



Original Research

## The Outcome of Prolactinoma in the Postpartum Period: a Study from a Tertiary Care Hospital in Pakistan

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### ABSTRACT

**Objective:** Prolactin is an essential hormone secreted by the pituitary gland of pregnant women. The pituitary gland undergoes growth, due to lactotroph hyperplasia in response to placental estrogen during pregnancy. Research on the postpartum outcomes of prolactinomas is less. This study evaluates the prevalence of Prolactinoma and the occurrence of spontaneous resolution of Prolactinomas after pregnancy.

**Materials and Methods:** A cross-section study was conducted at the Punjab Institute of Neurosciences, Lahore. 200 pregnant women were recruited; their blood samples were collected to evaluate serum prolactin levels. Women diagnosed with prolactinomas exhibiting positive symptoms were given dopamine agonists. The administration of dopamine agonist was discontinued at the 24th week of gestation. All participants were monitored till birth, at 40 days after delivery, and throughout breastfeeding. Their prolactin levels were evaluated, and magnetic resonance imaging (MRI) was conducted to verify the resolution of prolactinoma.

**Results:** The mean age of females in the study was  $29.03 \pm 7.20$  years. Out of 200, 40 (20%) females had prolactinoma. Out of 40, 13 (32.5%) were given Bromocriptine while 27 (67.5%) were given Cabergoline. At presentation, the mean serum prolactin level was  $138.91 \pm 149.02$  ng/ml, which reduced to  $21.38 \pm 9.80$  ng/ml. The mean tumor size at presentation was  $7.23 \pm 2.07$  mm, which reduced to  $0.79 \pm 0.66$  mm after delivery. Out of 40, 30 (75.0%) had spontaneous resolution.

**Conclusion:** The occurrence of prolactinoma is low in symptomatic patients and can resolve spontaneously after delivery in the majority of cases.

**Keywords:** Prolactinomas, pregnancy, serum prolactin, lactation, Cabergoline.

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### INTRODUCTION

Prolactin is a vital endocrine hormone that is synthesized and released by the pituitary gland.

Its primary function is to facilitate lactation in pregnant women and postpartum moms, hence supporting the production of breast milk for nourishing newborn infants. The incidence of prolactinomas, which account for 40 percent of all pituitary adenomas, is a significant contributing cause to elevated blood prolactin levels. These prolactinomas may be classified as either micro (less than 10 mm) or macro Prolactinomas.<sup>1</sup> Prolactin, a polypeptide hormone, plays a crucial role in several physiological processes, including breastfeeding, breast growth, and the regulation of homeostasis via numerous other mechanisms. The chemical structures of prolactin exhibit similarities to those of growth hormone and placental lactogen hormone.<sup>2</sup> In the case of teenage and younger women, various symptoms manifest concurrently, including oligomenorrhea, amenorrhea, galactorrhea, and/or infertility. The resolution of infertility is often achieved with the use of dopamine agonist therapy.<sup>3</sup> The pituitary gland undergoes a normal process of expansion during pregnancy, which is attributed to lactotroph hyperplasia in response to placental estrogen.<sup>4</sup> In men and non-lactating non-pregnant females, levels of prolactin are often reduced.<sup>5</sup> Prolactinoma represents the predominant form of secreting pituitary adenoma. The condition is distinguished by the excessive growth of lactotrophic cells in the anterior pituitary gland. The majority of prolactinomas, around 90%, are classified as microadenomas, characterized by a diameter of less than 1 cm, and typically do not exhibit any noticeable symptoms.<sup>5</sup>

The influence of Prolactinomas on pregnancy is characterized by a lower incidence of enlargement in microprolactinomas compared to macroprolactinomas.<sup>6</sup> Tumor expansion has been seen in a range of 2% to 3% of patients diagnosed with microadenomas, 20% to 30% of those with macroadenomas, and 4.7% of those who have had ablative therapy for macroadenomas.<sup>7,8</sup> Research primarily focused on

