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REVIEW

An update on clinical care for pregnant women with acromegaly

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ABSTRACT

Introduction: As pregnancy is rare in women with acromegaly, only case reports and few series have been published.

Areas covered: All case reports and publications dealing with pregnancy in patients with acromegaly were collated. Information concerning the effects of acromegaly on pregnancy outcomes, the impact of pregnancy on GH/IGF-I measurements, acromegaly comorbidity and pituitary adenoma size, the effects of treatment of acromegaly on fetus outcomes were retrieved and analyzed.

Expert commentary: Based on the small number of reported cases, pregnancy is generally uneventful, except for a potential increased incidence of gestational hypertension and diabetes mellitus. Medical therapy of acromegaly (dopamine agonists, somatostatin analogs, growth hormone-receptor antagonists) is generally interrupted before or at diagnosis of pregnancy. In very rare patients with a pituitary adenoma, particularly a macroadenoma that has not been surgically treated before pregnancy, or if a surgical remnant persists, or when acromegaly is revealed during pregnancy, tumor volume may increase and cause symptoms through a mass effect. Close monitoring of clinical manifestations and imaging are necessary during pregnancy in these cases. In the rare cases of symptomatic tumor enlargement during pregnancy, medical treatment with dopamine agonists or eventually somatostatin analogs may be attempted before resorting to transsphenoidal surgery.

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Pituitary; acromegaly; pregnancy; somatostatin analogs; dopamine agonists; GH-receptor antagonists; pituitary adenomas; mass-effect

1. Introduction

Acromegaly is a rare disabling disease due to excessive growth hormone (GH)/insulin-like growth factor-I (IGF-I) secretion [1–3]. Most patients harbor a benign GH-secreting pituitary adenoma. Diagnosis is generally made at middle age [in a large European multicenter survey, the median age at diagnosis in women was 46.4 years (IQR: 35.6–56.1) [4]], meaning that fertility and pregnancy are not major issues for the majority of female patients. Acromegaly in women of reproductive age is often associated with infertility, through several mechanisms, including hypopituitarism and a decreased gonadotropin reserve due to destruction or compression of gonadotroph cells (15%); hyperprolactinemia related to prolactin (PRL) hypersecretion by a mixed GH-PRL-secreting adenoma; and pituitary stalk compression resulting in hypothalamic–pituitary–ovarian axis dysfunction (30%). Moreover, excess GH/IGF-I secretion may have a direct effect on hypothalamic gonadotropin-releasing hormone (GnRH) secretion or induce polycystic ovary disease (PCOD)-like conditions that sensitize the ovaries to the stimulatory effects of gonadotropins (15%); or a mix of the previous ones (40%) [5]. All these mechanisms may contribute, alone or in combination, to ovarian dysfunction and infertility in women with acromegaly.

Current treatment modalities for acromegaly include transsphenoidal surgery, pituitary radiotherapy and medical therapy (dopamine agonists, somatostatin analogs, GH receptor antagonists). Depending on the size of the adenoma and the degree of GH/IGF-I hypersecretion, the latter can now be controlled, by a single therapeutic modality or a multimodal approach, thereby restoring fertility. As a result, an increasing number of women with acromegaly are able to become pregnant. In contrast, it should be noted that pituitary surgery and radiotherapy may result in permanent dysfunction of the hypothalamic-pituitary-ovarian axis and lead to infertility. Even in this case, however, ovulation can be achieved by gonadotropin administration, although some women with active acromegaly may have an excessive ovarian response to exogenous gonadotropins, resulting in ovarian hyperstimulation, multiple follicles and, thus multiple pregnancies [6].

Data about pregnancy in acromegaly have accumulated in the recent years, often as case reports [6–50], single-center retrospective [39,51–53], multicenter retrospective [54–57], or prospective studies [58].

Management of pregnancy can be complex in women with cured, controlled or uncontrolled acromegaly, whether treated or untreated as previously reviewed [39,59–65]. Several mechanisms may affect the outcome of pregnancy in this setting: (1) the effects of metabolic and cardiovascular complications of GH/IGF-I hypersecretion on the mother and fetus, (2) the effect of pregnancy on tumor size in patients with an

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unoperated GH-secreting pituitary adenoma or a postoperative remnant, (3) the effects of pregnancy on GH/IGF-I hypersecretion, and (4) the effects of surgery, radiotherapy and medical treatment on fetal development and outcome.

2. Potential impact of GH/IGF-I hypersecretion during pregnancy

In women with acromegaly, cardiovascular and metabolic complications of GH excess can potentially increase medical risks to the mother and fetus during pregnancy.

2.1. Effects of pregnancy on blood pressure and cardiomyopathy

In patients with GH/IGF-I hypersecretion, there is an increased sodium renal reabsorption and hypertension occurs in 25% to 35% of patients [66,67]. However, the prevalence of hypertension is much lower in younger female patients, particularly if acromegaly is controlled [68]. Cardiac involvement, generally as a hypertrophic cardiomyopathy, is present in about one-third of patients but also improve after effective treatment of acromegaly, particularly in younger patients [69].

Pregnancy in patients with acromegaly might thus, theoretically, increase the incidence of gestational hypertension. In fact, in the French retrospective multicenter study involving 46 women, hypertension was found in 13.6% of patients, while it is 5–15% in the French pregnant population [54]. Other smaller series have found a prevalence of 10% [56,58]. Hypertension was more frequent (45%) in a recent series of 37 cases, and was associated with preeclampsia or eclampsia in four cases [57].

Theoretically, hypertension, cardiomyopathy and vascular disease could adversely affect placental blood flow and fetal growth and development in these women with acromegaly [70]. However, during routine monitoring of pregnancy, hypertension and preeclampsia do not have untoward effects on fetal growth and development in pregnant patients with acromegaly [30,33,51,54,55,57,58], and none of these potential cardiovascular consequences of GH hypersecretion have been shown to adversely affect pregnancy in women with acromegaly who delivered healthy infants of normal height and weight in most cases.

