ENDOCRINOLOGY IN PREGNANCY

Management of the pregnant patient with a prolactinoma

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Abstract

A woman with a prolactinoma is usually infertile. Dopamine agonists usually restore ovulation and fertility and such treatment generally is preferred over transsphenoidal surgery because of higher efficacy and safety. Cabergoline is usually preferred over bromocriptine because of its better efficacy with fewer adverse effects. Either drug increases the rates of spontaneous abortions, preterm deliveries, multiple births, or congenital malformations over what may be expected. However, the number of pregnancies reporting such experience is about sevenfold greater for bromocriptine. Tumor growth causing significant symptoms and requiring intervention has been reported to occur in 2.4% of those with microadenomas, 21% in those with macroadenomas without prior surgery or irradiation, and 4.7% of those with macroadenomas with prior surgery or irradiation. Visual fields should be assessed periodically during gestation in women with macroadenomas. If significant tumor growth occurs, most patients respond well to reinstitution of the dopamine agonist. Delivery of the baby and placenta can also be considered if the pregnancy is sufficiently advanced. Transsphenoidal debulking of the tumor is rarely necessary.

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Prolactin and fertility

Women with hyperprolactinemia usually present with symptoms of galactorrhea, menstrual disorders (usually amenorrhea), and infertility. Hyperprolactinemia decreases luteinizing hormone (LH) pulse amplitude and frequency through suppression of gonadotropin-releasing hormone (GnRH) (1, 2). This effect appears to be mediated by an earlier step of suppressing the generation of

kisspeptin, a protein made by neurons in the arcuate and periventricular nuclei of the hypothalamus, which stimulates GnRH release (3). Hyperprolactinemia has been associated with loss of the positive estrogen feedback on gonadotropin secretion at mid-cycle (4) but whether this effect is mediated through kisspeptin is not known.

Direct prolactin (PRL) effects on ovarian granulosa cells include stimulation of the expression of type 2

Invited Author's profile

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3 β -hydroxysteroid dehydrogenase, the enzyme responsible for catalyzing the final step in progesterone biosynthesis and the secretion of insulin-like growth factor 2 (IGF2) (5, 6). PRL also directly suppresses progesterone and estrogen secretion from human ovaries (7). PRL can also decrease estrogen levels through direct effects on ovarian aromatase activity and by blocking the stimulatory effects of follicle-stimulating hormone (FSH) (8, 9). Although at low levels (<20 ng/ml) PRL is necessary for progesterone production in granulosa cell, at hyperprolactinemic levels it inhibits progesterone production (10).

It is likely that a short-luteal phase is the first evidence of interference in the normal cycle by hyperprolactinemia in women (11) and most hyperprolactinemic women become anovulatory with resultant amenorrhea and infertility. In a compilation of three series of infertility women (total 367), approximately one-third had hyperprolactinemia (12). Interestingly, 5.6% of 1328 women with regular menses and no galactorrhea were found to be hyperprolactinemic in a series of 1705 women with infertility, implying that they had ovulatory cycles; however, screening for macroprolactinemia was not done (13). That PRL excess may be important in this type of patient is suggested by the finding that treatment of similar patients with bromocriptine restored fertility (14). Transient hyperprolactinemia lasting for 1–2 days during the cycle has been shown in some infertile women, and such women may respond to dopamine agonists with increased progesterone during the luteal phase and improved fertility (15).

Pregnancy in women with prolactinomas

Correction of hyperprolactinemia with dopamine agonists restores ovulation in over 90% of women with amenorrhea and anovulation (16). Thus, dopamine agonists remain the standard treatment for women with hyperprolactinemia, although a minority with microadenomas or intrasellar macroadenomas may choose transsphenoidal surgery (17, 18, 19). In those patients who have prolactinomas as the cause of their hyperprolactinemia, there are two important issues that arise when pregnancy ensues: i) the effects of the dopamine agonist on early-fetal development; and ii) the effect of the high circulating levels of estrogen on prolactinoma size.

Effects of dopamine agonists on the developing fetus

To limit the exposure time of the developing fetus to dopamine agonists, it is helpful to know what the normal menstrual cycle timing is. Therefore, use of mechanical

contraception for the first two to three cycles will give the inter-menstrual interval. Then, the woman will know when she has missed a menstrual period, a pregnancy test can be performed quickly, and the dopamine agonist can be stopped if pregnancy is confirmed. In this way, the dopamine agonist will have been given for only about 3–4 weeks of the gestation. Bromocriptine has been shown to cross the placenta in human studies (20); cabergoline has been shown to do so in animal studies but such data are lacking in humans.

