Maternal and fetal effects of acromegaly on pregnancy.
Clinical Practice and Drug Treatment.

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ABSTRACT

INTRODUCTION:
Pregnancy in acromegaly is usually rare. Acromegaly is related with secondary hypogonadism, hyperandrogenemia, hyper prolactin and pregnancy is difficult in acromegaly, however, some women with acromegaly may become pregnant, which brings along questions about maternal and fetal effects and medical therapy and treatment. This review helps to address these points and helps clinical information.

METHODS: This review summarizes maternal and fetal effects of acromegaly on pregnancy and medical treatment

RESULTS AND CONCLUSION: Acromegaly can effect on pregnancy. In summary, fertility is usually compromised in acromegaly due to hyperandrogenemia, impairment of gonadotropin-secreting cells and decreased secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) as a result of tumoral mass effect (pituitary stalk compression) or treatment (surgery and radiotherapy) or hypopituitarism, high prolactin hormone levels due to pituitary stalk compression and a mixed GH-prolactin secreting adenoma and direct effect of excess GH/IGF-I on the gonadotropic axis.[1-6] Pregnancy may become complicated with gravid hypertension, preeclampsia and gestational diabetes mellitus. [7] Dopaminergic drugs, octreotide, pegvisomant and surgery are different modalities for treatment acromegaly in pregnancy. [8-13]

Keywords: Acromegaly; pregnancy; pituitary tumor; pituitary adenoma; Growth Hormone excess.

INTRODUCTION

Pregnancy in patients with acromegaly is really rare to less than 158 cases have been reported in the literature to date.[14] Fertility in patients with acromegaly is decreased, because of impairments
of the hypothalamo-pituitary–gonadal axis function and correlated potential causes.[3, 14] These include a tumoral mass effect; hyperprolactinemia, (about 30–40% of cases), due to stalk compression or prolactin co-secretion by the tumor; or a direct lactogenic effect of growth hormone (GH), itself.[3, 14, 15]. Nowadays, Pregnancy in women with acromegaly is more frequently encountered and that’s because of surgical and medical treatments and other reproductive techniques.[16] Pituitary dysfunction might lead to infertility or spontaneous abortion. GH is an insulin antagonist, and pregnant acromegalic patients are prone to added glucose intolerance, diabetes and hypertension. [3]Metabolic and cardiovascular complications of acromegaly can cause medical complications to mother and fetus during the pregnancy. [3, 15]Pregnancy is an insulin-resistant state and pregnant acromegalic patients have a risk of hyperglycemia much more than normal pregnant women. Incidence of hypertension and coronary artery disease increase in acromegalic patients, that poses potential risks to the fetus.[3, 15] Bromocriptine, octreotide, pegvisomant, and surgery are treatments for acromegaly in pregnancy.[16]

**DISCUSSION:**

**Etiologies of infertility in acromegalic patients:**
Fertility is impaired in women with acromegaly, due to hypopituitarism and a decreased gonadotropin reserve due to gonadotroph cells compression.[3] Increased prolactin levels is due to a mixed GH-prolactin adenoma; pituitary stalk compression; hypothalamic-pituitary-ovarian axis dysfunction; or excessive GH/IGF-I secretion, sensitizing the ovaries to gonadotropin stimulation. Treatments for acromegaly include transsphenoidal surgery, pituitary radiotherapy, and drugs (somatostatin analogs, dopaminergics and GH receptor antagonist). [3, 15] Effective treatment improves fertility, however, some procedures such as pituitary surgery and radiotherapy may lead to infertility via hypothalamic-pituitary-ovarian axis dysfunction.[3, 15]

