

**How to Cite:**

Idham, M., Hutajulu, R. B., & Novida, H. (2022). Management of a prolactinoma patient with manifestations of amenorrhea and infertility. *International Journal of Health Sciences*, 6(S6), 10492–10500. <https://doi.org/10.53730/ijhs.v6nS6.12853>

# Management of a prolactinoma patient with manifestations of amenorrhea and infertility

**Muhammad Idham**

Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga – Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

**Reynaldo Binsar Hutajulu**

Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga – Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

**Hermina Novida**

Division of Endocrinology, Metabolism and Diabetes, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga – Dr. Soetomo General Academic Hospital Surabaya, Indonesia

\*Corresponding author email: [hermina.n@fk.unair.ac.id](mailto:hermina.n@fk.unair.ac.id)

**Abstract**--Prolactinoma is an adenoma arising from the lactotroph cells of the pituitary gland that secrete prolactin. It is considered the most commonly diagnosed pituitary tumor and accounts for about 40% of all pituitary tumors. This study discusses a female patient suffering from prolactinoma with manifestations of amenorrhea and infertility. According to an MRI examination, the patient had a tumor with signs of apoplexy measuring  $\pm 2.7 \times 1.5 \times 1.9$  cm in the intrasellar, extending to the suprasellar. On the other hand, an examination indicated that the prolactin serum level of the patient was  $> 200$  ng/ml (increased). The patient had consulted a neurosurgeon for consideration of surgery due to the large size of the prolactinoma, but the patient temporarily refused surgery.

**Keywords**--prolactinoma, amenorrhea, infertility.

**Introduction**

Prolactinoma is an adenoma arising from lactotroph cells in the pituitary gland that secrete prolactin, and are considered the most frequently diagnosed type of pituitary tumor and account for approximately 40% of all pituitary adenomas. The prevalence and incidence of prolactinoma are 50 per 100,000 population and 3 to 5 new cases per 100,000 population per year. More than 90% of cases are small tumors confined to the *sella turcica*. In some cases, a prolactinoma can enlarge

into a pituitary macroadenoma that causes symptoms of neurological deficits and endocrinological disorders (Almalki et al., 2015; Chanson & Maiter, 2019).

Prolactinoma causes a wide variety of symptoms either due to the mass effect of the tumor or the hypersecretion of prolactin. Based on the tumor size, prolactinoma can be classified as macroprolactinoma (smaller than 10 mm), macroprolactinoma (larger than 10 mm), or giant prolactinoma (larger than 4 cm) (Pekic et al., 2019; Cooper & Greenman, 2018). The most common symptoms of prolactinoma in premenopausal women are amenorrhea and infertility. Galactorrhea occurs in approximately 80% of women of childbearing age. Menstruation can be normal or oligomenorrhea occurs. Endocrinological symptoms such as impotence, infertility, and decreased libido are also common (Carter et al., 1978; Nassiri et al., 2012).

Treatment decisions depend on the size of the tumor, the presence or absence of gonadal dysfunction, and the patient's wishes regarding infertility. The primary therapy for all prolactinomas is the dopamine agonist. The two commonly administered drugs include bromocriptine and cabergoline. The most common surgical approach is transsphenoidal surgery. External radiotherapy is performed in the event of a residual tumor after surgery (Schlechte, 2003; Duff et al., 2001). Prolactinoma therapy has four objectives: lowering prolactin levels and reversing clinical signs, reducing tumor size, restoring gonadal function and other pituitary hormone deficiencies, and preventing tumor recurrence and progression (Rabinovich et al., 2013). The following section reports the management of a prolactinoma patient with manifestations of amenorrhea and infertility.