2.2. Effect of pregnancy on glucose metabolism

GH is a potent insulin antagonist, resulting in glucose intolerance in 50% to 60% and overt diabetes mellitus in 13% to 32% of patients with acromegaly [67]. However, the incidence of glucose tolerance impairment is lower in younger patients [71]. As pregnancy itself is an insulin-resistant state, a woman with acromegaly should be at greater risk for glucose intolerance or hyperglycemia during pregnancy. Except in recent case series [57], review of the literature reveals only mild gestational diabetes mellitus [23,31,46,50,52], with an incidence (6.8%) very close to that of the general population [54,58] which correlates with GH/IGF-I control before pregnancy. Moreover, in most cases, it is easily controlled with diet, whereas most of the women with acromegaly did not develop such metabolic complications during pregnancy [54,58].

2.3. Potential fetal consequences of GH/IGF-I excess and its comorbidity

GH/IGF-I excess in the mother does not increase the risk of fetal malformations or preterm birth. Nevertheless, IGF-I may indirectly promote fetal growth (trophoblastic invasion, placental growth and maturation and trans-placental nutriment transport) [72,73]. Thus, a deleterious effect of IGF-I excess on fetal growth cannot be excluded. Increased birth weight has been suggested in some studies [33,43,48], but this was not confirmed in the French study, even in patients in whom GH/IGF-I hypersecretion was not controlled before pregnancy [54].

In summary, active acromegaly carries a theoretical increased risk of impaired maternal glucose tolerance, diabetes mellitus, hypertension, and preeclampsia, with potentially deleterious effects on the fetus. Therefore, acromegalic women who wish to conceive should first be treated for their GH/IGF-I excess and should be monitored closely during pregnancy in order to detect and treat early metabolic and cardiovascular consequences.

3. Potential impact of pregnancy on GH-secreting pituitary adenoma size

One of the main concerns in this setting is the impact of pregnancy on adenoma size. As most acromegalic women have GH-secreting pituitary macroadenomas, they are at risk of visual field defects due to chiasm compression and/or neurological complications (headaches, increased intracranial pressure, etc.).

3.1. Mechanisms of tumor expansion during pregnancy

During normal pregnancy the normal pituitary gland grows as a result of estrogen-stimulated hyperplasia and hypertrophy of the prolactin-producing lactotrophs [59,74,75]; pituitary size may increase by up to 45% during the first trimester of normal gestation. Due to the relative constrained inferior and lateral borders of the sella, this increase in size may only develop upwards, towards the optic chiasm. Thus, if a patient has already a tumor in the limited intrasellar space, the simple increase in size of the normal pituitary may be responsible for compressive symptoms [17].

In patients with GH-secreting adenomas, it is unclear if pregnancy, with the associated massive increase in estrogens levels, is able to cause true adenoma enlargement due to tumor growth. Two cases of apoplexy during pregnancy have been reported [13,20] but whether the pregnancy was responsible for these events or the association was fortuitous, is unknown. Indeed, according to a recent literature review, pituitary apoplexy during pregnancy is very unusual, particularly in patients with somatotroph adenomas [76].

Last, one must keep in mind that, after medical treatment that had caused shrinkage or reduction of adenoma size before pregnancy, the tumor volume increase might be due to

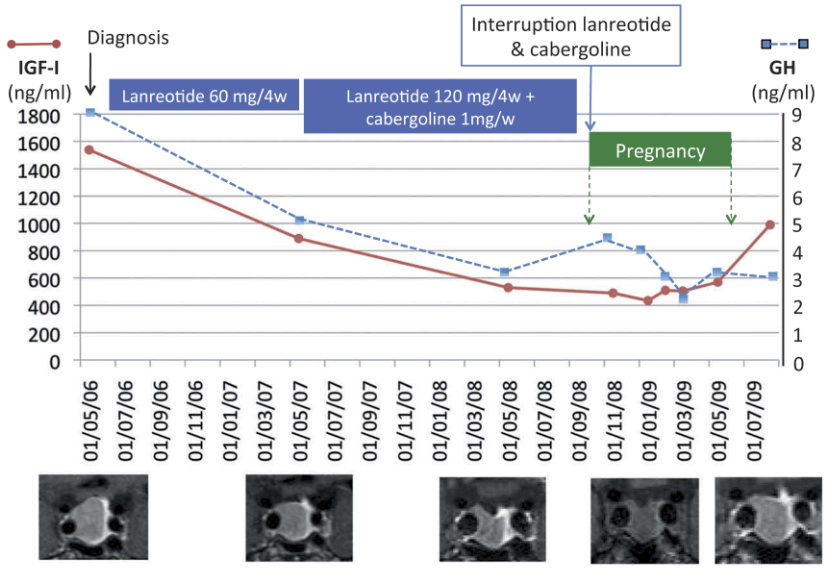

Figure 1. Course of serum GH and IGF-I levels and tumoral volume on MRI in a female patient with acromegaly, at the time of diagnosis, during treatment with somatostatin analog alone (lanreotide), during treatment with both somatostatin analog and dopamine agonist (cabergoline), after interruption of medical treatment during pregnancy and after pregnancy without any treatment (unpublished data).

discontinuation of the treatment (as exemplified in Figure 1), particularly somatostatin analogs, with re-expansion of the tumor up to pre-therapeutic size [16,51].

