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Original Article

Complementary health education and clinical guidance for treating women experiencing infertility along with unexplained resistant hyperprolactinemia

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Abstract This study prospective randomized controlled trial aims to test the impact of adding health education, awareness of some contributing factors and clinical guidance to therapeutic cabergoline given to infertile women with unexplained resistant hyperprolactinemia. It comprised 120 infertile women with unexplained persistent hyperprolactinemia not responding to therapeutic doses of cabergoline 1.5-2 mg/week who were subjected to proper history taking to exclude concomitant drug intake or possible brain problems in all cases. They were classified into group A (60 cases) who received health education and clinical guidance to search for possible contributing factors and were instructed to avoid them in addition to proper therapeutic doses of cabergoline, while group B (60 cases) received proper therapeutic doses of cabergoline only without clinical guidance. After 1 month, serum prolactin (PRL) was measured for all cases. All cases had high PRL level at the start of the study (79.9±28.4 [39-195] and 78.2±19.9 [42-189] in group A and B, respectively) without any significant difference. Pretreatment counselling revealed that lifestyle factors, sexual behaviors or feeding habits may contribute to resistant hyperprolactinemia in all cases without a significant difference between both groups. Serum PRL dropped significantly more in group A (20.14±10.31 [11-45] vs. 49.32±37.03 [12-100]) after combined health education, clinical guidance of the couple and proper treatment. It is concluded that lifestyle factors, sexual behaviors, and feeding habits would affect the response of hyperprolactinemia to treatment. Health education and clinical guidance with some advice to avoid them, would concomitantly improve the response of resistant hyperprolactinemia to therapeutic doses of dopamine agonists.

Key words: Prolactin, Hyperprolactinemia, Infertility, Health, Cabergoline

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INTRODUCTION

Pathological hyperprolactinemia is an unwanted prolactin hormone (PRL) overproduction that can affect both sexes, although women are more vulnerable to its harmful effects.[1] It may produce no symptoms or can cause infertility, a decline in libido, loss of bone mass, irregular menstruation, improper release of breast milk (galactorrhea), dryness of the vagina, or dyspareunia.[2,3] Regardless of the cause, dopamine agonists (DA) help the brain produce dopamine to reduce excessive PRL levels. DA can also reduce the prolactinoma tumor size.[4] Even when given the right amount of DA for an appropriate amount of time, several women may not respond to treatment and may experience symptoms. Resistant hyperprolactinemia is defined as the inability to reduce PRL levels to normal levels (normoprolactinemia)[5,6] despite the maximally tolerated recommended dose, type, and course of DA in an unexplained manner. For bromocriptine and cabergoline, the prevalence rates of resistant hyperprolactinemia were 20-30% and 10-12%, respectively. The conventional approach for managing cases of resistant hyperprolactinemia is to increase the dose or frequency of DA, which may increase the possibility of side effects, complications, and even drug toxicity. Alternatively, medical professionals may switch to different drug classes without significant improvement. Women frequently inquire regarding their non-response to treatment but rarely receive convincing responses. Approximately 10% of patients with hyperprolactinemia have pituitary adenomas. Therefore, medical professionals should rule them out, as well as other potential underlying causes, such as drug use.[7,8] Evidence-based suggestions for proper counselling, health education, and clinical guidance are provided to improve patient care. We hypothesized that educating women with resistant hyperprolactinemia on the important contributing factors and offering them expert advice on how to avoid them would help achieve normoprolactinemia. This study aimed to test the impact of adding health education, awareness on some contributing factors, and clinical guidance on therapeutic cabergoline administration in women experiencing infertility along with unexplained resistant hyperprolactinemia.

