

Acromegaly in Pregnancy—An Overview of the Key Issues

Trina McIlhargey, MD, PhD, FRCPC¹ and Bernard Corenblum, MD, FRCPC²

1. Fellow; 2. Professor, Division of Endocrinology and Metabolism, Department of Medicine, University of Calgary, Alberta, Canada

Abstract

Acromegaly in pregnancy is a rare occurrence and the literature regarding its diagnosis and management is limited. Normal pregnancies have a physiologic increase in growth hormone due to the production of a variant form by the placenta. Conventional assays are unable to differentiate pituitary from placental growth hormone and, as a result, making a diagnosis of acromegaly or assessing biochemical control in pregnancy is a challenge. While risks to the patient and fetus exist, they are mainly limited to complications associated with insulin resistance—which, if present, should be monitored and treated. Tumor enlargement may occur if therapy is discontinued at the start of pregnancy, but this is usually not the case and most have an uneventful pregnancy. Consequently, definitive diagnosis or treatment can often be delayed until after delivery—although, when indicated, treatment with dopamine agonists or somatostatin analogs is a reasonable option. To date, there are no data to suggest adverse outcomes with these agents; however, limited evidence is available and they should only be used in severely symptomatic acromegalics or those with symptomatic tumor enlargement. Transsphenoidal surgery is associated with an increased rate of pre-term labor and fetal loss, and should be considered only in emergency situations such as pituitary apoplexy.

Keywords

Acromegaly, pregnancy, diagnosis, management

Disclosure: The authors have no conflicts of interest to declare.

Received: June 3, 2012 **Accepted:** June 26, 2012 **Citation:** *US Endocrinology*, 2012;8(1):53–6 DOI: 10.17925/USE.2012.08.01.53

Correspondence: Bernard Corenblum, MD, FRCPC, Richmond Road Diagnostic and Treatment Center, 1888–1820 Richmond Road, Calgary, Alberta, T2T 5C5, Canada.
E: corenblu@ucalgary.ca

Acromegaly in pregnant women is an uncommon clinical problem. However, today, due to earlier diagnosis, women present with this concern at a younger age. In patients with pre-existing acromegaly, there may be difficulty conceiving, there are concerns regarding maternal and fetal outcomes, and there are no good data to fully assess the risk:benefit ratio of the various therapies that could be used during pregnancy. Acromegaly diagnosed for the first time during pregnancy is another clinical problem.

Acromegaly is a rare disease with an annual incidence of three to four per million people,¹ characterized by excessive production of growth hormone (GH) from somatotroph cells in the pituitary gland, almost always from an adenoma. Acromegaly in pregnancy is even more rare and limited data are available, mainly as a consequence of the reduced fertility often found in women with pre-existing pituitary disease.

Pituitary Changes in Normal Pregnancy

Magnetic resonance imaging (MRI) scans performed during pregnancy demonstrate a gradual increase in maternal pituitary volume over the course of gestation, with an increased final weight (660–760 mg) as well as a volume increase of 30 % above the pre-gestational volume.^{2,3} This enlargement results in a homogeneous upward convexity of the superior surface of the gland when visualized radiologically, and the gland reaches 12 mm in height a few days post-partum. It usually

does not increase more than 2.6 mm. The pituitary gland increases in all dimensions, with an average increase of 136 %.²

Rare reports exist of impingement on the optic chiasm, with resulting visual field changes, in women who have otherwise normal pregnancies.⁴ The pituitary stalk remains unchanged and is in the midline. These changes usually regress after delivery.