## **Case**

A case of prolactinoma with manifestations of amenorrhea and infertility occurred in a female patient with the initials M, 30 years old, Javanese, Muslim, working as a waitress at Pizza Hut, and domiciled at Pulo Wonokromo, Surabaya. The patient came to the Internal Medicine Polyclinic of Universitas Airlangga Hospital with a complaint of not having menstruation for one year. The patient initially complained of irregular menstruation and then went to a midwife for a pregnancy program and was given medicine. When the patient took the medicine, the patient had menstruation, but a month after the patient stopped taking it, the patient did not menstruate at all until now. The patient had underwent a pregnancy test but the result was negative. In December 2020, the patient had a motorcycle accident and was hit by a car, but only her hands and feet were blistered. The patient was conscious and wearing a helmet. The patient also complained that her vision began to be impaired on the external side vision and only in the left eye. In February 2021, the patient complained of intermittent impairment in her vision. Her external side vision was impaired, and only in the left eye. In March 2021, the patient went to the Wonokromo Health Center and was then referred to the Eye Polyclinic of Jemursari Islamic Hospital. The results of the head MRI at the Eye Polyclinic of Universitas Airlangga Hospital indicated that the patient had a tumor, and she was suggested to undergo surgery by the Neurosurgery Polyclinic.

The patient had intermittent headaches since the traffic accident. Sometimes she felt nauseous but no vomiting. The patient also complained of frequent nasal

congestion at night for the last six months. The patient also complained of nipple discharge in both breasts over the last year. The patient also complained that the vagina felt dry during sexual intercourse. She also had back pain for the last six months. She experienced no decrease in her libido. There were no complaints of difficulty opening her eyes or double vision, no complaints of thick or painful facial areas, and no complaints of a runny nose. There were no complaints of changes in the size of the hands and feet, rough facial skin, protrusion of the forehead, and changes in her voice. She experienced no weight gain and no excess hair growth.

The patient denied having a history of previous diseases such as hypertension, diabetes mellitus, stroke, heart disease, and allergies. However, the patient had a history of hospitalization for typhoid and dengue fever ten years ago. Prior to the previous year, the patient's menstrual cycle was always on time, with a cycle of 28 days ranging from 6 to 8 days, and no pain during menstruation. The patient also revealed that she had never underwent any contraception method. Then, regarding the history of inherited diseases, no family member of the patient suffered from the same disease as the patient. The patient lived with her husband who did not smoke. Regarding the history of drug use, the patient had routinely taken the Cripsa drug from the Endocrinology Polyclinic of Dr. Soetomo Hospital.

The physical examination showed that the patient's blood pressure was 120/80 mmHg with 88x pulses/minute, a regular rhythm, lifting strength, and normal amplitude. The cardiac examination indicated that the heart border was not dilated. S1 and S2 heart sounds were single, regular, and without heart murmurs, gallop rhythm, or pericardial friction. The lung examination signified resonant percussion and vesicular breath sounds in the left and right hemithorax, and no crackles or wheezing were found. The abdominal examination revealed a flat stomach, normal bowel sounds, no striae, no palpable mass, and no enlargement of the liver and spleen, while the extremity examination revealed warm dry red acral, and a capillary refill time of fewer than 2 seconds.

According to the laboratory examination conducted at the Universitas Airlangga Hospital, the prolactin level was >200 ng/ml, the FT4 level was 1.07 ng/dl, the TSHs level was 1.21 iu/ml, the cortisol level was 53.8 g/24 hours. The results of the MRI examination of the head with and without contrast (Figure 1) showed a solid mass, extra axial, with a cystic component and internal bleeding, with clear boundaries and regular edges, with a size of  $\pm 2.7 \times 1.5 \times 1.9$  cm in intrasellar extending to the suprasellar with ballooning sellar, and protrudes to the sphenoid sinus which appeared isointense on T1W1, slightly hyperintense on T2W1, restricted diffusion in the solid component, signal drop in the GRE, which on contrast enhancement showed contrast enhancement in the solid component, a mass pressing against the chiasma was found right and left opticum to the superior side, no R/L ICA encasement was found, and no normal pituitary appearance was found. Conclusion: Pituitary macroadenoma with signs of apoplexy measuring  $\pm 2.7 \times 1.5 \times 1.9$  cm in the intrasellar extending to the suprasellar (According to Hardy's Classification Grade IV), and no aneurysms/vascular malformations were found.