With such short-term exposure of generally <6 weeks, bromocriptine has not been found to cause any increase in spontaneous abortions, ectopic pregnancies, trophoblastic disease, multiple pregnancies, or congenital malformations (Table 1) (21, 22). A follow-up study of 64 children between the ages of 6 months and 9 years whose mothers took bromocriptine in this fashion showed no ill effects of this exposure on their development (23). Bromocriptine has been used throughout gestation in only a little over 100 women, with no abnormalities noted in the infants except for one with an undescended testicle and another with a talipes deformity (22, 24, 25, 26). In two studies in which bromocriptine was given before elective therapeutic abortions at 6–9 weeks (27) or 20 weeks (28) of gestation, there were no effects on estradiol, estriol, progesterone, testosterone, dehydroepiandrosterone, dehydroepiandrosterone sulfate, androstenedione, cortisol, or human placental lactogen.

Experience with the use of cabergoline in pregnancy is more limited (Table 1). Data on exposure of the fetus or embryo during the first several weeks of pregnancy have been reported in over 900 cases and such use has similarly not shown an increased percentage of spontaneous abortion, premature delivery, or multiple births (Table 1) (29, 30, 31). Outcome data with respect to malformations were available for 822 pregnancies with a finding of only 2.4% major malformations (29, 30, 31).

Long-term follow-up studies (up to 12 years) showed no abnormalities in physical or mental development in 83 children whose mothers received cabergoline to allow ovulation in one series (32). In their follow-up study of 88 children whose mothers received cabergoline, Lebbe *et al.* (33) found a slight retardation in verbal fluency in two children and difficulty in achieving complete continence in one child at age 4. In a third report of 61 such children, Stalldecker *et al.* (34) noted seizures in two children and ‘pervasive developmental disorder’, an autism spectrum disorder, in two additional children. There are reports of the use of cabergoline throughout gestation in only 15 women (35); healthy infants were delivered at term in

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Table 1 Pregnancy outcomes summarized for women who became pregnant while taking bromocriptine^a or cabergoline^b, compared to what is expected in the normal population^c.

	Bromocriptine (n (%))	Cabergoline (n (%))	Normal (%)
Pregnancies	6239 (100)	968 (100)	100
Spontaneous abortions	620 (9.9)	73 (7.5)	10–15
Terminations	75 (1.2)	63 ^d (6.5)	20
Ectopic	31 (0.5)	3 (0.3)	1.0–1.5
Hydatidiform moles	11 (0.2)	1 (0.1)	0.1–0.15
Deliveries (known duration)	4139 (100)	705 (100)	100
At term (> 37 weeks)	3620 (87.5)	634 ^e (89.9)	87.3
Preterm (< 37 weeks)	519 (12.5)	71 (10.1)	12.7
Deliveries (known outcome)	5120 (100)	629 (100)	100
Single births	5031 (98.3)	614 (97.6)	96.8
Multiple births	89 (1.7)	15 (2.4)	3.2
Babies (known details)	5213 (100)	822 (100)	100
Normal	5030 (98.2)	801 (97.4)	97
With malformations	93 (1.8)	21 (2.4)	3.0

^aData for bromocriptine from references (21, 22).

^bData for cabergoline from references (29, 30, 31).

^cData for normal births from references (36, 37, 38).

^dEleven of these terminations were for malformations

^eFive of these births were stillbirths.

13 and at 36 weeks in one but one had an intrauterine death at 34 weeks when the mother had severe preeclampsia (35). Table 1 also summarizes what is expected in the general population in the US (36, 37, 38) compared with women who became pregnant while taking bromocriptine or cabergoline. Based on this information, there do not appear to be any increases in adverse pregnancy outcomes with either drug compared with the general population.

In a review of 176 pregnancies, in which quinagolide was maintained for a median duration of 37 days, Webster (39) reported 24 spontaneous abortions, one ectopic pregnancy, and one stillbirth at 31 weeks of gestation. There were nine fetal malformations reported, including spina bifida, Trisomy 13, Down syndrome, talipes, cleft lip, arrhinencephaly, and Zellweger syndrome (39). Thus, quinagolide does not appear to be safe for the fetus if used when pregnancy is desired.