3.2. Prevalence and consequences of tumor expansion

However, in most patients with acromegaly, visual field studies during pregnancy did not reveal any defect, and computed tomography scan or magnetic resonance imaging (MRI) performed after delivery showed no significant growth of pituitary adenoma [7,33,70]. This was confirmed in two large series of patients [55,58]. On the other hand, in the French retrospective series, post-partum MRI performed in 27 cases showed increased tumor volume in three cases (11%) and in a prospective MRI study performed in six other French cases, tumor volume increase (asymptomatic) was noted in the two patients who had not been previously operated [53]. Overall, out of 71 reported patients with acromegaly who had postpartum MRI available, 16 (22%) did increase their adenoma size compared with pre-pregnancy MRI, while it decreased in 7 (10%) and remained stable in 48 (68%) [8,10,16,27,28,35,50,51,53,54,56,58].

But very few patients with GH-secreting pituitary tumors have been reported to enlarge their tumor during pregnancy with a resultant visual field defect [13,17,23,57]. Occurrence of headaches is more frequent [46,57,58,62].

The risk for the enlargement of GH-secreting pituitary adenoma during pregnancy is thus quite rare and highly dependent upon the tumor size and the patient's history. The risk of symptomatic tumor enlargement during pregnancy is low for microadenoma even in nonoperated patients and is reduced by previous surgery and/or radiotherapy of macroadenomas, whereas symptomatic growth of pituitary tumor may occur in patients who had been treated pharmacologically before onset of pregnancy [8,16,51] (as exemplified in Figure 1), or who had not been previously operated.

3.3. Management of symptomatic tumor growth during pregnancy

3.3.1. Pituitary surgery

Very few patients had a tumor growth requiring surgery. In three cases transsphenoidal surgery was performed because of pituitary apoplexy of GH-secreting macroadenoma [13,20,52] associated with progressive vision loss [52]. An emergency cesarean section was also performed in two cases [13,52]. In a third case, visual loss led to diagnose a pituitary tumor which was operated and proved to be a somatotropinoma [62]. In another case, the diagnosis of acromegaly was made shortly before pregnancy and examination showed visual impairment leading to propose surgery during the second trimester of pregnancy [24]. In four cases, the worsening of visual impairment which was already present at the time of initiation of pregnancy justified transsphenoidal surgery between 3 and 4 months of gestation [57]. The last reason for operating the patient was increased intracranial pressure [46].

During pregnancy of women with acromegaly, symptomatic tumor enlargement with visual field loss or neurological complications generally led to propose a medical treatment rather than a surgical approach. Indeed, even if the risk associated with nonobstetric surgery (stilbirth, preterm delivery, low birth weight baby, and cesarean section) is generally low [77], medical management should be considered first. Moreover, transsphenoidal surgery carries a small risk of new hypopituitarism (12%) or permanent diabetes insipidus (2.5%) [78]

3.3.2. Dopamine agonists

As symptomatic tumor enlargement may be related to physiological enlargement of the normal pituitary gland, which is mainly due to lactotrophs hyperplasia, it could be logical to try first dopamine agonists. This was the case for two women with acromegaly diagnosed in the second trimester of

pregnancy, in whom bromocriptine allowed to reverse visual field defects [15,31]. In the French series, two patients were also treated successfully by bromocriptine [62]. However, DA may not be successful in relieving visual impairment related to tumor enlargement [57].

The choice of dopamine agonists in this setting should depend on MRI findings: the ideal indication being if the somatotroph tumor did not grow, but optic chiasm compression is related to the increase in size of normal pituitary gland (due to hyperplasia of lactotrophs), provided previous MRI is available for assessing both somatotroph tumor and normal pituitary!

3.3.3. Somatostatin analogs

Somatostatin analogs have been used in few cases for tumor mass effects. Octreotide helped to improve headaches [8,39,48,62] or to reverse visual field impairment related to tumor growth [49].

3.4. Breastfeeding has no consequences on tumor growth

Breastfeeding might represent a theoretical problem in women with acromegaly (as for prolactinomas) due to the fear that suckling might stimulate the pituitary and thus promote the growth of normal pituitary. In fact, it is now well-known that if prolactinomas grow, this occurs eventually at the end of pregnancy but not after delivery at the time of breastfeeding [79]. This is also confirmed for women with acromegaly. All reported patients with micro- or macroadenomas who breastfed had no tumor problem [8,33,51–53,55,58,62].

There is, therefore, no reason to contraindicate breastfeeding for women who had uneventful pregnancies, as changes in prolactin levels associated with nursing do not appear to cause pituitary tumor expansion.

In summary, there is some evidence that pregnancy may cause symptomatic enlargement of GH-secreting pituitary macroadenomas in very rare cases, particularly when acromegaly is diagnosed during pregnancy or when acromegaly was treated by somatostatin analogs that have been interrupted at the onset of pregnancy. In clinical practice, women with acromegaly who wish to conceive should first receive surgical or medical treatment. MRI evaluation before conception is mandatory. During pregnancy, acromegaly women should be monitored for mass effect-related symptoms in the same way as women with prolactin-secreting adenomas [59]. They should have a clinical assessment and accurate visual field evaluation prior to pregnancy, then when pregnancy is diagnosed and serially for patients with macroadenoma (Figure 2). Careful monitoring is particularly indicated for women who have macroadenomas with suprasellar extension and/or who did not receive treatment before pregnancy. MRI (without gadolinium injection, and after the third month of pregnancy) should be performed each trimester if the tumor remnant is significant with a suprasellar extension close to the chiasm and if mass effect-related symptoms occur (headache, altered visual field). If the symptoms do not promptly yield to dopamine agonist therapy or somatostatin analogs, pituitary surgery should be envisaged. Breastfeeding is allowed if dopamine agonists are not used.

Recommendations from the Endocrine Society clinical practice guideline are on the same line [3].