Menstrual irregularities are common in acromegaly. Different etiologies may contribute to infertility and irregular mens in acromegaly. Hypogonadotropic Hypogonadism and hypopituitarism may be caused by the tumoral mass effect.[4] High prolactin levels may be seen in 30–40% of patients and results in hypothalamic-pituitary-ovarian axis dysfunction, including reduction in pulsatile GnRH secretion.[4, 6] GH and IGF-I effect on ovarian function. GH increases ovarian responsiveness to gonadotropins, thereby sensitizing the ovary to the stimulatory effects of gonadotropins.[6] GH also stimulates local IGF-I production in the ovarian follicles. Whether GH acts directly on the ovary or its sensitizing effect mediated by IGF-I is yet unclear.[5, 6]

One large study demonstrated that gonadal dysfunction is highly prevalent among acromegalic women of reproductive age.[3] Based on hormonal profiling and neuroradiological features and the patients’ menstrual histories before and after treatment of hypersomatotropism, we provided the evidence that besides hyperprolactinemia and a tumoral mass effect, GH/IGF-I hypersecretion may contribute to gonadal dysfunction in these women.[3, 4] In addition, though PCOS phenotype and hyperandrogenemia is relatively common in women with acromegaly, this issue provided the evidence that GH/IGF-I-induced PCOS, could participate in GH/IGF-I-induced ovarian dysfunction.[3, 4]

In summary, fertility is usually compromised in acromegaly due to 1) hyperandrogenemia 2) impairment of gonadotropin-secreting cells and decreased secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) as a result of tumoral mass effect (pituitary stalk compression) or treatment (surgery and radiotherapy) or hypopituitarism.
3) Increased prolactin levels due to pituitary stalk compression and a mixed GH-prolactin secreting adenoma
4) A direct effect of excess GH/IGF-I on the gonadotropic axis.[1-6, 15]

**GH changes in acromegaly and pregnancy:**
Philippe C and et al. evaluated the GH levels in pregnant acromegalic women.[7] Before conception the mean IGF-I level was 605+269 ng/ml, whereas during the first, second, and third trimesters, it was, respectively, 445+285 ng/ml, 366+150 ng/ml, and 440+188 ng/ml. These reductions were statistically significant during the first (P =0.02) and second trimesters (P <0.01).[7]
In some cases, IGF-I levels have been reported to decrease during the first trimester of pregnancy and not to increase during the last trimester of pregnancy.[17]
Increase in IGF-I secretion occurs despite stable pituitary GH secretion, proposing that the increased IGF-I levels are not pituitary GH dependent during late pregnancy.[18] Paradoxical GH secretion after TRH test occurs in pregnant acromegalic patients, but is not observed in normal pregnant control subjects.[18]
Renato C and et al. evaluated the GH levels in pregnant acromegalic women.[19] In their study, GH and IGF-I levels were 5.4 ± 0.8 and 430±58 mg/l (140±50% upper limit of normal range) respectively. During pregnancy, GH levels decreased by 50–90% in three women remained stable in three and increased only in one patient. IGF-I levels did not increase throughout pregnancy in any of the patients and remained near normal limits in all.[19] PRL increased physiologically. After delivery, GH levels increased in 1–5 months, IGF-I returned pathological, and PRL returned to before pregnancy values. GH-suppressive treatment was started again in all, within 5 months. Visual fields remained normal in all patients. At 1 month after delivery, MRI control did not show any difference in comparison to the last examination performed before pregnancy in all else one patient.[19]