METHODS

This prospective randomized controlled trial was approved by the Ethics Committee of the Assiut University Faculty of Medicine (IRB No. 17101033) and was conducted at the infertility and gynecologic outpatient clinics of the Women's Health University Hospital, Assiut, Egypt, between February 2020 and May 2023. ClinicalTrials.gov was registered under the registration number NCT04262024. Enzyme-linked immunosorbent assay testing at the institutional laboratory confirmed resistant pathologic hyperprolactinemia in all cases. Serum PRL levels between 2 and 20 ng/mL were considered normal. All the patients provided written informed consent to participate in the study. Pathologic hyperprolactinemia that did not respond (resistant) to conventional doses of cabergoline (1.5-2 mg/week, or half a pill at bedtime during meals every day) given consistently for at least 3 months as previously advised, was the inclusion criteria.[9] Patients with physiological hyperprolactinemia were excluded. Women using first- or second-generation antipsychiatric medications, oral contraceptives, antidepressants, antihypertensives, or opioid analgesics were excluded.[10] Based on standard examinations and the clinical absence of neurological symptoms, visual impairment, or headache, patients with systemic conditions, such as uremia, suspected pituitary adenoma, or pituitary stalk tumors, were also excluded. In some cases, magnetic resonance imaging (MRI) was requested to rule out a suspected brain etiology.

The sample size was calculated using the Epi Info program (Centers for Disease Control and Prevention, Atlanta, GA, USA) with a 95% confidence interval, 10% tolerable error, and 50% predicted frequency. The samples were divided into the study and control groups (60 patients each). In all cases, detailed personal, sociodemographic, menstrual, obstetric, and infertility histories were recorded. Additionally, questions were asked regarding aspects related to

lifestyle factors, sexual behavior, and feeding habits that may contribute to resistant hyperprolactinemia (addressed in the latter), and the last component was a follow-up form that had to be completed following treatment. To maintain security and obtain clear answers, interviews with couples were conducted in a different room. All the patients underwent general, systematic, and local examinations. Body mass index (BMI) was calculated as weight in kilograms per square meter of height. All cases were carefully examined clinically, and transvaginal ultrasonography was used to rule out any associated gynecologic problems requiring concomitant treatment. The chest wall and breasts of each patient were examined for galactorrhea (inappropriate milk secretion). All patients received requests for thyroid stimulating hormone (TSH) and regular tests, including creatinine tests. Using labelled papers (sealed envelopes), subjects with resistant hyperprolactinemia were randomly divided into two groups to begin the intervention phase. Group A included 60 cases receiving a therapeutic dose of cabergoline (1.5-2 mg/week during dinner for a month), along with health education and clinical guidance, while women in group B received the same medication without clinical guidance or health education. Free support pamphlets, lectures, and conversations on how to prevent certain activities that may increase serum PRL, such as lifestyle variables, sexual behaviors, or dietary habits, were part of the health education provided to group A participants (60 cases). The frequency and pattern of breast involvement during sexual activity, pressure on the chest or breast, direct harm to the breast, and the donning of a tight brassiere were thoroughly investigated. An inquiry was made about foods accused of causing hyperprolactinemia, such as sweet foods, especially flour sweetness (halvah), excessive fats, a high-protein diet, oils, or seeds, especially fenugreek and sesame seeds, nuts, and birds, such as chicken and pigeons, as reported in some textbooks of endocrinology.[11] The patients were advised to eat a variety of foods, including fruits, vegetables, seafood, omega-3 fatty acids, zinc, and proteins. Daily habits (e.g., watching another woman breastfeed, carrying children on the chest, getting too little sleep, strenuous exercise, stress, wearing tight clothing) that may cause hyperprolactinemia were discussed. In contrast, patients in group B (60 patients) were administered a therapeutic amount of cabergoline (1.5-2 mg/week) during dinner for a month while being warned about potential adverse effects and were also advised to take certain safety measures. No previously mentioned health education or clinical guidance topics were discussed. All patients visited the clinics after a month of treatment to reassess their PRL, discuss their compliance with the recommendations, and review any negative side effects.

Version 24 of the SPSS (IBM, Armonk, NY, USA) was used to analyze the data. Quantitative data were expressed as mean±standard deviations (SD). Frequencies and percentages were used to express the qualitative data. The mean (average) or sum of the values divided by the total number of values, was the central value of a discrete set of numbers. The dispersion of each group of values was measured using SD. In contrast to a high SD, which indicates that the values are dispersed over a greater range, a low SD implies that the values tend to be close to the established mean. An independent sample *t*-test of significance was applied when comparing two means (for normally distributed data). The Mann-Whitney *U* test was used to compare the two means (for abnormally distributed data). The chi-squared test was used to compare non-parametric data. Probability (*P*-value) <0.05 was considered significant, *P*<0.001 was considered as highly significant, and *P*>0.05 was considered non-significant.

