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EDITORIAL

Acromegaly and pregnancy[☆]

Acromegalia y gestación

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Pregnancy in acromegaly is a complex subject, and few data are available in the literature to answer three main questions:

1. Does pregnancy worsen acromegaly?
2. How does acromegaly influence pregnancy?
3. What are the consequences of medical treatment for the fetus?

Does pregnancy worsen acromegaly?

Hormone levels

Placental GH (GH-V) becomes the main component of circulating GH from the second term of pregnancy. GH-V is continuously secreted and induces production in maternal liver of IGF-I, which inhibits pituitary GH secretion in healthy women. In pregnant women with acromegaly, adenomatous somatotroph cells are resistant to IGF-I inhibitory feedback, and circulating levels of pituitary GH therefore remain elevated throughout pregnancy.¹ Since RIA or IRMA used in routine clinical practice do not detect GH-V, specific tests able to differentiate GH of pituitary origin from GH-V should be used to diagnose acromegaly during pregnancy. Serum IGF-I levels during pregnancy vary,

depending on the term. A decrease in IGF-I levels has been reported in healthy women during the first term, and also in women with hypopituitarism treated with GH and with type 1 diabetes.² However, serum IGF-I levels increase in most women during the second half of pregnancy through a mechanism independent of the pituitary gland.¹ A recent multicenter study conducted in France retrospectively analyzed 59 pregnancies in 46 acromegalic women, and IGF-I levels significantly decreased during the first and second term as compared to levels measured before conception.³ In a subgroup of 12 women with acromegaly who had been treated with dopamine agonists (DAs) (n = 8) or somatostatin analogs (SAs) (n = 7) before conception, IGF-I levels significantly decreased during the first term, maintaining stable GH production.³ In a recent systematic review of 47 pregnancies in patients with acromegaly reported in the previous 10 years, stable or decreased IGF-I levels were reported in most of them.⁴ Specifically, women with a macroadenoma or receiving medical treatment before pregnancy were more prone to have stable or reduced (by more than 30%) IGF-I levels at some time during pregnancy as compared to those with a microadenoma and those with no prior treatment, respectively.⁴

It should be noted that stable or reduced IGF-I levels in the third term were more frequently found in women who had received continuous treatment with somatostatin analogs during pregnancy than in those not given drugs.⁴ Thus, significant IGF-I reduction associated with subjective symptom improvement may be seen in pregnant women with acromegaly, particularly in the first term. This could be the consequence of a carryover effect of prior treatment but is, more probably, due to the inhibition of IGF-I production by hyperestrogenism.⁵

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Tumor size

During normal pregnancy, the pituitary gland enlarges, and its volume may increase by up to 45% during the first term, mainly due to hyperplasia of mature lactotroph cells and the subsequent reduction in the number of gonadotroph cells.⁶ Theoretically, the stimulating effect of peripheral hormones during pregnancy may cause enlargement of the GH-secreting adenoma, either by growth, hemorrhage, or tumor infarction. In addition, the normal increase in size of the pituitary gland during pregnancy also contributes to the mass effect on the optic nerve. In the French multicenter study, only four women experienced visual field defects during pregnancy, which led to a diagnosis of acromegaly in three of them. The remaining patient, who had a macroadenoma secreting GH and PRL and was being treated with bromocriptine, experienced intratumoral hemorrhage in the 34th week.³ Of the 27 patients for whom MRI was available within six months of delivery, 22 (20 with macroadenoma) had a stable adenoma size. Tumor size only increased in three patients (11%) with macroadenoma. One of these had previously been treated with surgery and bromocriptine, and the other two had visual defects.³ Seven patients reported headache, and one of them developed diplopia three months after delivery despite a stable MRI at 22 weeks of pregnancy.³ A review of cases reported to date shows that pregnancy aggravated acromegaly in four out of 24 patients (17%). In one patient, therapeutic abortion was decided upon in the 10th week due to severe symptom exacerbation.¹ The recurrence of GH hypersecretion and the return of clinical signs of acromegaly were documented in a single patient with macroadenoma in whom treatment with bromocriptine was discontinued at pregnancy onset.⁷ Another patient showed signs of increased intracranial pressure due to adenoma re-expansion in week 39 of pregnancy.⁸ Lactation was not associated with tumor growth in any of the 20 women with acromegaly reported in the French study. Therefore, it is usually not contraindicated, particularly in patients with minimal or no obvious residual tumor.^{3,4} Overall, it may be stated that pregnancy does not cause the growth of a GH-secreting tumor in most patients, particularly in those who have a microadenoma or macroadenoma previously treated by surgery and/or radiotherapy. However, close clinical monitoring, including evaluation of vision changes, should be performed in all pregnant acromegalic women with an adenoma greater than 1.2 cm in size, because of the potential risk of vision loss.

How does acromegaly influence pregnancy?