individuals diagnosed with microprolactinomas has consistently shown remission rates of hyperprolactinemia ranging from 10% to 68% among the participants.<sup>9</sup> The management of hyperprolactinemia is contingent upon the underlying etiology. The recommendation issued by the Endocrine Society advises against the use of dopamine agonists as a treatment for individuals with asymptomatic microadenomas. However, it does advocate the administration of dopamine agonist therapy for symptomatic patients who have microadenomas or macroadenomas, to reduce prolactin levels, decrease tumor size, and restore normal gonadal function. Cabergoline is the favored choice among dopamine agonists owing to its superior effectiveness in normalizing prolactin levels and inducing tumor shrinking. The administration of dopamine agonists, such as cabergoline and bromocriptine, is a widely used therapeutic approach.<sup>10</sup> The majority of individuals diagnosed with microprolactinomas exhibit a favorable prognosis and experience the normalization of prolactin levels upon receiving appropriate therapy. These individuals may be effectively treated with medicinal interventions over an extended duration. The efficacy of pituitary surgery is contingent upon several factors, including the dimensions of the tumor, the serum prolactin concentration, and the expertise of the neurosurgeon. There exists an inverse relationship between the success rate of pituitary surgery and both tumor size and prolactin levels..<sup>11</sup> In a research study conducted in South Asia, namely in India, it was shown that remission occurred in only 36.4% of macroprolactinoma cases after pregnancy, despite a decrease in tumor size detected in 95.8% of patients.<sup>12, 13</sup>

The objective of this research was to examine the incidence of prolactinomas in pregnant women, as well as the rate of spontaneous remission and changes in tumor size during pregnancy and/or breastfeeding in women diagnosed with prolactinomas who were not

undergoing dopamine agonist therapy, within the specific setting of Pakistan. The systematic practice of screening for prolactinomas by measuring prolactin levels is not often observed in Pakistan. Prolactinomas are often seen in females within the reproductive age demographic. Consequently, this research was undertaken to get empirical information that may contribute to the enhancement of our understanding and application within the local community.

## MATERIAL AND METHODS

### Study Design & Setting

A Cross-sectional study was conducted at the (Department of Neurosurgery) Punjab Institute of Neurosciences (PINS), Lahore, from June 2022 to June 2023

### Sample Size & Technique

A sample size of 200 cases was estimated by keeping the confidence level at 95%, the percentage of spontaneous remission at 36.4%,<sup>8</sup> with 7% absolute precision required. A Non-probability, consecutive sampling was considered.

### Inclusion Criteria

Females aged 18-40 years, parity <5, presenting with singleton pregnancy at gestational age >8 weeks with complaints of headaches and changes in vision.

### Exclusion Criteria

Females who already received treatment for prolactinoma in a current or previous pregnancy, diabetes, or any other neurological or psychiatric disorder were excluded from the study.

### Data Collection Procedure

After approval from the ethical review board, 200 pregnant females with symptoms were enrolled in

the study. Informed consent was taken before enrollment and demographics including name, age, gestational age, body mass index, and parity, were noted. All the data was recorded in proforma. Then blood sample was taken in a 5cc disposable syringe. All samples were stored in vials, containing EDTA to prevent clotting. All samples were sent to the laboratory of the hospital for assessment of prolactin level. Reports were assessed and levels were recorded. If the level was more than 130 ng/ml, then females were labeled as prolactinoma and underwent magnetic resonance imaging.

### Radiological Findings and Clinical Management

On magnetic resonance imaging, the size of the tumor was noted. Then females were prescribed dopamine agonists, either bromocriptine or cabergoline until 32 weeks of gestation. After 32 weeks, treatment was stopped and females were followed up until delivery. After delivery and 40 days of delivery, a blood sample was taken again. Reports were assessed and levels were recorded. If the level was less than 30 ng/ml, then a spontaneous resolution of prolactinoma was labeled and females underwent magnetic resonance imaging to confirm the reduction in the size of the tumor after the end of pregnancy.

### Data Analysis

Data analysis was done by using IBM SPSS version 26. The frequency of prolactinoma was presented as a graph and reduction in prolactin level was calculated as mean and standard deviation.

## RESULTS

### Patient Population

The mean age of females enrolled in the study was  $29.03 \pm 7.20$  years. The mean gestational age at presentation was  $22.35 \pm 6.88$  weeks. The

mean body mass index of females was  $25.93 \pm 4.62 \text{ kg/m}^2$ . Out of 200 females, 35 (17.5%) females were primiparous, 80 (40%) females had parity 1-2 and 85 (42.5%) females had parity 3-4.

### Prolactin Levels at Presentations

The mean serum prolactin level at presentation was  $138.91 \pm 149.02 \text{ ng/ml}$  (Table 1).