4. Potential impact of pregnancy on GH/IGF-I levels in acromegalic women

4.1. Serum placental GH and pituitary GH and IGF-I levels in normal pregnancy

During normal pregnancy the placenta produces a GH variant named placental GH [80]. Placental GH differs from pituitary GH in 13 aminoacids but has the same action as pituitary GH on target tissues [81]. However, if pituitary GH secretion is pulsatile, placental GH is secreted continuously. Distinction between placental GH and pituitary GH is difficult due to their strong homology. GH isoforms cross-react in most immunoassays, and specific measurement of placental GH is thus problematic [64,82,83]. Initially, placental GH was determined indirectly using two GH immunoassays, both based on

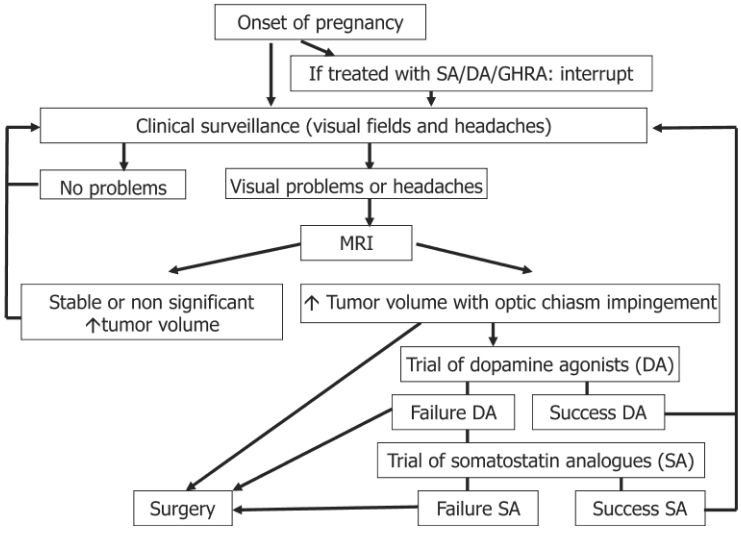

Figure 2. Proposed management of patients with acromegaly during pregnancy. DA, dopamine agonists; SA, somatostatin analogs; GHRA, GH receptor antagonists.

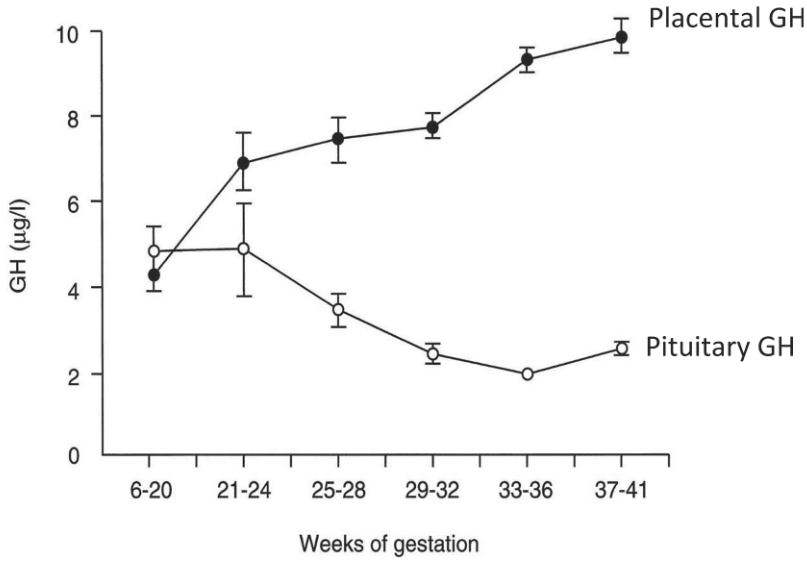

Figure 3. Course of placental GH and pituitary GH during normal pregnancy (adapted from [92] with permission).

monoclonal antibodies: one recognizing both the placental and the pituitary variant and the other only recognizing the pituitary variant. By subtracting the paired hormone concentration values obtained from each assay, the difference was assumed to represent the placental GH concentration [84,85]. Thereafter, specific assays for placental GH have been developed [80,86–88]. The newest monoclonal, ultrasensitive GH assays are quite specific for pituitary GH and practically do not cross-react with placental GH. Specific measurement of both allows to demonstrate that placental GH secretion increases gradually during gestation, while pituitary GH secretion is suppressed and pituitary GH serum levels become undetectable during the last trimester [84,89–91] (Figure 3).

Maternal IGF-I levels decrease by about 30% during the first trimester of normal pregnancy [93], probably due to the dramatic rise in estrogens levels which induces a state of hepatic GH resistance; thereafter maternal IGF-I levels increase during the second half of gestation and reach a peak at 37 weeks of gestation (IGF-I levels are about two-fold the pre-pregnancy levels) [94,95]. This is also observed in pituitary GH-deficient women, suggesting that this increase in IGF-I levels is independent of pituitary GH [35,73] and is secondary to increased placental GH secretion. The decrease in pituitary GH secretion observed during normal pregnancy is likely related to the negative feedback effect of increased serum IGF-I levels on the somatotrophs.

The diagnosis of acromegaly is thus challenging during pregnancy not only because IGF-I levels increase physiologically but also due to the difficulties in distinguishing between pituitary GH and placental GH by most of the assays available on the market.

4.2. Serum placental GH and pituitary GH and IGF-I levels in pregnant women with acromegaly

In women with acromegaly, even if serum IGF-I levels are already increased due to GH hypersecretion by the somatotroph adenoma, they increase further in the late stages of pregnancy, as observed in healthy women, confirming the role of placental GH stimulation. As GH hypersecretion by pituitary somatotroph adenoma cells is autonomous, it is not significantly affected by negative feedback control of IGF-I in most pregnant women with acromegaly, and, contrary to normal pregnancy, elevated serum pituitary GH levels persist throughout gestation [9,58]. This may be associated with aggravation of symptoms of acromegaly [17,21,46]. However, some pregnant women with acromegaly may not have this 'classical' pattern of GH/IGF-I serum levels, as decreased serum GH levels have been reported during the first trimester and also throughout gestation [18,27,51]. In patients receiving GH-suppressive medical treatment before pregnancy, enhanced sensitivity to and/or a prolonged effect of somatostatin analogs might explain the GH decrease during the first part of pregnancy, but octreotide concentrations were reported to be undetectable when the GH level was low [28], and decreased GH levels have been reported in women who were not treated with somatostatin analogs before/during pregnancy [50,51]. Therefore, pituitary GH secretion in acromegalic women may not be entirely autonomous during pregnancy and might be partly sensitive to the negative feedback control of IGF-I, as suggested in a pregnant woman with McCune Albright syndrome [22]. However, it must be emphasized that in the majority of these studies, GH immunoassays do not differentiate pituitary GH and placental GH justifying to interpret the data with caution.