Pregnant women with active acromegaly are potentially at risk because of their increased risk of glucose intolerance, diabetes mellitus, high blood pressure, and preeclampsia. Particularly, gestational diabetes may be more prevalent in acromegaly due to an insulin resistance state resulting from the anti-insulin effect of GH. However, only some cases of mild gestational diabetes, most of them controlled with dietary measures,^{9–11} are reported in the literature, while most patients with acromegaly do not experience clinically relevant metabolic or cardiovascular complications during pregnancy. However, Caron et al. noted a trend to an

increased prevalence of gestational diabetes and high blood pressure in acromegalic women as compared to the overall French population. No differences were seen between patients with and without preconception control of GH/IGF-I.³ Interestingly, the occurrence of these complications was not associated with the type of medical treatment, as only one woman who developed gestational diabetes had been treated with a somatostatin analog during the first half of pregnancy.^{3,4} As regards newborns from women with acromegaly, no malformation has been documented, and birth weight was normal in 83 of the 95 babies reported in the Cheng review,⁴ in agreement with the premise of placental impermeability to GH and IGF-I.⁹ In conclusion, although acromegaly itself does not appear to significantly affect the course of pregnancy, prospective studies of larger populations should be conducted to conclusively assess the metabolic and cardiovascular consequences of GH/IGF-I excess during pregnancy for both the mother and fetus.

What are the consequences of medical treatment for the fetus?

Dopamine analogs (DAs), particularly bromocriptine, have been shown to be safe during pregnancy.¹² However, in the recent systematic review conducted by Cheng et al., a greater prevalence of macrosomic fetuses was seen in women treated with DAs as compared to untreated women, and the difference was borderline significant.⁴ However, this result needs to be confirmed in larger prospective studies. There are currently few conclusive data about SAs. All five subtypes of somatostatin receptors are expressed in the placenta, including SST4 (which shows little affinity for octreotide).¹³ Maffei et al. detected a very low number of somatostatin receptors in placental cell membrane and umbilical cord tissues, which suggests that the maternal-fetal barrier is able to exert a weak functional response to SAs.¹² Although the fetus may be exposed to the drug in the first few weeks following conception, pregnancy is likely to continue without complications if treatment is discontinued after pregnancy is confirmed. In the few cases reported of women with acromegaly in whom treatment with SAs was continued during pregnancy, no maternal complication or fetal malformation was reported.^{8,13} However, delayed uterine growth was documented in the fetus of a woman treated with octreotide LAR throughout pregnancy.¹⁴ In fact, in the systematic review by Cheng, women treated with SAs during pregnancy were more likely to have low birth weight newborns as compared to untreated women.⁴ Maffei et al. documented transient reductions in uterine artery flow and systolic velocity after injections of short-acting octreotide in a pregnant woman with acromegaly.¹³ This may explain, at least partly, the association between delayed growth/microsomia and the previously mentioned use of SAs. The use of pegvisomant during pregnancy has been reported as being safe and effective in two cases.^{15,16} Fetal drug levels were minimal, suggesting low or no transplacental passage, while GH-V levels in maternal and cord blood were within the normal range.¹⁵ In conclusion, although the medical treatment of pregnant women with acromegaly is not associated with major side effects in the mother or fetus, drug

discontinuation is recommended during pregnancy. If drugs are used, strict monitoring of fetal development is recommended.

Conclusions

To sum up, although no adequate scientific evidence is available about the management of acromegalic women during pregnancy, the following suggestions may be made: (a) it is important to control GH/IGF-I hypersecretion before pregnancy is planned; (b) medical treatment should be discontinued at least two months before a planned pregnancy or upon pregnancy diagnosis, because pregnancy does not aggravate acromegaly in most cases, and may even lead to a reduction in IGF-I levels and an improvement in associated symptoms, particularly in the first half of pregnancy; (c) in women with microadenoma, clinical signs suggesting a potential tumor growth (such as headache and/or vision disturbances) should be monitored every term; (d) in women with macroadenoma, strict clinical control and visual field examination are recommended every six weeks, because symptomatic macroadenoma growth may occur during pregnancy, particularly if previously untreated or if given drug treatment only; (e) in patients with evidence of tumor enlargement, in addition to ophthalmological monitoring, a control MRI may be considered in the second term. In these patients, a cesarean section to minimize the risk of pituitary apoplexy should be considered. If vision impairment is documented, urgent transsphenoidal resection is recommended; (f) all pregnant women with acromegaly should be monitored because of the risk of the occurrence of diabetes and gestational hypertension; (g) the available evidence does not support the maintenance or restart of medical treatment for acromegaly during pregnancy, because of the potential increase in the risk of impaired fetal development; and (h) lactation may be permitted in pregnant women with acromegaly, particularly in those with minimal or no residual tumor.

However, little experience is available, and prospective multicenter studies will be needed to clarify whether or not acromegalic mothers and their fetuses have an increased risk during and after pregnancy as compared to normal pregnant women.

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