**Maternal and fetal disorders in acromegaly and pregnancy:**
Pregnant women with uncontrolled or active acromegaly become complicated with an increased blood sugar or risk of gestational diabetes and gravid hypertension.[7]
Pregnancy is occasionally associated with symptomatic enlargement of GH-secreting pituitary macroadenomas.[7] Some acromegalic women report an improvement in their symptoms during the first half of pregnancy.[18, 20]
In patients receiving GH-suppressive treatment, increased sensitivity or a prolonged effect of octreotide might explain the growth hormone decline during the first part of pregnancy.[17] but decreased GH levels have also been reported in acromegalic women who were not treated with octreotide during pregnancy.[19] On the other hand, pituitary growth hormone release in some acromegalic women may be partly sensitive to the negative feedback effect of IGF-I.[18]
In women with acromegaly, growth hormone release due to pituitary adenoma is not significantly altered by the negative feedback of increased IGF-I levels.[9] This explains why pituitary GH levels do not decrease in pregnant women with acromegaly, in contrast to healthy pregnant women, in whom pituitary GH levels decrease in parallel to the increase in placental GH.[9] Maternal-fetal transfer of somatostatin analogs has been shown in women with GH- or TSH-secreting tumors treated with these drugs.[21]
In most reported cases, women who were treated with somatostatin analogs only until the pregnancy were included, and no malformations were noted.[10, 22, 23] In acromegalic women treated with somatostatin analogs during pregnancy, the gestation was uneventful and all women delivered normal newborns. Interestingly, in one woman treated with octreotide-long-acting release, ultrasound assessments suggested the
possibility of fetal growth retardation; the somatostatin analog dose was reduced, and normal fetal growth resumed until delivery.[21] This could be related to hemodynamic changes in the maternofetal tissues, as recently reported in an acromegalic woman treated with octreotide during pregnancy.[24] Therefore, acromegalic women should be suggested to discontinue somatostatin analog treatment when pregnancy is considered or confirmed because withdrawal is usually safe.[19] Potential explanations include a marked decrease in pituitary GH secretion due to a possible carry over the effect of previous GH-suppressive treatment ;[20, 25] infarction of a GH-secreting adenoma or a decrease in IGF-I secretion secondary to increased estrogen levels.[20, 25] IGF-I levels have been determined to decrease during the first half of pregnancy in healthy women.[26]

**Diagnosis of acromegaly during pregnancy:**
Old radioimmunoassays technics for GH detection cannot distinguish between normal pituitary GH and the placental GH variant.[17] Special radioimmunoassays using antibodies that recognize specific epitopes on the two hormones must be used. Because placental growth hormone shares an N-terminal epitope with pituitary growth hormone, but losses an internal epitope present in pituitary GH, specific monoclonal antibodies have been used to distinguish between these two forms of GH. [17] When such specific assays are not available, it may be necessary to wait until after delivery to assess pituitary GH secretion accurately. Levels of the placental variant decrease to undetectable levels within 24 h of delivery, however, secretion of the placental GH variant and pituitary-induced GH in women with acromegaly differs in two ways in women without acromegaly, about 70% of patients respond to injection of thyrotropin-releasing hormone (TRH); whereas, the placental GH variant does not respond to this hormone.[17] OGGT has not been evaluated thoroughly in the diagnosis of acromegaly during pregnancy. However, it has been administered in a few cases in which both a non-specific assay and a specific assay for pituitary GH tumors. In all cases, no suppression of GH occurred after OGGT.[27, 28] It should be emphasized that placental GH in normal pregnancy is also not suppressible so that the GH response to OGGT using a non-specific GH assay may be difficult to interpret.[27, 28] Therefore clinical judgment is the choice option for diagnosis and treatment of acromegaly during pregnancy.

**Does pregnancy aggravate acromegaly?**
Leandro Kasuki et al. reported a rare case of pregnant woman with acromegaly who presented with growth of an aggressive tumor during pregnancy.[29] Her tumor presented with a high Ki-67 (11.6%) and a low aryl hydrocarbon receptor-interacting protein (AIP) expression. When she became pregnant, octreotide LAR was withdrawn, but remaining asymptomatic during pregnancy, tumor growth occurred with compressing surrounding structures.[29] In conclusion, pregnancy in acromegalic patients has usually a favorable prognosis with no tumor growth. However, in the presence of high Ki-67 labeling index and low AIP expression, tumor enlargement may occur and somatostatin analogue treatment throughout the pregnancy should be considered.[29] Many studies showed that the risk of visual loss is low in pregnant patients with harboring functioning and non-functioning pituitary microadenomas. However, patients with adenomas larger than 1.2 cm are at higher risk of developing visual loss during pregnancy. Imaging techniques employed in this latter study were more sensitive and precising than those used in previous studies.[30, 31]
In reviewing all cases reported in the literature, pregnancy exacerbated acromegaly is seen in about less than 25% of patients. Recurrence of GH hypersecretion and aggravate of clinical signs of acromegaly (including hypertension, headache, increase in glove and shoe size, and coarsening of facial features) was reported in a patient in whom bromocriptine treatment was discontinued at the start of pregnancy and the report of patient developed signs of increased intracranial pressure at 39 weeks gestation. Cesarean section was performed for fetal distress, and patients underwent transsphenoidal resection for reexpansion of the adenoma.[31]