The time course of serum IGF-I levels may sometimes be different from that generally observed in normal pregnancy [9]. Maternal IGF-I levels in acromegaly women may decrease during the first trimester and/or may not increase during the last part of pregnancy [16,18,26–28,43,53,54,57,58]. Contemporarily, some patients report an improvement in acromegaly symptoms during the first half of pregnancy [16,18,26,33,35,53]. These patients seem to represent a subset of women with acromegaly, particularly when GH/IGF-I levels are mildly elevated before pregnancy. Moreover, a significant decrease in mean IGF-I levels during the first trimester by comparison with pre-pregnancy levels is reported

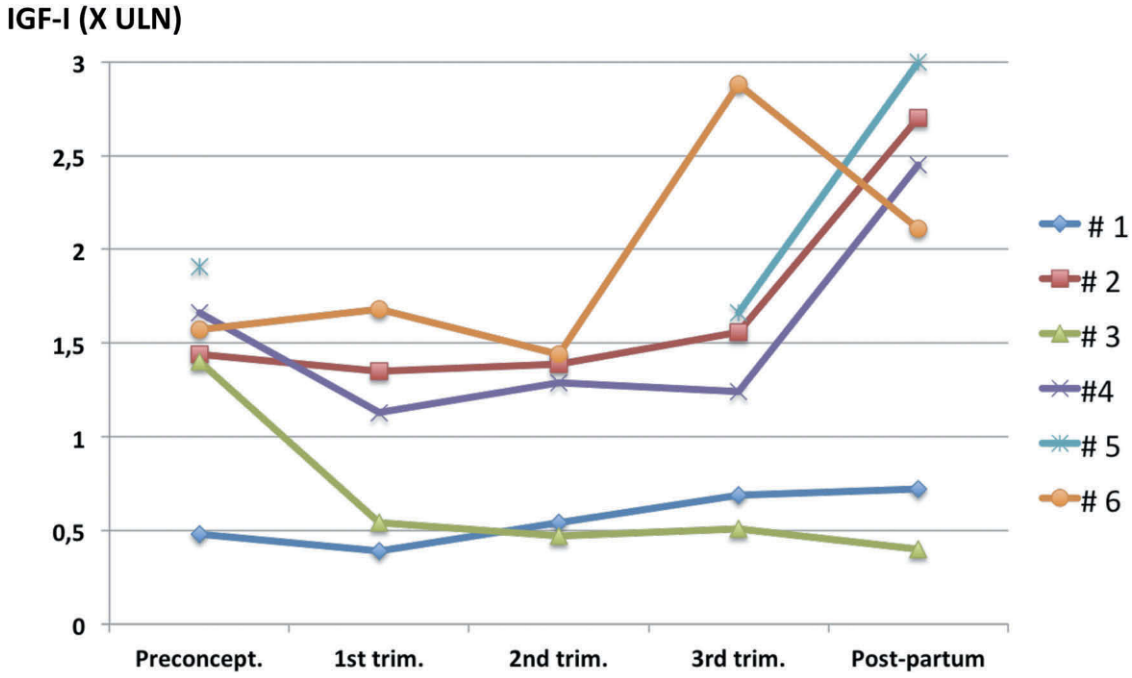

Figure 4. Changes in IGF-I (expressed as % of upper limit of normal, % ULN) along with pregnancy in five women with acromegaly (adapted from [53] with permission).

in some women, with no significant change (or eventually an increase) in GH levels [8,53,54] (Figure 4). As such a decrease in IGF-I levels has also been observed in women with panhypopituitarism treated with GH [35], this points to decreased hepatic production or increased turnover of IGF-I. In women with acromegaly, several mechanisms could potentially explain the decrease (and sometimes even the normalization) of IGF-I levels during pregnancy: 1) a marked decrease in pituitary GH secretion secondary to a possible carry-over effect of previous GH-suppressive treatments [26–28,35,43,51], but this could not account for the low IGF-I levels found in late gestation, when the treatment has been discontinued in early pregnancy and the drug is undetectable, or in patients who were not treated with somatostatin analogs or dopamine agonists before and during pregnancy [50,51], 2) infarction of a GH-secreting adenoma, but these women had no clinical signs of apoplexy, and acromegaly was still active after pregnancy, as shown by a re-increase in IGF-I levels after delivery, necessitating resumption of GH-suppressive treatment [16,18,28,53,54,58], and 3) a decrease in IGF-I secretion secondary to increased estrogen levels; indeed, estrogens act as GH antagonists, and estrogen administration to women with acromegaly is associated with decreased IGF-I levels and no significant change in GH levels, implying a state of relative hepatic GH resistance [96]. This state of relative GH resistance is also observed in GH-treated hypopituitary patients starting oral estrogen replacement therapy, in whom the GH dose must be increased to maintain IGF-I levels in the therapeutic range [97]. This is also the likely mechanism allowing decrease (and even normalization) of IGF-I levels in patients with acromegaly treated with estrogens or SERMs [98]. Therefore, the increasing estrogen concentration during early gestation is likely to inhibit IGF-I synthesis and improve the symptoms of acromegaly in a subset of patients. During the second half of pregnancy this antagonistic effect of estrogens may be overridden by the stimulation provided by increasing placental GH secretion, resulting in a variable increase in IGF-I levels in women with acromegaly [18,35].