Effect of Acromegaly on Fertility in Women

Menstrual irregularity is a common and early finding in acromegaly. Potential causes are impairment of the hypothalamic–pituitary–gonadal axis from anatomic compromise due to tumor mass effect, or hyperprolactinemia secondary to stalk compression (i.e., interference with dopamine action) or prolactin co-secretion.⁵ Prolactin-like effects of GH, specifically spillover, may contribute to the menstrual irregularity observed in acromegaly.⁶ In addition, recent evidence also suggests that there is a direct effect of GH and insulin-like growth factor 1 (IGF-1) on ovarian function.⁶

Hyperandrogenemia may result in a polycystic ovary syndrome (PCOS)-like pattern.⁷ Furthermore, previous surgery or radiotherapy may impair normal pituitary gonadotropin secretion. Correction of hyperprolactinemia may be necessary to restore normal ovulation in these patients. Recent advances in ovulation induction and medical or

Pituitary Disorders

surgical therapy have allowed pregnancy to occur in many women who would otherwise not have been able to become pregnant. Prior to attempting pregnancy or facilitating ovulation induction, underlying normal pituitary secretory function needs to be assessed and any deficiency in thyroxine or cortisol needs to be addressed. Breast-feeding does not affect the course of acromegaly and post-partum pituitary imaging generally demonstrates no increased tumor growth resulting from the pregnancy.

Growth Hormone and Insulin-like Growth Factor 1 Changes in Normal Pregnancy

Two genes encode for human growth hormone (hGH). The most common is hGH-N, which is expressed in the pituitary gland. A variant form, hGH-V, is referred to as placental growth hormone, as it is expressed exclusively in the syncytiotrophoblast.⁸ Both forms have a molecular weight of 22 kDa and are 191 amino acid, single-chain proteins that are generally quite homologous, differing by only 13 amino acids. In addition, hGH-V is more basic and contains an N-linked glycosylation site at asparagine 140.⁹

In pregnancy, the absolute number of somatotrophs is reduced and basal and stimulated maternal GH levels are suppressed by the second trimester. Paradoxically, IGF-1 levels are slightly increased throughout pregnancy, probably as a result of GH secretion by the syncytiotrophoblastic epithelium.¹⁰ In fact, patients with pituitary GH deficiency have normal IGF-1 levels in pregnancy. Placental GH is detectable as early as five weeks gestational age and increases through to term, achieving peak levels by 37 weeks.¹¹⁻¹³ Predictably, levels rapidly decline after delivery, with approximately 75 % of plasma hGH-V removed from the circulation by 30 minutes post-partum.¹⁴ Placental GH stimulates the production of maternal hepatic IGF-1, which likely suppresses the maternal pituitary secretion of GH through the normal negative feedback mechanism.¹⁵ Consequently, pregnancy is a state of physiological GH and IGF-1 excess.

The placenta also produces GH-releasing hormone and IGF-1. While the fetus also produces GH throughout pregnancy, whether this is responsible for fetal IGF-1 production is unclear, because anencephalic fetuses also demonstrate normal IGF-1 levels.

Conventional radioimmunoassay is not able to differentiate between hGH-N and hGH-V and, consequently, determining whether or not a pregnant patient with pre-existing acromegaly is biochemically controlled is difficult. Similarly, making a new diagnosis of acromegaly in a pregnant patient who is exhibiting clinical signs of acromegaly is a tremendous challenge. As previously mentioned, pregnancy itself is a state of physiological GH and IGF-1 excess; so elevated levels may erroneously result in a diagnosis of acromegaly. In fact, some otherwise normal pregnancies may be associated with acromegaloid-like phenotypic changes, which generally reverse after delivery.

So how can the clinician diagnose acromegaly or assess its control when GH and IGF-1 are elevated in a normal pregnancy? The answer may be obvious if there is an extreme elevation inconsistent with that observed in usual pregnancy, but for those who fall just outside the range of normal, this is a problem that does not readily have a solution.

Example Cases

Case 1: A 34-year-old woman was diagnosed with acromegaly due to a 1.2 cm pituitary adenoma. She chose treatment with octreotide, which normalized her serum insulin-like growth factor 1 (IGF-1) to the normal range for her age and gender, resulting in regression of soft tissue changes. One year later, she conceived a planned pregnancy. It was unknown whether the octreotide would be without risk during the pregnancy, nor whether the pregnancy would benefit from its use. After discussion, she discontinued the octreotide. The pregnancy was uneventful and she delivered a full-term healthy infant. She decided not to lactate, and when her serum IGF-1 was found to be elevated two months post-partum, octreotide was re-instituted. Her case illustrates the clinical problem of optimal management of a known acromegaly during pregnancy, regarding both maternal and fetal outcomes.