**TREATMENT:**

**Bromocriptine:** Bromocriptine is an agonist of dopamine which has not been associated with increased risk of complications during pregnancy or with congenital malformations when prescribed through the first few weeks of gestation in hyperprolactinemic patients.[4]

Bromocriptine historically has been the longest used medication in the treatment of Prolactinomas and acromegaly and pregnancy. In general when terminated at the time of definitive diagnosis of pregnancy, it is considered to be safe for the fetus. In more than 6000 pregnancies whereby bromocriptine was being administered at conception, it was not found to cause any increase in ectopic pregnancies, spontaneous abortion, trophoblastic disease, or frequency of multiple pregnancies, and caused congenital malformations in only 1.8% of births, that was comparable if was not lower than the congenital defects rate found in the general population.[16, 30, 32]

Usually, up to 20 mg/day of bromocriptine lowers GH—a dose higher than that is required to suppress PRL in patients with harboring prolactinomas.[33] Approximately 15% of patients in the world have been reported to have suppressed levels of GH (<5 µg/L) at the time of taking the medication (7.5 to 80 mg/day) and IGF1 is normalized in fewer than 10% of patients. Dopamine agonist efficacy appears to be independent of PRL concentration.[33] The drug causes minimal tumor shrinkage, but some of the patients experience subjective clinical improvement despite persistent elevated serum GH or IGF1 levels.[33]

Nine years of follow-up of children born from mothers treated with bromocriptine in the first few weeks of pregnancy showed no differences in teratogenicity compared to expected rates. Several amenorrheic acromegalic patients conceived after treatment and normalization of hyperprolactinemia with bromocriptine. Uncomplicated delivery of normal infants occurs even when bromocriptine treatment is continued throughout the pregnancy. [16, 30, 32]

**Octreotide:** There are several reported cases of pregnant acromegalic patients treated with octreotide during early pregnancy.[9-12] The pregnancies and deliveries were uneventful, and the infants were normal. However, octreotide should be discontinued during pregnancy else it is necessary for treatment.[9-12] Some women exposed to SSAs throughout all pregnancy have been reported so far without any serious adverse events regarding pregnancy, delivery, and newborn development. Somatostatin analogues can cross the placenta and reach both the fetal circulation and the feto-maternal biological fluids.[8-12]

**Pegvisomant:** Beckers et al. reported that GHV was not suppressed during pregnancy in acromegalic patients demonstrating that its secretion is not suppressed by pituitary GH hypersecretion.[17]

But in acromegalic patients treated with pegvisomant the GHV concentration remaining within the normal range suggests that it is constitutively secreted from placenta without the negative feedback of maternal GH or IGF-I and it is safe.[18, 34]

There is no evidence of significant secretion into breast milk, although, admittedly, even if ingested
by the baby, gastric hydrolysis would likely rapidly inactivate this peptide.[34]

Schreiber et al. conducted an observational study that described 2 years’ medication experience in more than 85% of all German patients with acromegaly who received pegvisomant therapy in 2004–2005. Of 229 participants, about 71% reached normal IGF-I concentrations.[35] This level of efficacy was ascribed to lack of treatment standardization, owing to limitations of the study design.[35] Overall, monotherapy with pegvisomant at daily doses of up to 40 mg is efficacious in patients with acromegaly.[35]