Figure 1. Head MRI examination with contrast

Based on the history, physical examination, investigations, and consultation with the relevant departments, the patient was diagnosed with pituitary macroadenoma (prolactinoma) + secondary amenorrhea + infertility + impaired visual field pro evaluation. Planning diagnosis is monitoring prolactin levels and MRI of the head after medical therapy. The treatment was performed by administering bromocriptine 1 x 2.5 mg for one month, increased to 1 x 5 mg for the next one month.

### Disease Course

On June 8, 2021, the patient came to the Endocrine Polyclinic of Dr. Soetomo General Hospital. The patient was previously given bromocriptine at Universitas Airlangga Hospital, but the patient did not take it regularly because the medicine she bought herself was expensive. The patient said that she still had not menstruated and still experienced nipple discharge, and intermittent headaches, but her vision began to improve. The patient was planned for the administration of bromocriptine 1 x 2.5 mg for 1 month, followed by prolactin level checking and consultations with an ophthalmologist and neurosurgeon. On June 17, 2021, the patient came to the Neurosurgery Polyclinic of Dr. Soetomo General Hospital with complaints of intermittent headaches, and nipple discharge. The patient had not menstruated, but she experienced improved vision.

The results of the consultation with a neurosurgeon: it is recommended to evaluate prolactin levels after bromocriptine administration. If the bromocriptine levels fall 50% with the maximum dose, non-operative management is recommended, and a visual field examination is suggested. On July 8, the patient came to the Endocrine Polyclinic of Dr. Soetomo General Hospital with complaints that she had not menstruated but had no intermittent headaches and nipple discharge, and her vision improved significantly. The patient was planned to

undergo a head MRI and prolactin check next month for evaluation of therapy. On August 21, the patient came to the Endocrine Polyclinic of the Dr. Soetomo General Hospital with complaints of occasional abdominal cramps and difficulty in defecating. The patient had not menstruated but had no intermittent headaches and nipple discharge, and experienced improved vision.

On October 7, the patient came to the Endocrine Polyclinic of Dr. Soetomo General Hospital with no complaints of impaired vision. The patient still had not menstruated but experienced no intermittent headaches and nipple discharge. On October 19, the patient went to the Endocrine Polyclinic of Dr. Soetomo General Hospital for laboratory examination with the results of serum prolactin level of 469.9 uIU/ml, FT4 level of 1.27 ng/dl, TSH level of 0.617 uIU/ml, FSH level of 4.15 mIU/ml, LH level of 3.79 mIU/ml.

### **Discussion**

Primary amenorrhea is defined as the lifetime absence of menstruation, requiring evaluation if menarche has not occurred by the age of 15 years or three years post-thelarche. Secondary amenorrhea is characterized by the cessation of menstruation that was previously regular for three months or menstruation that was previously irregular for six months and requires evaluation. The differential diagnosis of amenorrhea is outflow tract disorders, primary ovarian insufficiency, hypothalamic or pituitary disorders, other endocrine gland disorders, and sequelae of chronic, physiological, or induced diseases (Klein et al., 2019). The anamnesis of the patient should include menstrual onset and pattern, eating and exercise habits, presence of psychosocial stressors, weight changes, drug use, galactorrhea, and chronic illness. Additional questions should target neurologic, vasomotor, hyperandrogenic, or thyroid-related symptoms. Physical examination should identify anthropometric and pubertal developmental trends. All patients should undergo a pregnancy test and assessment of FSH, LH, prolactin, and TSH hormone levels (Klein et al., 2019).