Bromocriptine clearly has the largest safety database and has a proven safety record for pregnancy. The database for the use of cabergoline in pregnancy is smaller, but there is no evidence at present indicating that it exerts deleterious effects on the developing fetus. The risk of malformations with either drug is not greater than that what is found in the general population.

Effect of pregnancy on prolactinoma size

The increasing amount of estrogen produced by the placenta stimulates lactotroph hyperplasia and a gradual increase in PRL levels over the course of pregnancy

(40, 41, 42, 43). This rise in PRL level is thought to prepare the breast for lactation. Magnetic resonance imaging (MRI) scans show a gradual increase in pituitary volume over the course of gestation, beginning by the second month and peaking the first week *postpartum* with a final height reaching to almost 12 mm (44, 45).

Prolactinomas can enlarge during pregnancy (Fig. 1) as a result of both the stimulatory effect of these high estrogen levels and the discontinuation of the dopamine agonist that might have caused tumor shrinkage. In a previous review of the literature, I analyzed the risk of symptomatic tumor enlargement in pregnant women with prolactinomas, divided according to their status as micro- or macroprolactinomas (29), and those data are given again in this study with data from two additional series (Table 2). The reports included in that review are quite heterogeneous, as they dated back to the 1970s when CT scans were just starting to be used. Although some early case reports and small series were included in earlier summaries that were in that review (46, 47), the reports after 1985 were included only if they had five or more cases (30, 31, 32, 33, 34, 48, 49, 50, 51, 52, 53, 54). With respect to denoting patients with clinically significant tumor enlargement criteria were quite variable and in most of those series, symptoms consisted of progressive, severe headaches and/or visual field defects. Asymptomatic increases in tumor size without visual field defects found on scans were not counted in that review. Furthermore, in some series some pregnancies did not go to term and how tumor progression in such patients was

Figure 1

Coronal (left) and sagittal (right) MRI scans of an intrasellar prolactin-secreting macroadenoma in a woman before conception (above) and at 7 months of gestation (below). Note the marked tumor enlargement at the latter point, at which time the patient was complaining of headaches. (From Molitch ME. Medical treatment of prolactinomas. *Endocrinology and Metabolism Clinics of North America* 1999 **28** 143–170 (73)).

counted was not clear. Table 2, therefore, is a summary of this data, but the limitations of these numbers based on the information outlined above should be recognized. The risk of symptomatic tumor enlargement for microadenomas was 2.4% (18/764), for macroadenomas that had not had prior surgery or irradiation was 21.0% (50/238), and for macroadenomas with prior surgery/irradiation was 4.7% (7/148). Routine MRI scans were performed between 24 and 32 weeks of gestation in 34 women in whom cabergoline had been stopped when pregnancy was diagnosed, finding that five of the 12 with macroadenomas had no change in tumor size, three had an increase of <5 mm, and four had an increase of >5 mm in size and nine of the 22 with microadenomas had no change in tumor size, three had a decrease, eight had an increase of <5 mm in size, and two had an increase of >5 mm in size (33). In one uncontrolled study of 22 patients, prior treatment with bromocriptine for more than 12 months seemed to reduce the risk of tumor enlargement (48); however, this finding awaits confirmation by other studies with either bromocriptine or cabergoline. In many cases with tumor enlargement, reintroduction of the dopamine

agonist, usually bromocriptine, was successful in reversing the problem and surgery was very rarely required; others were managed conservatively without medication or surgery. Cabergoline was restarted in six patients because of symptomatic headaches and/or vision-threatening increases in size of the adenomas (31, 33).

In some patients, *postpartum* PRL levels and tumor sizes are actually reduced as compared with values before pregnancy (55), but this has not been observed in all series (56). Domingue *et al.* (31) reported that of 56 hyperprolactinemic women, 23 had normal PRL levels *postpartum* and, of the 33 with persistent hyperprolactinemia, 31% had levels that were decreased by more than 50%. Therefore, many women may be ovulatory *postpartum* and would not need resumption of a dopamine agonist. Ikegami *et al.* (57) found that patients cured by transsphenoidal surgery had lower PRL levels *postpartum* compared with those treated with surgery plus bromocriptine or bromocriptine alone and had decreased milk production with poorer breast feeding. They also found that nursing did not cause an increase in PRL levels nor headaches or visual disturbances, which would suggest tumor enlargement (57). Therefore, breast-feeding need not be restricted but dopamine agonists cannot be used until desired breast-feeding has been completed.