RESULTS

This study included 120 women experiencing infertility along with unexplained persistent pathological hyperprolactinemia despite proper treatment. A BMI >25 kg/m^2 was reported in 35 (58.3%) and 38 (63.3%) patients in both groups, respectively. Patients were divided into two groups: proper cabergoline therapy with (group A) and without (group B) health education and clinical guidance. There were no statistically significant differences between the groups regarding sociodemographic data (apart from the education

level), infertility details, or medical and obstetric histories. All cases had high PRL levels at the start of the study without any significant difference (Table 1). Irregular menstrual cycles were encountered in 11 (18.3%) and 14 (23.3%) patients in the two groups, respectively, with no significant difference. Table 2 shows some possible contributing factors to the resistant hyperprolactinemia encountered in all cases in both groups, without any statistically significant differences. Achievement of normoprolactinemia 1 month after therapy for hyperprolactinemia is shown in Table 3, with a statistically significant decline in PRL values after 1 month of therapy in group A (20.14±10.31 [11-45] vs. 49.32±37.03 [12-100]).

DISCUSSION

This study included 120 women with infertility and pathological hyperprolactinemia. Although other contributing factors to infertility were assessed, data were excluded since the primary outcome was laboratory improvement of hyperprolactinemia rather than the pregnancy rate. Although it is commonly known that nipple or breast stimulation may increase serum PRL levels, we believe it is of academic value to prove this in a prospective randomized controlled trial pre-registered on ClinicalTrials.gov. Pathologic hyperprolactinemia should be thoroughly evaluated as it has a direct impact on women's health.[12] Careful history, examination, and transvaginal ultrasonography, followed by laboratory tests and diagnostic imaging of the Sella turcica, are mandatory prerequisites for identifying the underlying explanatory cause,[13] as shown in this study. Serious causes were excluded from this study owing to the absence of neurological symptoms, visual impairment, headache, and a normal coned-down plain X-ray. Moreover, a detailed drug history was obtained for all cases to exclude any possible association with hyperprolactinemia. Thus, all possible explanatory

Table 1. Sociodemographic data of the studied patients

Variable	Study group (n=60)*	Control group (n=60)*	*P*-value†
Age (years)	29.38 (18-39)	30.19 (21-40)	0.0708
Residence			
Urban	28 (46.6)	33 (55.0)	0.0821
Rural	32 (53.4)	27 (45.0)	
Education			
Illiterate	2 (3.3)	3 (5.0)	0.4325
Basic education	8 (13.3)	7 (11.6)	
Secondary school	27 (45.1)	24 (40.2)	
University	23 (38.3)	26 (43.2)	
Woman 's Occupation			
House wife	27 (45.0)	30 (50.0)	0.0996
Employed	33 (55.0)	30 (50.0)	
Duration of marriage (years)	6.14 (1-18)	6.37 (1-20)	1.0000
Type of infertility			
Primary, no prior pregnancy	35 (58.3)	32 (53.3)	0.0755
Secondary, prior pregnancy	25 (41.7)	28 (46.7)	
Body mass index (Kg/m^2)	26.15 (19-31)	25.71 (20-29)	0.2892
Pre-treatment mean prolactin level (ng/mL)	79.9±28.4 (39-195)	78.2±19.9 (42-189)	0.7048

Values are presented as mean (range), mean±standard deviation (range) or number (%).

*Chi square test for qualitative data between the two groups and independent *t*-test for quantitative data between the two groups.

†Significant level at $P<0.05$.

Table 2. Possible contributing factors* for resistant hyperprolactinemia in both groups (without significant differences)