The data collected during the past years show that pegvisomant presents an efficacious and safe treatment for acromegaly if patients are carefully selected for therapy and its use is tailored individually.[36] Patients who have previously undergone surgery, particularly for tumor reduction, and those who are intolerant or resistant to somatostatin analogs will probably benefit most.[37] Importantly, unlike the analogs of somatostatin, pegvisomant does not cause tumor shrinkage. Higher doses than 40 mg could normalize IGF-I in patients with very high levels of GH. Co-administration of somatostatin analogs might increase the efficacy of therapy if pegvisomant doses need to be reduced.[37]

Adverse events might require temporary or permanent cessation of therapy with pegvisomant; treatment with somatostatin analogs, or repeated surgery should also be discussed. These recommendations might change as more information become available.[35, 37, 38]

**Surgery:** There are limited data’s pertaining specifically to the impact of transsphenoidal surgery during pregnancy. However no increased incidence of congenital abnormalities is reported, surgery during early pregnancy may be associated with an increased incidence of spontaneous abortion, may be because of anesthesia effects and usually will be performed when the patient is at risk of visual loss.[13]

**Approach to patients:**

Patients with microadenomas who are biochemically tolerant and responsive to medical management (bromocriptine or octreotide) can continue medical management and should be advised to discontinue treatment when pregnancy is confirmed.[39] This approach has been shown to be safe for the fetus, and the risk of tumor enlargement for the mother is low. Alternatively, transsphenoidal resection of microadenomas before conception usually does not impair fertility.[39] Pregnant patients with microadenomas should be assessed clinically during each trimester for symptoms of tumor enlargement (clinical assessment: headache, visual disturbances and hormone assay).[39] Pregnant patients with macroadenomas should be assessed clinically monthly for symptoms of tumor enlargement (clinical assessment: headache, visual disturbances, hormone assay, and MRI at 4 months).[39] Transsphenoidal resection of GH-secreting macroadenomas before conception pose a greater risk of postoperative hypopituitarism, with concomitant compromise of fertility. On the other hand, if macroadenomas are not eliminated before pregnancy, the risk of pituitary enlargement with possible visual loss is high.[39]

In addition, it is recommended that early in pregnancy medical therapies be discontinued despite the rare concomitant risk of tumor reexpansion. Visual fields evaluation in patients with macroadenomas should be done when pregnancy is diagnosed and every 6 weeks thereafter.[39] Pituitary MRI is indicated for patients harboring micro- and macroadenomas before conception and should be repeated during pregnancy only if there is evidence of visual field loss or headache. However, MRI is only recommended after 4 months gestation.[39] MRI for micro- as well as macroadenomas can be repeated postpartum in the absence of clinical evidence of tumor expansion.[40] When there is an evidence of tumor enlargement associated with pregnancy like visual loss, emergency transsphenoidal resection should be
recommended.[40] Pituitary MRI should be repeated postpartum in patients with micro- and macroadenomas to assess tumor size. If the tumor has been enlarged, patients should be followed by repeat imaging at 4-6-month intervals.[40]

CONCLUSION:
Acromegaly can effect on pregnancy. In summary, fertility is usually compromised in acromegaly due to hyperandrogenemia, impairment of gonadotropin-secreting cells and decreased secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) as a result of tumoral mass effect (pituitary stalk compression) or treatment (surgery and radiotherapy) or hypopituitarism, high prolactin hormone levels due to pituitary stalk compression and a mixed GH-prolactin secreting adenoma and direct effect of excess GH/IGF-I on the gonadotropic axis.[1-6] Pregnancy may become complicated with gravid hypertension, preeclampsia and gestational diabetes mellitus. [7] Dopaminergic drugs, octreotide, pegvisomant and surgery are different modalities for treatment acromegaly in pregnancy. [8-13]

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