Invited Review
Turk J Endocrinol Metab 2018;22:54-56

Review of Clinical Recommendations on Prolactinoma and Pregnancy

Prolaktinoma ve Gebeliğe Dair Klinik Önerilerin Gözden Geçirilmesi

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Abstract

Prolactinomas are the most common hormone-secreting pituitary adenomas. Prolactinomas account for nearly 30–40 percent of all the pituitary adenomas. Although it affects individuals over a wide age range, it is more common in 20–40-year-old female patients, who are in their reproductive age. Prolactinomas may cause hypogonadism, menstrual cycle dysfunction (oligomenorrhea or amenorrhea) and infertility (luteal phase abnormalities or anovulation) in premenopausal women. When pregnancy is excluded, hyperprolactinemia in approximately 10 to 20 percent of the patients results in amenorrhea. Women with untreated prolactinomas are generally unable to achieve pregnancy, as the hyperprolactinemia affects the pulsatility of gonadotropin-releasing hormone (GnRH) and diminishes follicle-stimulating hormone (FSH) as well as luteinizing hormone (LH) secretion. The sum of these effects induces amenorrhea, infertility, and hypogonadism, thereby posing difficulties in fertility. Therefore, in most women prolactinoma is diagnosed prior to conception. However, ovulation and fertility usually improve after proper diagnosis and treatment of prolactinoma. Therefore, during the surveillance of these patients, the onset of pregnancy is a common phenomenon. Management of these pregnancies may sometimes be challenging and require a multidisciplinary approach involving an endocrinologist, a gynecologist, a radiologist and an experienced neurosurgeon in order to achieve the best outcomes both for the patient as well the infant. In this report, the authors aim to summarize the consensus statements and the current guidelines for clinical practice.

Keywords: Prolactinoma; pregnancy; dopamine agonists

Özet

Prolaktinomalar en sık görülen fonksiyonel hipofiz adenomları olup tüm hipofiz adenomlarının yaklaşık %30-40 kadarını oluşturmaktadır. Her yaşta görülebilmekle birlikte 20-40 yaşları arasındaki üreme çağındaki kadınlarda daha sık ortaya çıkmaktadırlar. Prolaktinomada klinik tablo prolaktin düzeylerinin yüksekliği ile ilişkili olup galaktore ve gonadal fonksiyonlar üzerindeki sekonder etkiler sonucu ortaya çıkmaktadır. Premenapozal kadınlarda hipogonadizm, menstruel siklus bozuklukları (oligomenore ya da amenore) ve infertilite (luteal faz defekti ya da anovulasyon) ile prezente olabilmektedir. Hiperprolaktinemi, gebelik olmaksızın gelişen amenore nedenlerinin yaklaşık %10-20 kadarını oluşturmaktadır. Yüksek serum prolaktin düzeyleri, gonadotropin salgılatıcı hormon düzeylerini baskılayarak luteinizan hormon (LH) ve follikül stimulan hormon (FSH) salgısını azaltarak menstruel siklus düzensizlikleri ve hipogonadizme neden olduğundan tedavi edilmeyen prolaktinomalı kadınlarda genellikle fertilitede azalma söz konusudur. Bu nedenle prolaktinoma hastalarında tanı, gebelik öncesi fertilite tetkikleri sırasında da konulabilmekte olup çoğunlukla konsepsiyon öncesinde ortaya çıkmaktadır. Ancak prolaktinomanın doğru tanı ve tedavisi sonrası genellikle ovulasyon ve fertilite düzeldiğinden, prolaktinoma hastalarının takipleri sırasında gebelik gelişimi de nadir rastlanılan bir durum değildir. Sonuç olarak prolaktinoma tedavisi sırasında araya giren gebeliklerin yönetimleri sırasında bir takım zorluklarla karşılaşılabileceğinden endokrinolog, jinekolog, radyolog ve tecrübeli bir beyin cerrahisi uzmanı tarafından multidisipliner bir yaklaşımla ele alınmaları önerilmektedir. Bu derlemede mevcut klinik kılavuzlar ve konsensus önerilerinin ışığında prolaktinoma ve gebelik konusundaki güncel yaklaşımlar özetlenmektedir.

Anahtar kelimeler: Prolaktinoma; gebelik; dopamin agonistleri

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DOI: 10.25179/tjem.2017-57578

Prolactinomas are the most common out of all the hormone-secreting pituitary adenomas. Women with untreated prolactinomas are not able to achieve pregnancy, as the hyperprolactinemia affects the pulsatility of GnRH, diminishes FSH and LH secretion and induces amenorrhea, infertility, and hypogonadism, thereby posing difficulties in fertility (1). For this reason, in most cases, prolactinoma is diagnosed prior to conception. Nevertheless, ovulation and fertility are normally improved by proper diagnosis and treatment. As a result, prolactinomas in a pregnant woman are certainly challenging and require a multidisciplinary approach involving an endocrinologist, a gynecologist, a radiologist and an experienced neurosurgeon to achieve the best outcome. In this report, the authors aim to summarize the consensus statements and the current guidelines for clinical practice.

Guideline Recommendations Regarding Preconception Period in Patients with Prolactinomas

The risk of enlargement of a microprolactinoma during pregnancy is nearly 1.5–4.5% with symptomatic growth occurring in about 2% of the cases. However, the risk of symptomatic enlargement of a macroprolactinoma is greater than 15% (2, 3). The currently available dopamine agonists (DAs) include bromocriptine, cabergoline, and quinagolide (the latter is not approved for use in the United States). It should be noted that the restoration of ovulation, once DA therapy has been started, occurs even before normoprolactinemia is achieved and the patient should be informed about this outcome (4). In women who are treated before conception, DA may also induce shrinkage of the pituitary tumor (a reduction of greater than 25% is expected in the tumor size in around 70% of the patients) (5).