Case 2: Identical twins presented with acromegaly-like changes during the third trimester of each of their first pregnancies, six months apart. Pre-pregnancy photographs were normal. Each had noticed soft-tissue facial changes, including lip and tongue enlargement, and clinically appeared to have acromegalic facies. There were neither symptoms nor signs of a sellar mass. After delivery, the soft-tissue changes did regress and clinically the patients no longer appeared to have acromegalic facies. At that time, glucose suppression test for growth hormone (GH) and serum IGF-1 were normal. Each underwent a second pregnancy and the acromegalic-like changes occurred again, most noticeably during the third trimester. Once more, regression occurred post-partum. Again, post-partum testing of serum GH and IGF-1 were normal—and they have remained normal ever since. Their grandmother stated similar changes had occurred during her only pregnancy. Their case illustrates the difficulty of diagnosing acromegaly during pregnancy.

Case 3: A 19-year-old woman presented with amenorrhea for one year, headaches, visual field changes and a 2.5 cm sellar mass. At the time of admission for transsphenoidal resection, early acromegalic changes were noted. Pathology demonstrated a pluri-hormonal tumor with GH immunostaining. Serum IGF-1 was elevated after surgery and residual tumor tissue was observed on magnetic resonance imaging. As she had experienced rapid onset and progression, it was decided that she would undergo a course of pituitary radiotherapy. She was then treated with octreotide for several years. Eventually the treatment was stopped, as her serum IGF-1 was normal without octreotide and her serum GH was 0.4 ug/l after glucose. There was no further growth of the residual pituitary mass. Menses did return after surgery, but after several years they stopped again, with the finding of low normal serum luteinizing hormone, follicle-stimulating hormone, and prolactin. Radiation-induced partial hypopituitarism was diagnosed. Pregnancy was desired. She failed to respond to a trial of pulsatile gonadotropin-releasing hormone, so exogenous gonadotropins were administered, resulting in two separate singleton pregnancies that were otherwise uneventful. Her case illustrates the problem of subfertility in women with acromegaly—treated or untreated.

Suppression of GH to glucose has not been well tested in pregnancy, and placental GH would not be expected to change.¹⁶ If the patient is pregnant and acromegaly is clinically suspected but has not been diagnosed, definitive diagnosis may not be possible until after delivery. Clues to the presence of a true increase in pituitary GH include a documentation of pulsatility, which is characteristic of acromegaly,¹⁷ while placental GH secretion is continuous and apulsatile. When clinical findings and the limited laboratory examination suggest acromegaly, imaging of the sella with MRI, without gadolinium, is warranted to document the presence of a tumor. Gadolinium is classified as category C in pregnancy by the US Food and Drug Administration. There is a lack of human clinical data to address its potential toxicity.¹⁸ Gadolinium is teratogenic in animal studies and does cross the placenta. It should only be used if clinically necessary.¹⁹ Performing computed tomography (CT) scans and coned-down views of the sella is not recommended in pregnancy due to radiation exposure.

As a result of the structural differences between hGH-N and hGH-V, methods using specific monoclonal antibodies to distinguish the two have been developed.^{9,20} Unfortunately, such methods are laborious and have traditionally been used for research purposes only. More recently, an enzyme-linked immunosorbent assay (ELISA) kit has been developed that makes the assay easier to perform on a larger scale, but this too is only intended for research purposes. At present, no commercial assay is available to the endocrinologist who is facing this difficult question.