In summary, serum pituitary GH and IGF-I concentrations show variable profiles during pregnancy in women with acromegaly, indicating that monitoring of GH and IGF-I levels is not necessary. Moreover, their results will not change the management of these patients. The Endocrine Society clinical practice guideline even suggests against monitoring GH and/or IGF-I levels during pregnancy [3]. A spontaneous decrease in IGF-I levels is frequent during pregnancy in women with acromegaly, implying that GH-suppressive treatment may safely be discontinued when early pregnancy is not associated with exacerbation of signs and symptoms of acromegaly [18,35,54,59,70]. This discontinuation has indeed been shown to be safe for both the mother and the fetus.

Shortly after delivery, a net rebound of both IGF-I and clinical activity is generally observed [16,50,53,57,58,62], implying a rapid resumption of treatment of acromegaly. This is likely related to the fall in estrogens levels following delivery, associated with a reversal of the state of hepatic resistance to GH. Rare patients do not need resumption of treatment after pregnancy [53].

5. Effects of treatments for acromegaly on the fetus

Treatments for patients with GH-secreting pituitary adenomas (transsphenoidal surgery, pituitary radiotherapy, dopamine agonists, somatostatin analogs, or GH-receptor antagonist) may potentially have adverse effects on the unborn child. Fortunately, as shown previously, pregnancy, by itself, is often associated with an improvement in acromegaly symptoms

allowing to interrupt medical treatments or postponing surgical intervention until the postpartum period.

5.1. Transsphenoidal surgery

Transsphenoidal surgery during the first trimester of pregnancy, like all operations requiring general anesthesia, may be associated with an increased incidence of miscarriage and premature delivery, most likely due to the anesthesia (see above). This surgery is not associated with an increased risk of congenital malformations. Thus, if necessary, neurosurgery is preferrably performed during the second trimester since teratogenicity and fetal congenital malformations more commonly occur in the first trimester, and emergency delivery should be taken into consideration during the third trimester [99–101]. While craniotomies are associated with high fetal and maternal morbidity and mortality [102], there are no clear data on the risks of transsphenoidal surgery, as only few case reports, concerning essentially Cushing's disease or pituitary apoplexy, have been reported.

5.2. Radiotherapy

One case of radiotherapy during the first trimester of pregnancy was reported in a 36-year-old woman after failure of two pituitary operations. The pregnancy was unknown at the time of radiotherapy which ended at the 14th week of gestation [43]. Neither complication nor congenital malformation was reported. Obviously, radiotherapy of GH-secreting pituitary adenomas is contraindicated during pregnancy.

5.3. Dopamine agonists

Dopamine agonists are considered to normalize GH/IGF-I levels in a small proportion of acromegalic patients, being particularly effective in those with mixed GH-PRL-secreting adenomas and low or moderate GH hypersecretion [103]. A meta-analysis showed that IGF-I levels normalized in one-third of patients treated with cabergoline, and in half of those treated with cabergoline plus a somatostatin analog [104].

Some women with active acromegaly diagnosed during pregnancy have received bromocriptine throughout pregnancy in order to control symptoms and tumor growth [29,31]. Dopamine agonists may also be useful for treating lactotroph hyperplasia, which may contribute to tumor expansion during pregnancy. Therefore, dopamine agonists may be indicated for women with acromegaly, before or during pregnancy.

All dopamine agonists have been shown to cross the placenta in humans and/or animals. Dopamine agonists are usually discontinued when pregnancy is diagnosed. However, the fetus is likely to be exposed to these drugs for at least three or four weeks, during the period between conception and diagnosis of pregnancy, particularly with cabergoline treatment. Nevertheless, experience gained with dopamine agonists, bromocriptine and cabergoline, in a very large number of pregnancies, particularly in patients with prolactinomas, confirms their safety for the mother and fetus [105]; these reports include acromegaly patients treated with dopamine agonists, including the repeatable parenteral depot form [19,31,36,38,52]. There are also a few reports of patients with acromegaly who received bromocriptine for symptomatic tumor enlargement during pregnancy with visual complications and/or neurological signs, in whom no untoward effects on the fetus were noted. Finally, a few infants whose mothers received bromocriptine throughout pregnancy had a low birth weight for gestational age, but no malformations were noted [12,29,37].

In summary, dopamine agonists should generally be discontinued during pregnancy in women with acromegaly, even though exposure early in gestation is reported to be safe for the fetus.

5.4. Somatostatin analogs

First-generation somatostatin analogs, namely octreotide and lanreotide, are the mainstay of medical treatment for acromegaly. They normalize GH/IGF-I secretion in 55% of patients, according to a recent meta-analysis [106], and induce significant tumor shrinkage in more than 60% of patients who have not had surgery [103]. Little information is available on the use of such somatostatin analogs in pregnant acromegalic women, and there are no clinical studies to confirm the safety of somatostatin analogs during pregnancy. Somatostatin analogs cross the placental barrier in animals and humans, but no signs of fetal toxicity were observed in rats and rabbits receiving octreotide doses up to 16 times above the maximum human dose, based on body surface area. Maternal-fetal transfer of octreotide has been shown in patients with GH- or TSH-secreting tumors [42,44,107,108]. Octreotide does not inhibit placental GH secretion [109], because most of the somatostatin receptors present on the placenta are of the sst4 subtype, which have low affinity for octreotide. Treatment with octreotide during the last part of pregnancy did not affect blood levels of TSH, thyroid hormones or IGF-I in the newborns [42,108], presumably because somatostatin receptors are not immediately functional at birth [42,107].