The patient complained of not having children since 2016 even though the patient had been sexually active without contraception since 2016. Based on the anamnesis, physical examination, laboratory examination, and radiological examination, the patient was diagnosed as having a pituitary macroadenoma (prolactinoma). There are three categories of pituitary adenoma based on their size through MRI imaging, namely microadenoma (with a diameter of less than 1 cm), macroadenoma (with a diameter of 1-4 cm), and giant adenoma (with a diameter of more than 4 cm) (Cecilia & Hidayati, 2021). Prolactinoma is usually of concern because the symptoms or signs are associated with hyperprolactinemia or with tumor size or tumor invasion. Table 2 below presents the signs and symptoms of prolactinoma related to tumor mass, namely the suppression effect and associated with high serum prolactin levels (Melmed, 2021).

Table 2  
Prolactinoma Signs and Symptoms (Melmed, 2021)

<b>Associated with tumor mass</b>	<b>Associated with hyperprolactinemia</b>
Impaired visual field	Amenorrhea, oligomenorrhea, infertility

Blurred vision or decreased visual acuity Hypopituitarism Symptoms Headache Cranial nerve paralysis Pituitary apoplexy Seizure (temporal lobe) Hydrocephalus (infrequent) Unilateral exophthalmos (infrequent)	Decreased libido, impotence, premature ejaculation, oligospermia Galactorrhea Osteoporosis
---	--

The optimal treatment for prolactinomas is normal prolactin levels and complete tumor removal or shrinkage with reversal of the mass effect of the tumor. In particular, previously abnormal sexual and fertility functions should be restored, galactorrhea discontinued, impaired bone density improved, tumors removed or reduced in size without interfering with pituitary or hypothalamic function, and vision normalized, if impaired. Medical management of prolactinoma with dopamine agonist drugs has been widely recommended as the treatment of choice. Bromocriptine, a semisynthetic ergot alkaloid dopamine agonist, reduces elevated prolactin levels, restores abnormal menstrual function in 80-90% of patients, shrinks prolactinomas, reverses impaired sexual function, and treats galactorrhea. Bromocriptine shrinks prolactinomas by shrinking the size of tumor cells, including the cytoplasm, nucleus, and nucleolar area. Histological sections appear very dense as a result of the small cell size and nuclear agglomeration. Prolactin mRNA is synthesized and prolactin is inhibited, exocytosis is reduced, PRL secretory granules are reduced, and the rough endoplasmic reticulum and Golgi apparatus undergo involution. The end result is reduced cell volume, and tumor necrosis can also occur. The initial dose is 1.25 mg daily, increased gradually, until it can be tolerated, or decreased depending on the tolerability of the patient, and should be administered in a small initial dose with food before bedtime (Melmed, 2021).

In addition, the patient was also diagnosed with secondary amenorrhea. Secondary amenorrhea is caused by an adenoma, evaluation of gynecological organs within normal limits. Infertility is defined as failure to achieve pregnancy within twelve months after unprotected sexual intercourse or therapeutic donor insemination in women under the age of 35 years or within six months in women over 35 years (The American College of Obstetricians and Gynecologists, 2019). The patient was also diagnosed with primary infertility based on her anamnesis, physical examination, laboratory examination, and radiological examination. Infertility is divided into primary and secondary infertilities. Primary infertility is when a person has never achieved a pregnancy, and secondary infertility is when at least one previous pregnancy has been achieved (WHO, 2021). Infertility can be caused by several factors, including male factors, ovulatory dysfunction, uterine abnormalities, tubal obstruction, peritoneal factors, or cervical factors.

Anamnesis and physical examination can help guide the evaluation. Figure 2 describes the infertility evaluation algorithm. Men should undergo evaluation with sperm analysis. Ovulation should be documented by measuring the serum progesterone level on day 21 of the menstrual cycle. Evaluation of the uterus and fallopian tubes can be performed by hysterosalpingography in women without the

risk of obstruction. For patients with a history of endometriosis, pelvic infection, or ectopic pregnancy, hysteroscopy or laparoscopy is recommended (Lindsay & Vitrikas, 2014).