Out of 200 females, 40 (20%) females had prolactinoma, diagnosed based on serum

### Prolactinomas after Treatment

Out of 40 females who were confirmed with prolactinoma, 13 (32.5%) females were given Bromocriptine while 27 (67.5%) females were given Cabergoline. At presentation, the mean serum prolactin level was  $138.91 \pm 149.02 \text{ ng/ml}$ . After delivery, the mean prolactin level was reduced to  $21.38 \pm 9.80 \text{ ng/ml}$ . The mean tumor size at presentation was  $7.23 \pm 2.07 \text{ mm}$  on magnetic resonance imaging, which was reduced to  $0.79 \pm 0.66 \text{ mm}$  after delivery. Out of 40 females, 30 (75.0%) females had spontaneous resolution while 10 (25.0%) females still showed prolactinoma (Table 2).

**Table 1:** Basic information of pregnant females enrolled in the study (n = 200).

Feature	Mean $\pm$ SD
Age (in years)	$29.03 \pm 7.20$
Gestational age (in weeks)	$22.35 \pm 6.88$
Body mass index (in $\text{kg/m}^2$ )	$25.93 \pm 4.62$
Serum prolactin level (ng/ml)	$138.91 \pm 149.02$
Parity	Frequencies (%)
Primiparous	35 (17.5%)
Parity 1-2	80 (40%)
Parity 3-4	85 (42.5%)

**Table 2:** Frequency of prolactinoma in pregnant females.

Total Patients	200 (100%)
Prolactinoma present	40 (20%)
Prolactinoma absent	160 (80%)

prolactin level and confirmed on magnetic resonance imaging (Table 2).

**Table 3:** Change in serum prolactin level and tumor size after treatment (n = 40).

(i) Medical Treatment	Frequencies (%)
Bromocriptine	13 (32.5%)
Cabergoline	27 (67.5%)
(ii) Prolactin Levels and Tumor Size	Mean $\pm$ SD
Serum prolactin level (ng/ml) at presentation	$138.91 \pm 149.02$
Serum prolactin level (ng/ml) after delivery	$21.38 \pm 9.80$
Tumor size at presentation	$7.23 \pm 2.07$
Tumor size after treatment	$0.79 \pm 0.66$
(iii) Tumor Outcome	Frequencies (%)
Spontaneous resolution of tumor	30 (75.0%)
Tumor remained present	10 (25.0%)

### DISCUSSION

The objective of the current study was to evaluate the prevalence of Prolactinomas and the occurrence of spontaneous resolution of Prolactinomas after pregnancy. The hormone known as prolactin is produced and released only by the lactotroph cells located in the anterior pituitary gland. The secretion rate of prolactin ranges from around 200 to 536 micrograms per day per square meter, whereas its half-life is estimated to be between 25 and 50 minutes. The metabolism of prolactin occurs mostly in the liver, accounting for 75% of its breakdown, while the remaining 25% is metabolized in the kidney. The typical baseline level of prolactin in women is around 13 ng/ml, whereas in males, it is approximately 5 ng/ml. The typical range for blood prolactin levels in the majority of labs is between 15 and 20 ng/ml.<sup>14</sup> Approximately 50% of individuals diagnosed with macroprolactinoma achieve remission after surgical intervention. In instances where tumors exhibit invasiveness, achieving full resection may be challenging, resulting in a limited success rate of prolactin normalization among patients, estimated at

around 32%. Moreover, the recurrence rate for such cases stands at approximately 19%.<sup>11</sup>

The primary function of prolactin in animals is the control of breastfeeding. Prolactin, an endocrine hormone, is primarily produced and released by lactotroph cells located in the anterior pituitary gland. The process of prolactin signaling is mediated by a distinct transmembrane receptor specific to prolactin.<sup>15</sup>

In the present investigation, the prevalence of prolactinoma among pregnant women exhibiting symptoms such as headache and impaired vision was determined to be 20%. These individuals had an average serum prolactin level of  $138.91 \pm 149.02$  ng/ml at enrolment, which subsequently decreased to  $21.38 \pm 9.80$  ng/ml during 40 days after delivery. The average tumor size at first examination was  $7.23 \pm 2.07$  mm, and this measurement decreased to  $0.79 \pm 0.66$  mm during the delivery process. Among a sample size of 40 female individuals, it was observed that 30 individuals, accounting for 75.0% of the total, had spontaneous resolution.