The literature describes more than 90 women treated with somatostatin analogs during pregnancy, using the subcutaneous short-acting analog octreotide [27,30,33,34,43–49,56,57] or long-acting formulations such as octreotide-LAR [8,14,16,26,28,35,42,51,53–58] and lanreotide LP [10,14,18,25,40,53,54]. So far, to our knowledge, only one woman treated with the second-generation somatostatin receptor agonist pasireotide has been published [57]. In most cases, somatostatin analog therapy lasted only until the pregnancy was confirmed, but this meant that the embryo was still exposed to octreotide or lanreotide during the first weeks of gestation, particularly when long-acting formulations were used. In up to 70% of these women the somatostatin analogs were stopped before the end of the first trimester [8,10,14,18,27,28,30,33–35,40,48,51,53,56,57,62,110], others were treated during the second and third trimesters, or even throughout gestation [26,33,42–45,48,49,55,57], generally because of persistent analgesic-resistant headaches, of presence of macroadenoma with suprasellar expansion close to the optic chiasm or of severe signs and symptoms of acromegaly. The pregnancy was usually uneventful and most of the

women delivered healthy babies at a normal term of appropriate height and weight, apart from one case of a large newborn.

However, it should be stressed that most reports only provide information on neonatal status. In one study performed on six cases (of whom five were treated with somatostatin analogs at time of conception), the general health status and IQ scores of children from women with and without acromegaly were found similar [14] confirming previous reports in two children followed until 2 and 6 years of age, respectively [44,45].

In one case of octreotide-LAR treatment during pregnancy, ultrasound follow-up suggested fetal growth retardation, while growth resumed normally until delivery when the somatostatin analog dose was reduced [42].

In two series, however, the risk of low birth weight was found to increase with somatostatin analog treatment of the mother: in Colao's report the mean birth weight of babies born to mothers treated with somatostatin analogs (3.9 kg, n = 3) was lower than that of babies born to untreated acromegalic mothers (4.7 kg, n = 5) [33]; in the study by the French Pituitary Group, comparison of birth weights of infants born to 14 women treated during pregnancy with somatostatin analogs (alone or in combination with dopamine agonists) and control women with acromegaly not treated with somatostatin analogs showed a significant risk of neonatal hypotrophy in the former [54]. Interestingly, in a case report describing an acromegalic woman with severe and resistant headache, each daily subcutaneous injection of the somatostatin analog octreotide given throughout pregnancy (1200–-2400 µg/d) induced an acute fall in uterine artery blood flow [44]. No effect on fetal outcome was noted, however.

Lastly, no excess teratogenic risk of somatostatin analogs was reported but the number of exposed pregnancies was too low to conclude on the total safety of these drugs. It must be pointed out that the only case of severe congenital malformation (unilateral congenital cataract, craniosynostosis and microcephaly) was observed in a baby born from a patient with acromegaly which was untreated [56]. In the only patient treated by pasireotide at the onset of pregnancy, the patient had a miscarriage but she already had had previous miscarriages [57].

In summary, as clinical data on the safety of somatostatin analogs are limited, women of childbearing age who receive somatostatin analogs should discontinue the treatment when pregnancy is considered or confirmed.

5.5. GH-receptor antagonist therapy

Pegvisomant has a totally different mechanism of action as it prevents the effect of GH on its receptor and thus acts as a GH receptor antagonist. Only three pregnancies occurring in patients treated with this GH-receptor antagonist have been reported [11,23]. One woman conceived after *in vitro* fertilization and intracytoplasmic sperm injection, and pegvisomant was discontinued 2 weeks after the embryos were transferred. The pregnancy was complicated by gestational diabetes, pituitary gland enlargement and deteriorating visual fields. A healthy boy was delivered by Cesarean section at 32 weeks of gestation [23]. In the other case, pegvisomant treatment lasted throughout pregnancy and no complications occurred [11]. In a third report [55], pegvisomant was given in association with octreotide until the 12th week of gestation. A normal baby was born on full term. Transplacental passage of pegvisomant seems to be either absent or minimal, with concentrations that are highly unlikely to have any significant pharmacodynamic effects on the fetal GH or IGF-I system [11]. There is no evidence of substantial pegvisomant secretion into human breast milk, and gastric hydrolysis would inactivate pegvisomant in the baby.

A recent publication summarizes all available data on pregnancy outcome in acromegaly patients exposed to pegvisomant during pregnancy as present in the Pfizer's Global Safety Database [111]. Data on 35 pregnancies (27 involving maternal and 8 paternal pegvisomant exposure) in whom pegvisomant was interrupted as soon as the pregnancy was diagnosed do not suggest adverse consequences of pegvisomant on pregnancy outcome. But the number is very small and it seems reasonable not to use pegvisomant during pregnancy and to contraindicate breastfeeding in patients with acromegaly treated with pegvisomant.

In conclusion, published data on a relatively small number of pregnant acromegalic women suggest that medical treatments, whether somatostatin analogs or GH receptor antagonists, used to control GH and/or IGF-I hypersecretion are not associated with significant fetal complications. As a rule, however, it is best to discontinue these treatments when pregnancy is diagnosed. Interruption of medical treatment during pregnancy is unlikely to have major adverse effects on long-term maternal outcome, as 1) physiological secretion of placental GH during normal pregnancy leads to an increase in IGF-I levels during the second half of gestation, 2) pregnancy does not alter the course of acromegaly in the majority of women, and even ameliorates clinical and hormonal activity of the disease in a subset of them 3) withdrawal of medical treatment has no maternal or fetal consequences in the majority of acromegalic women, and 4) most patients have had a GH/IGF-I excess for 8 to 10 years before diagnosis of acromegaly. Medical treatment can thus be safely withdrawn during gestation and resumed after hormonal and MRI evaluation 3 or 6 months after delivery.