Factor	Study group (60 cases)	Control group (60 cases)
Sedentary life	17 (28.3)	19 (31.6)
Seeing another woman breast feeding	10 (16.6)	9 (15.0)
Carrying children on the chest	8 (13.3)	7 (11.6)
Insufficient sleep	11 (18.3)	12 (20.0)
Excessive exercise	4 (0.7)	3 (5.0)
Stress	6 (10.0)	7 (11.6)
Wearing tight clothes or brassiere	4 (6.6)	3 (5.0)
Nipple or areola stimulation by hand	15 (25.0)	16 (26.6)
Nipple suckling by the partner	29 (48.3)	27 (45.0)
Breast manipulation or compression	22 (36.6)	24 (40.0)
Chest wall compression	10 (16.6)	11 (18.3)
Excess fats, up to 10% of a person's total energy consumption	10 (16.6)	9 (15.0)
Fenugreek hot drink, yes	7 (11.6)	5 (8.3)
Frequent pigeons and chicken eating, arbitrary	18 (30.0)	17 (28.3)
Sweets especially flour sweetness (halvah), arbitrary	14 (23.3)	15 (25.0)
Eating sesame seeds, yes	15 (25.0)	14 (23.3)

Values are presented as number (%).

*More than factor in the same patient.

Table 3. Follow-up prolactin level after 1 month of therapy in both groups

Prolactin level	Study group (60 cases)	Control group (60 cases)	*P*-value
Normal	46 (76.6)	29 (48.3)	<0.05*
Abnormal	14 (23.3)	31 (51.7)	<0.05*
Mean±SD (range)	20.14±10.31 (11-45)	49.32±37.03 (12-100)	<0.0001†

Values are presented as number (%) unless othermise indicated.

SD: standard deviation.

*The chi-square statistics is 10.2756 and the *P*-value is 0.001348. The result is significant at $P<0.05$.

†95% confidence interval is 19.3531 to 39.0069 and *t*-statistics was 5.880.

causes of pathological hyperprolactinemia were excluded. In this study, not all patients with hyperprolactinemia had galactorrhea; however, there was a high prevalence of galactorrhea among the studied patients (70% and 65% in both groups, respectively), as reported by others.[14,15] Its incidence is as high as 90% in women with hyperprolactinemia. The marked variability is likely a result of the difference in how milk is expressed and how galactorrhea is defined.[16] Others have found that only 15-68% of patients with excessive PRL secretion develop galactorrhea, which can be attributed to differences in examination techniques, the investigator's definition of galactorrhea, and the patient population studied.[17] Emotion and stress are important factors contributing to the development of galactorrhea.[18] Another explanation is the heterogeneity of PRL hormones (bioactive and immunoactive forms). Therefore, patients can have all features of hyperprolactinemia with normal serum prolactin levels.[19] The predominant form is monomeric PRL (small PRL, 23 kDa), which accounts for 80-95% of total PRL. Other forms include dimeric PRL (big PRL, 48-56 kDa), representing up to 10% of the total PRL, and macroPRL (big-big PRL, >150 kDa), which accounts for less than 1%.[20] Monomeric PRL is biologically and immunologically active, whereas macroPRL has limited bioactivity *in vivo* since it is confined to the

vascular system and has limited access to the PRL receptors in target organs, resulting in asymptomatic hyperprolactinemia. It persists in the serum despite the disappearance of monomeric PRL.[21,22] This issue should be included during follow-up visits and better excluded by sophisticated testing (which was unfortunately not available at our institution), such as gel filtration chromatography, immunoassays of serum PRL before and after removal of macroprolactin by ultrafiltration, immunoadsorption of immunoglobulin G (IgG) species with protein A, protein G, or anti-human IgG, and precipitation with polyethylene glycol.[23] Nevertheless, the decision to treat patients with galactorrhea should be based on serum prolactin levels, severity of galactorrhea, and the patient's desire for fertility.[24]

In this study, abnormally high BMIs were observed in 35 (58.3%) and 38 (63.3%) patients in the two groups, respectively. Obesity can lead to hyperprolactinemia and vice versa. It may also lead to adverse effects, such as insulin resistance and metabolic syndrome, whereas hyperprolactinemia may cause abnormal lipid profiles, weight gain, and cardiovascular diseases.[25] In one study, 65.2% of the patients were overweight or obese, and the authors concluded that the prevalence of obesity was significantly higher in patients with hyperprolactinemia, regardless of the degree of obesity or the cause of hyperprolactinemia.[26] Treatment with DA has been shown to reduce body weight and improve metabolic parameters; however, one study failed to prove decreased weight even after 6 months of therapy, but with reported improvement in metabolic parameters.[27] Health education for obese women with hyperprolactinemia should include instructions for weight reduction through physical activity, exercise, and a decrease in fat and carbohydrate diets, as done in this study.