This patient was initially treated with bromocriptine at a dose of 2.5 mg every 24 hours for four weeks, followed by a dose of 2.5 mg every 12 hours for four weeks, then a dose of 2.5 mg every 8 hours until now. Cabergoline therapy was not used in this case. Cabergoline has a longer duration of action than bromocriptine and is usually administered once or twice a week. Cabergoline's long half-life results from its high affinity for the lactotroph D2 receptor and the greater tendency of the drug to remain in the pituitary tissue. It is also more effective than bromocriptine in restoring ovulation cycles and fertility, and is better tolerated than bromocriptine. Cabergoline can also produce significant improvement from prolactinoma-related headaches. The initial dose is 0.25 mg once a week. The dose can be increased gradually if well tolerated, and can be decreased according to the patient's tolerability, and should also be taken with food before bedtime. Cabergoline is considered superior to bromocriptine as first-line therapy for most patients unless the pregnancy is desired. Therefore, the patient was not given cabergoline therapy (Melman, 2021).



Figure 2. Post Optimal Prolactinoma Therapy

Linear accelerator radiotherapy is effective in controlling or reducing the size of prolactinomas. However, this therapy takes years to achieve maximum effect. The recommended radiation dose is 4,500 to 4,600 cGy, and normalization of prolactin was achieved in 18 of 36 patients with an average of 7.3 years after treatment. Hypopituitarism occurs as a side effect of radiation. Therefore, this patient was not given radiotherapy (Melman, 2021). Endoscopic transsphenoidal endonasal surgery has been utilized for macroadenoma resection (Destiansyah et al., 2022; Nabilah et al., 2022). Most patients with microprolactinomas have normalized prolactin levels and approximately 50% of patients with macroprolactinomas go into remission after surgery. The success rate is determined by the experience of the surgeon and is inversely correlated with tumor size and prolactin serum concentration (Ummah & Adi, 2021). However, a high recurrence rate of hyperprolactinemia is commonly encountered postoperatively. Complete resection of macroprolactinomas, especially for large invasive tumors, is difficult to achieve and postoperative prolactin serum levels

are normal in only 32% of patients, with a recurrence rate of 19-45%. Although the results of medical therapy are superior to surgery, there is still a role for surgery, especially in those who are resistant to dopamine agonist therapy. If the tumor is only partially removed, additional radiation therapy may be considered, as a second surgery is usually associated with a higher complication rate. Prophylactic transsphenoidal surgery should be considered in women whose prolactinomas are large enough to threaten vision during pregnancy (Melmed, 2021). Accordingly, surgery was considered for the patient because of the large size of the prolactinoma, visual impairment, and impairment due to compression of the prolactinoma. However, surgery could not be performed because the patient temporarily refused surgery.

## **Conclusions**

According to the case of the young woman with a pituitary macroadenoma (prolactinoma) and clinical manifestations of secondary amenorrhea and primary infertility, the clinical presentations in this patient include no menstruation, have not had children, impaired vision, headache, infrequent nausea, nasal congestion at night, nipple discharge from both breasts, vaginal dryness during sexual intercourse, and back pain. The visual field examination indicated an impaired visual field. The MRI revealed a pituitary macroadenoma. Therefore, the patient was diagnosed with pituitary macroadenoma with secondary amenorrhea and primary infertility. As a follow-up, the patient was treated with bromocriptine pharmacological therapy.

## **Acknowledgement**

We offer our gratitude to the staff, doctors, nurses, and administrators for giving us the necessary permission and support to conduct this study.

## **Conflict of Interest**

The authors declare there is no conflict of interest in this study.