Recommendations for management of pregnancy

In anovulatory women with PRL-secreting microadenomas, choices to restore fertility include use of dopamine agonists or transsphenoidal selective adenomectomy. Because of their efficacy in restoring ovulation and very low (2.4%) risk of tumor enlargement, dopamine agonists are generally preferred. The safety record with cabergoline is equal to that of bromocriptine; furthermore, cabergoline has greater efficacy with fewer adverse effects. Because of the differences in the size of the safety database for the two drugs, in some countries cabergoline is not approved for use in women planning pregnancy and the clinician is advised to check on such approval in his/her country. In contrast, transsphenoidal surgery results in a permanent normalization of PRL levels in only 60% of cases and is associated with some morbidity and mortality (19, 58). With either dopamine agonists or surgery, successful pregnancy can be achieved in over 85% of patients (16, 32, 56). Rare patients who do not respond to either modality may need additional strategies to facilitate ovulation, such as clomiphene citrate or human chorionic gonadotropin (59, 60), or IVF. The risk of tumor

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Table 2 Enlargement of prolactinomas during pregnancy.

References	Microadenomas		Macroadenomas		Macroadenomas with prior treatment	
	Total	No. enlarged	Total	No. enlarged	Total	No. enlarged
(46)	85	5	46	20	70	5
(47)	246	4	45	7	46	2
(48)	26	3	4	2	5	0
(49)	8	1	1	0	4	0
(50)	54	0	4	4	0	0
(51)	22	2	3	1	2	0
(52)	16	0	0	0	0	0
(53)	5	0	3	1	0	0
(54)	48	1	30	11	21	0
(32)	56	0	29	0	0	0
(33)	45	2	15	3	0	0
(34)	47	0	34	0	0	0
(30)	76	0	10	0	0	0
(31) ^a	30	0	14	1	0	0
Total	764	18 (2.4%)	238	50 (21.0%)	148	7 (4.7%)

^aAnalysis of tumor growth from this series – personal communication from D Maiter.

enlargement is much lower than the risk of known complications of radiotherapy, especially hypopituitarism, so that pre-pregnancy radiotherapy is certainly not indicated (61).

Routine clinical assessment without measurement of PRL levels during the pregnancy is all that is necessary for a patient with a microadenoma treated only with a dopamine agonist. In normal women, PRL levels rise with gestation, but PRL levels do not always rise with tumor enlargement and tumor enlargement can occur without change in PRL levels (62). During the first 6–10 weeks after stopping a dopamine agonist during gestation, PRL levels rise but later there is no further increase (63). Periodic checking of PRL levels, therefore, is of no diagnostic benefit and can be misleading. A rise in PRL may well not indicate tumor enlargement and therefore may cause unnecessary worry. In contrast, the lack of a rise in PRL may be falsely reassuring in a patient with headaches or other evidence of tumor enlargement. Tumor enlargement is very uncommon, so that routine visual field testing is not cost effective. Visual field testing and MRI scanning should be carried out only in patients who develop symptoms and when intervention may be indicated. There are no data documenting harm to the developing fetus from either MRI scans or gadolinium (64, 65, 66, 67); nonetheless, the ideal time to perform an MRI and the use of gadolinium during pregnancy are still the matters of debate among radiologists. However, in the face of symptoms of headaches that may be nonspecific, it is important to document a significant increase in tumor size before instituting an intervention, such as initiating

a dopamine agonist or surgery. If the headache is sudden, it may be caused by pituitary apoplexy, which may require an entirely different management course, including hormone replacement if there is sudden onset of hypopituitarism (68). MRI may be very helpful in distinguishing between hemorrhage into a tumor vs simple tumor enlargement (68).

The patient with a small intrasellar or inferiorly extending macroadenoma can probably be managed as those with microadenomas, i.e., with dopamine agonists. The risk that such a tumor will enlarge sufficiently to cause clinically serious complications is probably only marginally higher than the risk in patients with microadenomas.

A woman with a larger macroadenoma, especially one with suprasellar extension, has a 23% risk of clinically significant tumor enlargement during pregnancy when only dopamine agonists are used. An MRI should be done before pregnancy, if possible, to document any prior tumor shrinkage and to serve as a baseline for comparison with MRIs done during pregnancy. There is no best therapeutic approach in such a patient and this has to be a highly individualized decision that the patient has to make after a clear, documented discussion of the various therapeutic alternatives. The following discussion assumes that the patient had been responsive to the dopamine agonist; if the patient is nonresponsive, surgery will be needed. The most common approach in the dopamine agonist-responsive patient is to stop the dopamine agonist after pregnancy is diagnosed, as in the patient with a microadenoma. Another approach is transsphenoidal surgery, being careful to spare the normal pituitary.