According to a research study conducted at Shaukat Khanum Cancer Memorial Hospital, it was observed that the average levels of prolactin reduced significantly from an initial value of 3162.8 ng/ml to a final value of 1.52 ng/ml. A significant reduction in tumor size was seen via the implementation of medical intervention, as shown by a drop in mean adenoma size from 2.18 cm to 1.04 cm. The administration of cabergoline resulted in a biochemical cure rate of 83.3%, but bromocriptine exhibited a lower rate of 60.4%. The observed radiological response rates in the groups treated with cabergoline and bromocriptine were 65.45% and 60%, respectively. Thirteen individuals exhibited complete remission of adenoma, with nine cases involving microadenomas, two cases involving macroadenomas, and two cases involving gigantic adenomas.<sup>16</sup>

In a research study done by Laway et al., it was shown that out of a sample of 25 pregnant

women diagnosed with prolactinoma and treated with cabergoline throughout pregnancy, 41.6% achieved remission, indicated by the normalization of prolactin levels during pregnancy and/or breastfeeding. Among a cohort of women, it was observed that a reduction in adenoma size above 50% occurred in 25% of cases. In 33% of cases, no change in adenoma size was seen, while in 42% of cases, the drop in adenoma size was less than 50% after pregnancy and/or breastfeeding. The length of cabergoline medication before pregnancy among patients who attained remission was found to be 60 months, while those who did not reach remission had a median treatment duration of 24 months. The women who had remission showed, a median pre-pregnancy adenoma size of 5.5 mm, but the median pre-pregnancy adenoma size was seen to be 8 mm in women who did not achieve remission.<sup>9</sup>

Multiple case studies and case series were conducted in the 1980s which showed a positive impact of pregnancies on prolactinomas. These studies have shown that pregnancies led to decreased tumor size and a return to normal serum prolactin levels after birth.<sup>13</sup> Of the 76% of individuals with non-tumoral hyperprolactinemia had a remission in pregnancy, 70% of patients with microprolactinomas had remission while 64% of patients with macroprolactinomas had remission after pregnancy. Patients of macroprolactinomas and microprolactinomas with visible tumors on MRI have a higher risk of recurrence.<sup>17</sup> A 10-year survey carried out in 2013 has shown that individuals with non-tumoral hyperprolactinemia achieved a remission rate of 100%. The patients with microprolactinomas exhibited a remission rate of 66%, and the patients with macroprolactinomas achieved a remission rate of 70%. The precise processes responsible for this phenomenon remained unknown; however, it is hypothesized that the autoinfarction of the tumor is the primary contributing factor.<sup>18</sup>



The dopamine agonists are the preferred therapeutic approach for prolactinomas, owing to their ability to reduce tumor size and reduction in the prolactin level. Those patients who are exhibiting resistance or intolerance to dopamine agonist treatment are reserved for surgery. Radiation is used only in cases where the patient shows resistance to dopamine agonists and surgical intervention has also proven ineffective.<sup>19</sup>

Since the approval of Cabergoline as a dopamine agonist in 1985, it was preferred over Bromocriptine. Its superior performance in suppressing prolactin levels and reducing tumor size. Its treatment potential has been shown in patients who have shown resistance to Bromocriptine.<sup>20</sup> A cohort of 40 women diagnosed with prolactinoma was examined. Out of which 13 women (32.5%) were treated with Bromocriptine, while 27 women (67.5%) were given Cabergoline. Research conducted on a sample of 2,587 pregnant women revealed that among them, 2,437 were found to possess factors that increased the likelihood of experiencing spontaneous abortion, congenital abnormalities, or multiple pregnancies. However, these factors did not have any considerable impact on the development of the infants after birth.<sup>21</sup> In a study, a cohort of 6,329 patients who received Bromocriptine during the first half of pregnancy were evaluated. The study showed that the incidence of spontaneous abortions in this group was 9.9%, which is comparable to the rate seen in the general community (10.9%).<sup>22, 23</sup>

## CONCLUSION

The findings of this study suggest that the prevalence of prolactinoma is low in patients having symptoms, and in most cases, there was pregnancy-induced remission. Our research concluded that the prevalence of prolactinoma is low in our local population and also established the safety of dopamine agonists in the treatment of prolactinoma during pregnancy. However, it is

recommended that further research should be undertaken to examine the impact of dopamine agonists on fetal outcomes.

