3 ± 9.4	10.9 ± 8.9	0.74
Glucose (mg/dL)	92.7 ± 10.0	93.1 ± 16.5	0.82
*FAI (%)	(n = 40) 4.8 ± 3.6	(n =401) 5.5 ± 8.7	0.63
17-Hydroxyprogesterone (ng/mL)	(n = 69) 1.3 ± 1.1	(n = 678) 1.3 ± 1.4	0.99
Androstenedione (ng/mL)	(n = 69) 2.5 ± 0.93	(n = 678) 2.6 ± 1.4	0.54
**S-DHEA (µg/dL)	(n = 65) 157.9 ± 80.2	(n = 619) 156.4 ± 81.0	0.88

*Free Androgen Index; **Dehydroepiandrosterone sulfate.

menstrual cycles who conceived spontaneously and had no reported medical history of PCOS[26]. The prevalence of hyperprolactinemia was lower than that reported in our study. Likewise, a retrospective study reported that 528 women with PCOS showed hyperprolactinemia in 11.4%, of which 43.2% of these women had pituitary adenomas[27], which is slightly higher than the present study that found hyperprolactinemia in 23 of 268 (8.6%) women with PCOS.

Elevated levels of prolactin in the blood could lead to anovulation by blocking the luteinizing hormone pulse and interfering with the positive feedback mechanism of estradiol at the hypothalamic level through estrogen receptor blockade[6,15]. Actions on the ovary may be due to a decreased affinity of LH receptors in the corpus luteum and an associated decrease in the production and secretion of progesterone[28], which it is associated with a reduction in the production and secretion of progesterone, which could explain the clinical finding of infertile women with luteal phase deficiency and low progesterone levels[6,15,28]. However, in the present study, there were no significant differences in the number of women with oligo-anovulation, and the progesterone level was significantly higher in the hyperprolactinemia group compared to the non-hyperprolactinemia group. The relatively low level of prolactin could explain this cause of anovulation; 83% of our study population had prolactin levels between 25 and 60, and none had galactorrhea.

The strength of this study is the sample size, which is representative of the population with infertility issues, and the fact that women with any type of hypothyroidism and those taking any dopaminergic medication were excluded.

Among the limitations of this study, it can be highlighted that the data were retrospectively collected and only included one national reference center for infertility women in Mexico, which could increase the prevalence. There is no strong evidence in Mexican women with pituitary imaging studies (magnetic resonance imaging or computed tomography), and only three patients had such studies.

Similarly, in the current study, it was observed that women with hyperprolactinemia who had experienced at least one prior pregnancy were more likely to have a history of one or more miscarriages. Chen and Lina conducted a study investigating the treatment of recurrent

miscarriages in women with hyperprolactinemia. The inclusion criteria were women aged 24-40 with idiopathic hyperprolactinemia and a history of 2-4 spontaneous abortions[20] and reported a direct correlation between elevated prolactin levels and the recurrence of miscarriages. In the present study, in women with hyperprolactinemia and secondary infertility, there was a significantly higher prevalence of one or more miscarriages; however, in women with two or more miscarriages, there was a trend toward being higher in the hyperprolactinemia group, but this difference was not significant, p = 0.12.

There is a controversy regarding whether to treat asymptomatic women with hyperprolactinemia and regular ovulatory cycles, as the cost-benefit relationship has not been well established. Further studies on this matter are needed[20].

In the future, it is suggested to conduct prospective studies that include imaging studies, as well as the outcomes of infertility treatment and, if applicable, perinatal outcomes in women with hyperprolactinemia.

Conclusion

This study reveals a notable prevalence of hyperprolactinemia (9.6%) in Mexican women experiencing infertility, particularly in those with secondary infertility who also exhibited a higher incidence of previous miscarriages. This research is the first to document the prevalence of hyperprolactinemia in this specific population.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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