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Prolactinomas in pregnancy: considerations before conception and during pregnancy

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Abstract
Prolactinomas are the most common pituitary tumors and pathological hyperprolactinemia. Therefore, women harboring prolactinomas frequently present infertility due to the gonadal axis impairment. The gold-standard treatment is dopamine agonist (DA) which can reverse hyperprolactinemia and hypogonadism, and promote tumor shrinkage in the majority of cases. Therefore, reports of pregnancy in such cohort become more common. In this scenario, bromocriptine is still the DA of choice due to its shorter half-life and larger experience as compared to cabergoline. In DA resistant cases, transsphenoidal pituitary surgery is indicated. However, potential risks of DA-induced pregnancies include fetal exposition and symptomatic tumor growth. Dopamine agonist should be discontinued as soon as pregnancy is confirmed in microprolactinomas and intrasellar macroprolactinomas (MAC). Concerning expansive/invasive MAC, DA maintenance should be considered. Periodically clinical evaluation should be performed during pregnancy, being sellar imaging indicated if tumor symptomatic growth is suspected. In such cases, if DA treatment fails, neurosurgery is indicated.

Keywords Infertility · Prolactinoma · Pregnancy · Bromocriptine · Cabergoline

Introduction

Prolactinomas which affect 100 cases per million-year [1], mostly women in their 3rd and 4th decades of life, often lead to hypogonadotrophic hypogonadism and infertility [2]. The main mechanism involves inhibition of GnRH pulsatility, via kisspeptin [3, 4], but also direct effects on inhibition of gonadotrophins secretion and gonadal steroidogenesis are described.

Prolactinoma diagnosis is based on clinical, laboratory and imaging characteristics. Most women harbor microprolactinomas in which symptomatology is related to hypogonadism and galactorrhea. Patients with macroprolactinomas often present, in addition, mass effects symptoms, as headache, visual disturbances and additional hypopituitarism. Therefore, infertility is frequent in women with prolactinomas. In fact, the development of effective clinical and surgical treatments turned pregnancy possible in most cases. Nevertheless, proper management should be indicated in order to minimize maternal–fetal complications [5] (Fig. 1).

Medical treatment with dopamine agonists (DA), the gold standard approach for MIC and MAC, effectively restores eugonadism and promotes tumor reduction. Cabergoline (CAB), due to better tolerability and higher affinity to D2R as compared to bromocriptine (BRC), is currently the preferred DA. Nonetheless, due to its shorter half-life, with a faster clearance than CAB, BRC is still the recommended drug in the pregnancy context. However, although DA is usually withdrawal after pregnancy confirmation, the embryo is exposed to the drug in an important embryogenesis period, even when BRC is used [6].

Another important issue concerns the increase of tumor and pituitary dimensions during pregnancy [7, 8] due to lactotroph hyperplasia as a consequence of the high placental estrogen levels. Moreover, the recruitment and dedifferentiation of somatotrophs to lactotrophs additionally contribute to the pituitary gland increases, in weight and volume [9]. Serum PRL levels gradually increase to about ten times the non-pregnant levels at the end of the third trimester [10–12].