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This reduces the risk of serious tumor enlargement, but cases of tumor expansion during pregnancy after such surgery have been reported (69). If there has been only partial removal for debulking purposes, a dopamine agonist will be required to normalize PRL levels and allow ovulation. A third approach, that of giving the dopamine agonist continuously throughout gestation, has been used but data of effects on the fetus are quite meager (see above); therefore, such treatment cannot be recommended without reservation. Should pregnancy at an advanced stage be discovered in a woman taking bromocriptine or cabergoline; however, the data that exist are reassuring and would not justify therapeutic abortion. A special case might be patients with very large tumors in whom the growth of that tumor was initially slow and any effects of pressure on surrounding brain structures was very gradual and usually of no consequence. If there was substantial tumor shrinkage with the dopamine agonist, then stopping the drug abruptly might cause a sudden enlargement of the tumor with potential pressure on surrounding structures. Admittedly, this is a theoretical concern and no cases with deleterious outcomes like this have been reported.

For patients with macroadenomas treated with a dopamine agonist alone or after surgery, careful follow-up with 1–3 monthly formal visual field testing is warranted. Repeat MRI scanning is reserved for patients with symptoms of tumor enlargement and/or evidence of a developing visual field defect or both as outlined above for patients with microadenomas. Detection of asymptomatic tumor enlargement with MRI scanning after delivery may be useful.

Dopamine agonists are probably less harmful to the mother and child than surgery to reduced symptomatic tumor growth. Many cases have been reported, in which reinstitution of dopamine agonists has caused rapid shrinkage of tumors with no adverse effects (see above). Surgery of any type results in a 1.5-fold increase in fetal loss in the first trimester and a fivefold increase in the second trimester; however, such surgery does not cause an increased risk of congenital malformations (70, 71). Therefore, reinstitution of a dopamine agonist is preferable to surgical decompression. But use of dopamine agonist should be closely monitored, and surgery or delivery (if the pregnancy is sufficiently advanced) should be performed if there is no response to the dopamine agonist or if there is a worsening of vision.

Almalki *et al.* (72) recently reported how these general recommendations for management are actually carried out in practice by collecting responses to three theoretical

cases with either i) microadenoma, ii) macroadenoma, or iii) large macroadenoma (2.9 cm) from endocrinologists in practice in several Provinces in Canada. Discontinuation of the dopamine agonist when pregnancy was diagnosed was done for 94% of patients with microadenomas but only 65% of patients with macroadenomas and only 18% of those with 'large' macroadenomas. Regular monitoring of visual fields with formal testing was carried in 32% of patients with microadenomas, 60% of those with macroadenomas, and 94% of those with large macroadenomas. Regular monitoring with MRI scans was carried out for 30% of those with macroadenomas and 49% of those with large macroadenomas.

Conclusions

Treatment with dopamine agonists usually restores ovulation and fertility with cabergoline generally being preferred to bromocriptine because of its higher therapeutic efficacy/adverse effects ratio. Experience with both drugs shows no increase in spontaneous abortions, preterm deliveries, multiple births, or congenital malformations, compared with what is expected in the normal population. Clinically significant tumor growth may occur in 2.4% of women with microadenomas and 21.0% of those with macroadenomas without prior ablative treatment. Women with macroadenomas need periodic visual fields during gestation; if visual field defects or progressive headaches develop, an MRI should be done. Reinstitution of a dopamine agonist is usually successful in causing shrinkage should symptomatic tumor growth occur. Alternatively, if the pregnancy is sufficiently advanced, delivery is an option. Surgical debulking is rarely necessary.

A number of questions remain about women with prolactinomas who wish to become pregnant. About 18% of patients are resistant to cabergoline and require larger than conventional doses to achieve normal PRL levels and to ovulate (32). Additional safety information is needed when cabergoline is given in larger than conventional doses for both short- and long-term. A large macroadenoma that has been greatly reduced in size by dopamine agonists represents a particular safety issue if the dopamine agonist is stopped abruptly at the same time as estrogen levels are increasing; reports of any patients who may have had adverse consequences in that setting would be of interest. Additional safety information is needed for doing MRIs and for administering gadolinium during pregnancy.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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