6. Conclusion

As acromegaly generally occurs in middle age, fertility and pregnancy are rarely a concern. Pregnancy is generally uneventful in women with acromegaly, although blood pressure and glucose metabolism need to be monitored closely because of the small increased risk of gestational hypertension and diabetes mellitus. Mass effect-related symptoms also need to be monitored, particularly in patients with macroadenomas who have not had surgery or who have significant tumor remnants and were medically treated until pregnancy.

Medical therapy of acromegaly is generally interrupted before or immediately after diagnosis of pregnancy. In the rare cases in which symptomatic tumor enlargement occurs

during pregnancy, dopamine agonist or even somatostatin analog therapy may be tried before resorting to transsphenoidal surgery.

7. Expert commentary

Pregnancy in acromegaly is rare because acromegaly is often diagnosed in middle-aged women. When it begins in women of reproductive age, it is often associated with infertility, through several mechanisms, including hypopituitarism; hyperprolactinemia related to PRL hypersecretion by a mixed GH-PRL-secreting adenoma; and pituitary stalk compression resulting in hypothalamic-pituitary-ovarian axis dysfunction.

During pregnancy, active acromegaly carries a small increased risk of impaired maternal glucose tolerance, diabetes mellitus, hypertension, and preeclampsia, with potentially deleterious effects on the mother and the fetus. Therefore, acromegaly women who wish to conceive should first be treated for their GH/IGF-I excess and should be monitored closely during pregnancy in order to detect and treat early metabolic and cardiovascular consequences.

There is some evidence that pregnancy may cause symptomatic enlargement of GH-secreting pituitary macroadenomas in very rare women, particularly when acromegaly is diagnosed during pregnancy. In clinical practice, women with acromegaly who wish to conceive should first receive surgical or medical treatment. MRI evaluation before conception is mandatory. During pregnancy, women with acromegaly should be monitored for mass effect-related symptoms in the same way as women with PRL-secreting adenomas. They should have a clinical assessment and accurate visual field evaluation prior to pregnancy, then when pregnancy is diagnosed and serially during pregnancy in case of macroadenoma, in accordance with the Endocrine Society clinical practice guideline. Careful monitoring is particularly indicated for women who have macroadenomas with suprasellar extension and/or who did not receive long-term medical treatment before pregnancy. MRI (without gadolinium injection, and after the third month of pregnancy) should be performed if mass effect-related symptoms occur (headache, altered visual field). If the symptoms do not promptly yield to dopamine agonist therapy, or eventually somatostatin analogs, pituitary surgery should be envisaged. Breastfeeding is allowed if dopamine agonists are not used. The Endocrine Society Clinical Practice Guideline recommends that acromegaly medical therapy be withheld during pregnancy and administered only for tumor and headache control.

Serum GH and IGF-I concentrations show variable profiles during pregnancy in women with acromegaly, indicating that monitoring of GH and IGF-I levels is not necessary. Moreover, their results will not change the management of these patients. The Endocrine Society clinical practice guideline even suggests against monitoring GH and/or IGF-I levels during pregnancy.

A spontaneous decrease in IGF-I levels is frequent during the first part of pregnancy in women with acromegaly, implying that GH-suppressive treatment may safely be discontinued when early pregnancy is not associated with exacerbation of signs and symptoms of acromegaly. This discontinuation has indeed been shown to be safe for both the mother and the fetus.

Dopamine agonists, when used in the treatment of acromegaly (or of infertility related to hyperprolactinemia), should generally be discontinued during pregnancy, even though exposure early in gestation is reported to be safe for the fetus.

As clinical data on the safety of first generation of somatostatin analogs for the fetus are limited, somatostatin analog treatment should be discontinued when pregnancy is considered or confirmed. As data are even more limited for pegvisomant, the same recommendations apply for this drug. The Endocrine Society clinical practice guideline suggests discontinuing long-acting somatostatin analog formulations and pegvisomant approximately 2 months before attempts to conceive, with use of short-acting octreotide as necessary until conception.

Published data on a relatively small number of pregnant women with acromegaly suggest that medical treatments used to control GH and IGF-I hypersecretion are not associated with significant maternal complications. As a rule, however, it is best to discontinue these treatments when pregnancy is diagnosed. Interruption of medical treatment during pregnancy is unlikely to have major adverse effects on long-term maternal outcome.

There is no evidence from the available literature that acromegaly is *per se* an indication of a specific modality of delivery (eutocic vs. cesarean).

Medical treatment that was safely withdrawn during gestation will be resumed after hormonal and MRI evaluation 3 or 6 months after delivery, or earlier if the rebound in hormonal and clinical activity of acromegaly that is frequently observed is severe.

8. Five-year view

As acromegaly is a rare disease, and pregnancy occurs rarely in acromegaly, experience about pregnancy in acromegaly would only come from future report of cohorts where management attitudes and description of outcomes will accumulate and allow more accurate recommendations to be provided. Registers of all cases may be helpful in this objective.

Key issues

- Recommendations concerning the management of pregnancy in patients with acromegaly are based on few published descriptions of these pregnant women. Thus, they may be a matter of controversy.
- However, the data are relatively concordant and allow to conclude that, in general, pregnancy is uneventful (the increased risk of impaired maternal glucose tolerance, diabetes mellitus, hypertension, and preeclampsia is small), maybe because pregnancy is associated with a hepatic resistance to GH which ameliorates the consequences of the GH/IGF-I excess.

- Also these women benefit from improvement in the management of acromegaly and comorbidity during the past decades and are likely to have a less active disease at the beginning of their pregnancy.
- This means that onset of pregnancy often occurs at a time when the woman is treated, in particular with first generation somatostatin analogs. Even if the number of pregnancies exposed to this treatment is low, data on pregnancy and baby outcome seems to be reassuring.
- A closed surveillance is necessary in case of persistence of an important tumoral remnant which could increase in size and produce mass effects in very rare women. When it occurs, a surgical resection may be proposed either immediately, or when a short trial of dopamine agonists and eventually somatostatin analogs has failed.

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