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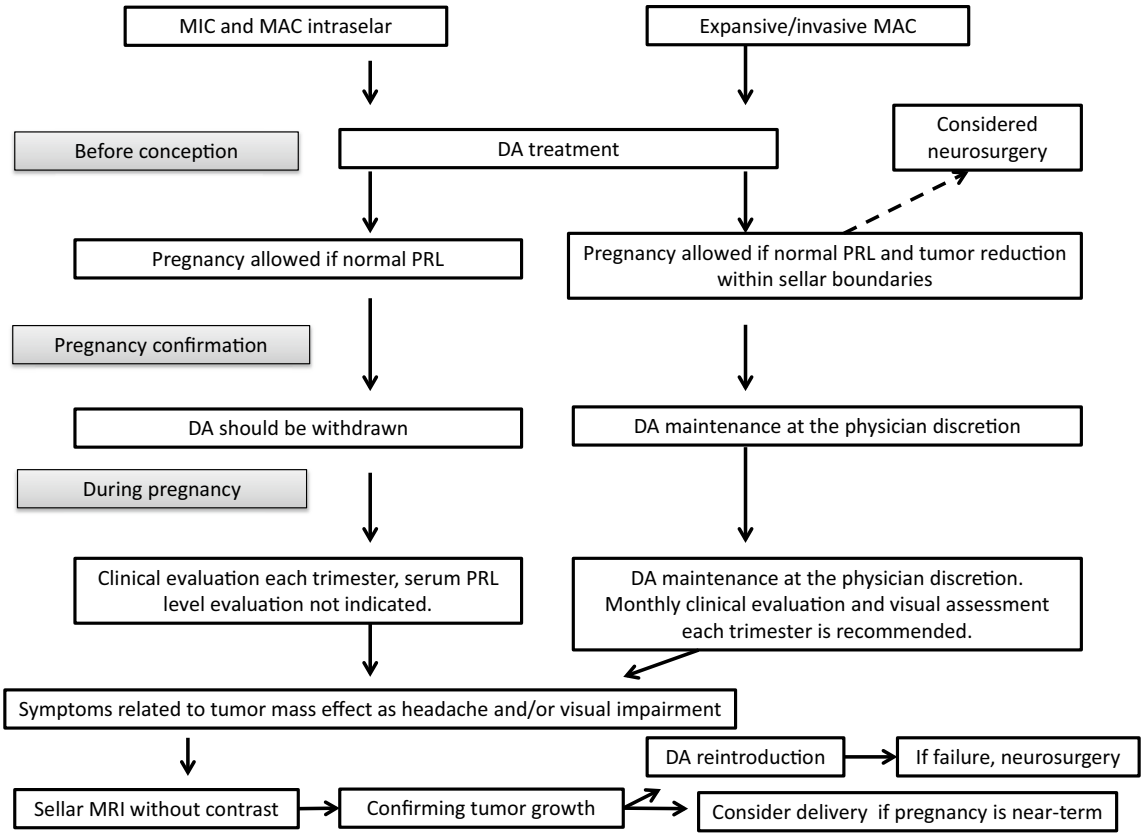

Fig. 1 Suggested algorithm for the management of prolactinomas before and during pregnancy

Therefore, mass effects symptoms as visual disturbances and headache may occur and deserve active surveillance.

Molitch reviewed tumor growth [13] in 800 microprolactinomas, in 288 macroprolactinomas without previous surgery or radiotherapy and in 148 macroprolactinomas with previous surgery and/or radiotherapy and rates were: 2.5%, 18% and in 4.7%, respectively. In fact, surgery, by the transsphenoidal approach, does not seem to impair the gonadal axis in the majority of cases, mainly concerning MIC. Nevertheless, surgical results depend on the surgeon skillfulness and experience. Colao reviewing large series from the literature, including both genders, reported hyperprolactinemia remission in 73.3% of 1211 MICs and in 38.0% of 1480 MACs [14]. Concerning surgical series addressing only women at child-bearing age, data are limited. In one study, in 138 patients harboring prolactinomas younger than 40 yrs submitted to transsphenoidal surgery, normal PRL levels were achieved in 86% of 21 MIC and in 74% of 117 MAC, with better results in non-invasive cases. Hypopituitarism was described in only two patients (1.5%). [15]. Other authors described normal PRL values in 81% of MIC and 52% of MAC, amongst 99 females at child-bearing age operated on, and gestation was achieved in 14 from 17 patients willing this outcome. Complications rates, including hypopituitarism, were not reported [16]. Yi et al. evaluated sixty-three females harboring prolactinomas (31 MIC and 32 MAC) submitted to transsphenoidal surgery. Of patients with menstrual disorders, 85% regained regular menstrual cycles after surgery and from nineteen patients who desired pregnancy, 15 successfully gave birth [17].

Surgery before pregnancy can be a therapeutic option in patients resistant to DA and in those without tumor shrinkage even in the presence of PRL normalization [7]. Despite the effectiveness and relative safety of pituitary surgery, mainly in MIC, this approach should be reserved for resistant/intolerant tumors or patient preference. Additionally, surgery may be indicated for another complication related to pregnancy: pituitary tumor apoplexy with severe neurologic and visual symptoms. Although pituitary apoplexy during pregnancy is an exceedingly rare event, with an estimated prevalence of 1 per 10,000 gestations in one series [18], the prevalence amongst women with DA induced pregnancy is not established. Oğuz et al. reviewing the literature, reported pituitary apoplexy in 19 prolactinomas: 6 MIC, 9 MAC and four with unavailable data regarding tumor size before pregnancy. Symptoms occurred at median gestational age of 23 (8–39) weeks, being sudden severe headache and visual disturbance the most common clinical picture. Regarding

outcomes 14 live births were described, being 11 at term. A multidisciplinary and skilled team should decide management individually [19–34].

As far as radiotherapy is concerned, the long time span until normoprolactinemia achievement in addition to complications as hypopituitarism, limit its indication for patients in reproductive age, except for those harboring aggressive/invasive tumors [5].