All patients in this study were infertile. Classically, hyperprolactinemia can decrease estrogen production, directly cause infertility, and affect testosterone levels. Recent data suggest that hyperprolactinemia lowers kisspeptin production in the hypothalamus by affecting kisspeptin-1 neurons expressing the PRL receptor and is responsible for decreased kisspeptin-1 and gonadotrophin releasing hormone (GnRH) secretion. As a result, decreased pituitary gonadotropin synthesis and secretion (lutinizing hormone [LH] and follicle stimulating hormone [FSH]) are associated with loss of gonadal stimulation (hypogonadotropic hypogonadism), anovulation, and infertility.[1,28] Moreover, the persistent effect of high serum PRL levels on the endometrium during the proliferative phase in the presence of estradiol (E2) may induce abnormal proliferation of endometrial glandular cells via the enhanced endometrial receptivity (ER) and PRL receptor in hyperprolactinemic women.[29] At the peripheral level, PRL directly inhibits estrogen and progesterone synthesis. A defective luteal phase, inconsistent ovulation, and chronic anovulation are the final results of hyperprolactinemia.[29] Some studies have highlighted the central role of PRL in the reproductive system, describing two types of PRL: pituitary and peripheral.[30] In a pathway different from that of pituitary PRL, peripheral PRL is directly synthesized by the endometrium under the stimulatory action of progesterone and myometrium, which directly promotes uterine smooth muscle cell growth and proliferation. Hyperprolactinemia has been reported in patients with cervical or endometrial cancers, as well as uterine premalignant lesions; therefore, it can be used as a discriminative biomarker in patients with uterine cancers. A potential application of DA in the therapeutic algorithm of women with malignant, premalignant, and benign uterine lesions has been suggested.[31] All these findings send a message to healthcare providers that hyperprolactinemia should be meticulously evaluated, and ruling out any associated gynecologic lesions suggestive of malignant or premalignant lesions should be a priority through detailed clinical and sonographic assessments in all cases, as in this study.

Healthcare providers must be able to identify and provide an initial assessment for women with possible hyperprolactinemia. Once the cause of hyperprolactinemia is determined, practitioners can inform women about the management options appropriate for their specific needs.[32] In this study, healthcare providers played a central role in identifying an explanation for persistent hyperprolactinemia despite proper treatment, by simply offering patients more

time to discuss some hidden causes of hyperprolactinemia ignored by the patients and usually not addressed by busy physicians. To our knowledge, this is the first detailed study to highlight the crucial role of clinical guidance and health education in the management of hyperprolactinemia in conjunction with medical treatments. Owing to the pre-intervention questionnaire, booklets, lectures, and kind discussions, women were cooperative and described their previous lifestyles, dietary habits, and sexual behaviors, which may have contributed to the persistence of hyperprolactinemia. For instance, our results showed that some sexual behaviors, such as nipple suckling are important contributing factors to hyperprolactinemia. The best-known physiological stimulus for prolactin secretion is breast suckling, which results in a reduction in dopamine release into the portal blood, with a lower level reaching the anterior pituitary gland, thus essentially relieving lactotrophs from tonic inhibition.[33,34] Nipple suckling leads to a sharp rise in PRL within 1-3 minutes from the onset of action. This study showed that health education seems to be an essential cofactor for the success of hyperprolactinemia treatment and that the role of healthcare providers should be addressed in all busy centers interested in the management of hyperprolactinemia. Nevertheless, this study has some limitations, including a small sample size, short duration of therapy, short follow-up period, and lack of reporting of pregnancy rates after the full course of treatment. Missing reports of pregnancy after these lines of therapy in women experiencing infertility are an additional drawback. It is unknown whether avoidance of nipple or breast stimulation, weight reduction, and diet modification caused a decrease in PRL; therefore, another study addressing more stratification of the possible causes in subgroups is required. All these limitations could be overcome by the construction of a large sample size or a better yet multicentric study in the future. This study concluded that lifestyle factors, sexual behaviors, and feeding habits would affect the response of patients with hyperprolactinemia to treatment. Health education to increase the awareness of women experiencing infertility to possible contributing factors and clinical guidance with advice to avoid them would concomitantly improve the response of resistant hyperprolactinemia to therapeutic doses of DA.

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