## REFERENCES

1. Chanson P, Maiter D. The epidemiology, diagnosis and treatment of Prolactinomas: The old and the new. *Best practice & research Clinical endocrinology & metabolism*. 2019;33(2):101290.
2. Jin Y, Fan M. Treatment of gynecomastia with prednisone: case report and literature review. *The Journal of international medical research*. 2019;47(5):2288-95.
3. Woodmansee WW. Pituitary disorders in pregnancy. *Neurologic clinics*. 2019;37(1):63-83.
4. Chrisoulidou A, Boudina M, Karavitaki N, Bill E, Wass J. Pituitary disorders in pregnancy. *Hormones*. 2015;14(1):70-80.
5. Li H, Huang Y, Li Y, Zheng B, Cui J, Liu M. Endocrine Manifestations in POEMS Syndrome: a case report and literature review. *BMC endocrine disorders*. 2019;19(1):33.
6. Valassi E. Pituitary disease and pregnancy. *Endocrinología, Diabetes y Nutrición (English ed)*. 2021;68(3):184-95.
7. Nagaishi VS, Cardinali LI, Zampieri TT, Furigo IC, Metzger M, Donato Jr J. Possible crosstalk between leptin and prolactin during pregnancy. *Neuroscience*. 2014;259:71-83.
8. Yip SH, Romano N, Gustafson P, Hodson DJ, Williams EJ, Kokay IC, et al. Elevated prolactin during pregnancy drives a phenotypic switch in mouse hypothalamic dopaminergic neurons. *Cell reports*. 2019;26(7):1787-99. e5.
9. Laway BA, Baba MS, Bansiwal SK, Choh NA. Prolactinoma Outcome After Pregnancy and Lactation: A Cohort Study. *Indian Journal of Endocrinology and Metabolism*. 2021;25(6):559.
10. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism*. 2011;96(2):273-88.
11. Thapa S, Bhusal K. Hyperprolactinemia. 2019.
12. Araujo B, Belo S, Carvalho D. Pregnancy and tumor outcomes in women with prolactinoma.

- Experimental and Clinical Endocrinology & Diabetes. 2017;125(10):642-8.
13. Rastogi A, Bhadada SK, Bhansali A. Pregnancy and tumor outcomes in infertile women with macroprolactinoma on cabergoline therapy. *Gynecological Endocrinology*. 2017;33(4):270-3.
  14. Chahal J, Schlechte J. Hyperprolactinemia. *Pituitary*. 2008;11(2):141-6.
  15. Bernard V, Young J, Binart N. Prolactin – a pleiotropic factor in health and disease. *Nature reviews Endocrinology*. 2019;15(6):356-65.
  16. Irfan H, Shafiq W, Siddiqi AI, Ashfaq S, Attaullah S, Munir Alvi A, et al. Prolactinoma: Clinical Characteristics, Management and Outcome. *Cureus*. 2022;14(10):e29822.
  17. Colao A, Di Sarno A, Cappabianca P, Di Somma C, Pivonello R, Lombardi G. Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. *New England Journal of Medicine*. 2003;349(21):2023-33.
  18. Auriemma RS, Perone Y, Di Sarno A, Grasso LF, Guerra E, Gasperi M, et al. Results of a single-center observational 10-year survey study on recurrence of hyperprolactinemia after pregnancy and lactation. *The Journal of Clinical Endocrinology & Metabolism*. 2013;98(1):372-9.
  19. Almalki MH, Alzahrani S, Alshahrani F, Alsherbeni S, Almoharib O, Aljohani N, et al. Managing Prolactinomas during Pregnancy. *Frontiers in Endocrinology*. 2015;6.
  20. Shahzad H, Sheikh A, Sheikh L. Cabergoline therapy for macroprolactinoma during pregnancy: a case report. *BMC research notes*. 2012;5(1):1-4.
  21. Webster J. A comparative review of the tolerability profiles of dopamine agonists in the treatment of hyperprolactinaemia and inhibition of lactation. *Drug safety*. 1996;14:228-38.
  22. Andersen A-MN, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. *Bmj*. 2000;320(7251):1708-12.
  23. Gillam MP, Molitch ME, Lombardi G, Colao A. Advances in the treatment of prolactinomas. *Endocrine reviews*. 2006;27(5):485-534.

## Additional Information

**Disclosures:** Authors report no conflict of interest.

**Ethical Review Board Approval:** The study conformed to the ethical review board requirements.

**Human Subjects:** Consent was obtained by all patients/participants in this study.

### Conflicts of Interest:

In compliance with the ICMJE uniform disclosure form, all authors declare the following:

**Financial Relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

**Other Relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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### **AUTHORS CONTRIBUTION**

<b>S. No.</b>	<b>Author's Full Name</b>	<b>Intellectual Contribution to Paper in Terms of:</b>
1.	Shirin Gul Suhail	Study design and methodology.
2.	Rizwan Ahmad Khan	Literature review and referencing.
3.	Omair Afzal	Final review and approval.
4.	Shirin Gul Suhail	Data collection and calculations.
5.	Zahra Safdar	Interpretation of results.
6.	Uzma Zia	Analysis of data.