Therefore, in patients with extrasselar tumors, pregnancy should be allowed only after tumor shrinks within sellar boundaries [35], especially those with suprasellar extension, preferably after at least 1 year of treatment [36]. Regarding cavernous sinus extension, the potential risk of cranial nerve impairment should be considered. Resistant cases both regarding PRL normalization and tumor reduction should be operated on.

Concerning the DA choice for pregnancy-induction, BRC is still the preferred one due to its larger published data and shorter half-life, as compared to CAB [6, 37]. Although, BRC and CAB were formerly classified as category B by the FDA [38], in an Australian classification BRC is category A (no human risks, similar miscarriage rates, no increase in malformations and no teratogenic effects) and CAB is category B (no animal risks, waiting for more human data) [39]. A recent review confirms no impairments in maternal–fetal outcomes in BRC-induced pregnancies (6272 cases) as well as in CAB-induced pregnancies (1061 cases) regarding premature labor, abortions and fetal malformations [13]. It is worth of point out that usually DA has been withdrawn as soon as pregnancy is confirmed [6].

In fact, DA has been used throughout pregnancy in a limited number of patients. Amongst 100 women who maintained BRC, one case of cryptorchidism and another case of congenital talipes were described [40–44]. Regarding CAB maintenance throughout gestation, we reviewed 15 pregnancies resulting in 14 healthy newborns and one fetal death related to pre-eclampsia [45]. More recently, Rastogi et al. described three malformations (neural tube defect) only in the group of patients on CAB throughout gestation (n = 25), compared to no cases in the group of patients who withdrew the DA after pregnancy confirmation (n = 23) [46]. In another study, from 32 pregnancies induced by CAB the drug was maintained in six, without evidences of harmful outcomes [47].

As dopamine is a ubiquitous neurotransmitter, the impact of DA on DA brain circuitry could potentially interfere in the neuropsychological development of children. Additionally, other abnormalities could also be related to DA impact on embryogenesis. With BRC, no impairments were described in two studies including 64 children [41] between the ages of 6 months and 9 years, and 988 children [40], 4 months to 9 years-old, respectively. However, Bronstein reported one case of idiopathic hydrocephalus, one with tuberous sclerosis and another one with precocious puberty amongst 70 children, followed up during 12 to 240 months [48]. Data related to CAB are scarcer. No abnormalities were found by Bronstein [48] in five children, followed until 41 months and by Ono et al. [49] in 83 children, until 12 years. Nevertheless, Lebbe et al. described two cases of slight delay in verbal fluency and one patient without complete continence at the expected age in 88 children [50] and Stalldecker et al. described two cases of seizures and two cases of pervasive developmental disorder in among 61 children [51].

Concerning the follow-up of pregnant women harboring prolactinomas, the following recommendations can be made:

1. Before conception:
   - DA of choice: BRC has been the recommended drug for pregnancy induction, although cumulative data do not point to harmful outcomes with CAB.
   - MIC and intrasselar MAC: pregnancy can be recommended once the gonadotrophic axis is restored.
   - Expansive/invasive MAC: pregnancy can be recommended once the gonadotrophic axis is restored and only after tumor is reduced within the sellar boundaries, especially in those with suprasellar expansion. Otherwise, pituitary surgery is indicated.
2. Pregnancy confirmation:
   - MIC and intrasselar MAC: DA should be withdrawn.
   - Expansive/invasive MAC: DA maintenance at the physician discretion and frequent monitoring.
3. During pregnancy:
   - MIC and intrasselar MAC: clinical evaluation each trimester, serum PRL level evaluation not indicated. If symptoms related to tumor growth as headache and/or visual impairment occur, sellar MRI without contrast and neuroophtalmologic evaluation must be performed.
   - Expansive/invasive MAC: DA maintenance at the physician discretion. Monthly clinical evaluation and visual assessment each trimester is recommended. If symptoms related to tumor mass effect as headache and/or visual impairment occur, sellar MRI without contrast must be performed.
   - If sellar MRI depicts significant tumor growth related to clinical picture, reintroduction of DA is the first approach. In case of failure, neurosurgery is indicated, preferentially at the second trimester. If gestation is near-term, delivery can be considered.

Conclusion

In conclusion, due to advances in clinical and surgical approaches, pregnancy became a common event in women harboring prolactinomas. In this context, DA more studies with CAB induced pregnancies are necessary to reassure safety of this current more prescribed DA in maternal and fetal outcomes. A multidisciplinary team should indicate and follow the gestation in order to minimize possible complications, especially in MAC.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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