## **References**

- Carter, J. N., Tyson, J. E., Tolis, G., Van Vliet, S., Faiman, C., & Friesen, H. G. (1978). Prolactin-screening tumors and hypogonadism in 22 men. *The New England journal of medicine*, 299(16), 847–852. <https://doi.org/10.1056/NEJM197810192991602>
- Cecilia, C., & Hidayati, H. B. (2021). A comprehensive approach in pituitary adenoma management. *International Medical Journal*, 28(3), 289-292.
- Cooper, O., & Greenman, Y. (2018). Dopamine Agonists for Pituitary Adenomas. *Frontiers in endocrinology*, 9, 469. <https://doi.org/10.3389/fendo.2018.00469>
- Destiansyah, R. A., Savitri, C. M. A., Wisnawa, I. W. W., Susilo, R. I., Wahyuhadi, J., & Haq, I. B. I. (2022). Remote extradural hematoma as a complication of endoscopic transsphenoidal surgery: A case report with literature review. *International Journal of Surgery Case Reports*, 96, [107341]. <https://doi.org/10.1016/j.ijscr.2022.107341>



- Duff, J. M., Dietrich, P. I., and de Tribolet, N. (2001). Current therapy for primary brain tumor. In: *Brain Tumor Immunotherapy*. Editors: Liau LM, Becker DP, Cloughesy TI, Bigner DD. Totowa, New Jersey: Humana Press. p.73 – 90.
- Klein, D. A., Paradise, S. L., & Reeder, R. M. (2019). Amenorrhea: A Systematic Approach to Diagnosis and Management. *American family physician*, 100(1), 39–48.
- Lindsay, T. J., & Vitrikas, K. R. (2015). Evaluation and treatment of infertility. *American family physician*, 91(5), 308–314.
- Melmed, S. (2020). Pituitary Masses and Tumors. In: *Williams Textbook of Endocrinology 14th edition*. Philadelphia: Elsevier. 236-302.
- Nabilah, Wibisono, S., Libriansyah, Wahyuhadi, J., & Arifianto, M. R. (2022). Diagnostic problems and management of pituitary gigantism leading to ischemic stroke and atrial myxoma in young adult patient: a case report. *Bali Medical Journal*, 11(1), 238-240. <https://doi.org/10.15562/bmj.v11i1.3171>
- Nassiri, F., Cusimano, M. D., Scheithauer, B. W., Rotondo, F., Fazio, A., Syro, L. V., Kovacs, K., & Lloyd R. V. (2012). Prolactinomas: diagnosis and treatment. *Expert Review of Endocrinology & Metabolism*, 7(2), 233-241. DOI: 10.1586/eem.12.4
- Pekic, S., Soldatovic, I., Miljic, D. (2019). Familial Cancer Clustering in Patients with Prolactinoma. *HORM CANC* 10, 45–50. <https://doi.org/10.1007/s12672-018-0348-3>
- Rabinovich, I. H., Gomez, R. C., Mauriz, M. G. (2013). Clinical guidelines for diagnosis and treatment of prolactinoma and hyperprolactinemia. *Endocrinol Nutr.* 60(6), 308-319. Doi: 10.1016/j.endoen.2012.11.009
- Schlechte J. A. (2003). Clinical practice. Prolactinoma. *The New England journal of medicine*, 349(21), 2035–2041. <https://doi.org/10.1056/NEJMcp025334>
- The American College of Obstetricians and Gynecologists . (2019). Infertility Workup for the Women's Health Specialist: ACOG Committee Opinion, Number 781. *Obstetrics and gynecology*, 133(6), e377–e384. <https://doi.org/10.1097/AOG.0000000000003271>
- The American College of Obstetricians and Gynecologists, 2019. Infertility Workup for the Women's Health Specialist. *Obstet Gynecol.* 133(6): e377-e384. Doi: 10.1097/AOG.0000000000003272
- Ummah, K., & Adi, S. (2021). Management Of Residual Pituitary Adenoma Patient With Manifestation of Acromegaly and Hyperprolactinemia. *Current Internal Medicine Research and Practice Surabaya Journal*, 2(2), 49–55. <https://doi.org/10.20473/cimrj.v2i2.26284>
- World Health Organization. (2020). Infertility. [Online] Available from: <https://www.who.int/news-room/fact-sheets/detail/infertility>.