- Achieving a normalization of PRL levels and a tumor size <10 mm before conception is recommended for macroadenomas (6, 7).
- In women of childbearing age, the use of mechanical contraception should be advised once drug treatment has been initiated for macroadenomas. This is because ovulation and fertility may rapidly be recovered after the normalization of PRL levels (6, 8).
- Transsphenoidal adenomectomy may be an option for women with microadenoma or macroadenoma that is either intolerant or refractory to Das, or prepregnancy tumor debulking by surgery (thereby decreasing the risk of clinically significant enlargement during pregnancy) would be an option in cases of macroadenomas that do not decrease in size with DA treatment or in those who cannot tolerate bromocriptine or cabergoline (6, 8). Transsphenoidal surgery may also cause hypopituitarism, thus requiring the subsequent use of assisted reproduction techniques such as induction of ovulation with gonadotropins and lifelong hormone replacement therapy (6-9). It is for this reason that resumption of the DA is probably less harmful to the mother and the fetus as compared to surgery (6). Therefore, the teamwork of multidisciplinary specialists is required for the careful planning of pregnancy in women with prolactinoma. Ideally, this should arise before conception, so that a full assessment of the risks and benefits of DA therapy can be assessed during pregnancy (10).
- Whenever pregnancy is planned or detected in macroadenomas, cabergoline should be discontinued and bromocriptine should be introduced although this drug also crosses the placental barrier (6). Bromocriptine is the "oldest" of all the dopamine agonists and has been tested more extensively than the other compounds, but there is far less published experience with cabergoline (8). Therefore, bromocriptine has been shown to be safe for use during early gestation (up to the first four weeks after conception, a critical period for early organogenesis).
- In women with microprolactinomas who want to become pregnant, the use of clomiphene citrate or gonadotropin therapy is suggested when ovulation cannot be restored by DAs alone (6).

Guideline Recommendations Related to pregnancy in Patients with Prolactinoma

- Women with prolactinomas must be instructed to discontinue DA therapy as soon as they discover that they are pregnant (6-8, 10). In selected patients with macroadenomas who are on DA therapy and become pregnant and who have not had prior tumor debulking by surgery, it may be sensible to continue DA throughout the pregnancy, especially if the tumor is invasive or is abutting the optic chiasm (6, 8, 10).
- When symptomatic tumor growth occurs (presence of a headache or visual deterioration), treatment with bromocriptine should be restarted, if previously discontinued (6, 8). If the enlarged tumor does not respond to reinstitution with DA therapy within 2–3 weeks, transsphenoidal surgery (in the second trimester) or deliv-

ery (if the pregnancy is far enough) must be considered (6-8, 10).

- There is no evidence of increased teratogenicity associated with the use of bromocriptine or cabergoline during pregnancy (6, 8, 10). Quinagolide, on the other hand, has shown a poor safety profile in the relatively small number of pregnancies that have been reported, and it should not be prescribed to women who wish to become pregnant (8).
- In pregnant patients with prolactinomas, performing serum prolactin measurements during pregnancy is not recommended. This is for the reason that in normal pregnancy, serum prolactin levels increase 10-fold, reaching levels of 150 to 300 g/Liter by term (6-8).
- In general, microprolactinomas and macroprolactinomas that are localized to the sella do not undergo symptomatic growth during pregnancy, therefore the use of routine pituitary MRI during pregnancy is not recommended in these patients. Because the risk of symptomatic tumor growth is low, these patients may be followed up by clinical examination during each trimester, unless there is clinical evidence of tumor growth by symptoms such as headaches or visual deterioration (6-10). However, formal assessment of the visual fields in macroprolactinoma should be performed every three months or even more frequently if the adenoma prior to conception is close to the optic chiasm (8). When such clinical manifestations appear, imaging must be performed with unenhanced MRI. If the growth of the pituitary mass is identified, re-institution of DA (preferably bromocriptine) for the remainder of the pregnancy may provide a control over the tumor and in addition, monthly clinical assessment is required (including visual fields).Therefore, the onset of a new or a worsening headache, or a change in vision or both, mandates the urgent performance of formal visual field testing and a pituitary MRI without the use of gadolinium (6-8).

Guideline Recommendations Related to the Postpartum Period in Patients with Prolactinoma

- Women wishing to breastfeed their infants should not be given DA because the resulting decrease in serum PRL levels will impair lactation. There are no data available suggesting that breastfeeding leads to an increase in tumor size (6, 7).
- The spontaneous remission of hyperprolactinemia has only been reported in women with microprolactinomas. In these cases, long-term discontinuation of treatment with DAs after birth, along with regular monitoring for at least five years may be considered (6).

Source of Finance: During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest: No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Sema Yarman, Gülşah Yalın; Design: Gülşah Yalın, Sema Yarman; Control/Supervision: Sema Yarman; Data Collection and/or Processing: Gülşah Yalın, Sema Doğanşen; Analysis and/or Interpretation: Sema Yarman, Gülşah Yalın; Literature Review: Gülşah Yalın, Sema Doğanşen; Writing the Article: Sema Yarman, Gülşah Yalın; Critical Review: Sema Yarman; References and Fundings: Sema Yarman; Materials: Gülşah Yalın, Sema Yarman.

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