Effect of Acromegaly and its Therapy on Pregnancy

Although we currently lack the capability to readily distinguish pituitary from placental GH, is there truly a need to control or diagnose acromegaly in pregnancy? Maternal GH and IGF-1 do not cross the placenta,^{21,22} but nonetheless, there are risks to the fetus when women experience active acromegaly during pregnancy. There is an increase in insulin resistance and thus an increase in the risk of gestational diabetes and hypertension—up to 6.8 % and 13.6 %, respectively, in a recent case series.²³ This was especially evident in women who had not had their GH and IGF-1 levels controlled prior to conception. Another study of 47 cases showed no maternal complications other than gestational diabetes in one.²⁴ In the mother, pre-existing cardiac disease—resulting from the metabolic syndrome, hypertension, or acromegaly-associated cardiomegaly—may become symptomatic during pregnancy.

Medical therapy may be used at the onset of the pregnancy and then discontinued, maintained throughout the pregnancy, or reintroduced if there is symptomatic change suggestive of sellar mass enlargement. Data on the medical treatment of acromegaly during pregnancy are limited and none have been adequately evaluated. However, dopamine agonists used to treat prolactinomas in pregnancy have been shown to be safe,²⁵ despite evidence that they cross the placenta.

Somatostatin analogs, such as octreotide and lanreotide, have also been successfully used, with no major adverse effects noted, during the course of pregnancy.^{26–30} These agents have been used during pregnancy for other diseases, again with little adverse effect on fetal outcomes. Birthweight appears to be unaffected in pregnancies exposed to

somatostatin analogs. However, octreotide has been shown to cross the placenta and its safety during pregnancy has not been established. Thus its use should be limited during pregnancy. There are retrospective observations that microsomia may occur more often with the use of somatostatin analogs, and macrosomia more often with the use of dopamine agonists.²³ The latter has not been observed in women with prolactinomas taking dopamine agonists during pregnancy. Octreotide has short-term effects on placental hemodynamic function, but no clinical effect has been established.²³⁰ One report showed that a child exposed to octreotide throughout pregnancy had normal birthweight and length, and normal linear growth up to six years of age.³⁰

The GH antagonist pegvisomant is very effective at normalizing IGF-1, but its use in pregnancy has only been reported in two cases.^{31,32} In one case, pegvisomant had been used throughout pregnancy and, while it was detected in cord blood, either by placental transfer or contamination, no adverse outcomes were noted at follow-up after six months.³² At present, data on the use of pegvisomant during pregnancy are insufficient to support using this agent in anything but an exceptional situation. Despite the initial favorable outcomes, due to the sparsity of case reports and the lack of controlled studies, this agent is best avoided during pregnancy—other than in clinically indicated situations.

Effect of Pregnancy on Acromegaly

Pregnancy has not been found to alter the course of acromegaly other than in rare reported cases of asymptomatic tumor enlargement, which may or may not be related to physiologic pituitary hyperplasia typical in normal pregnancy, or to adenoma growth/apoplexy. Symptomatic sellar mass increase would be less likely with small tumor size and previous therapy with surgery or radiotherapy. Post-partum pituitary visualization found the tumor larger in three, smaller in two and unchanged in 22 patients.²³ Tumor enlargement may theoretically occur if pre-existing therapies such as somatostatin analogs are discontinued with the onset of pregnancy; however, women with pre-existing acromegaly who have had their drug therapy withdrawn usually have an uneventful pregnancy.³³ Symptomatic tumor growth during pregnancy has been reported.³⁴ Rare complications such as pituitary apoplexy may require surgical excision, but elective surgery is best delayed until after delivery due to the risk of fetal loss.³⁵ If sellar mass symptoms occur, a trial of dopamine agonists may act on the normal hyperplastic pituitary gland and rapidly decrease the mass effects.

Conversely, acromegalic symptoms may improve during pregnancy,³⁶ possibly from the increased estrogen resulting in increased production of GH-binding protein or in decreasing hepatic IGF-1.³⁷ Serum IGF-1 levels may decrease in pregnancy, without a change in GH, presumably due to estrogen decreasing the effect of GH on hepatic IGF-1 production.³⁸ In addition, estrogen inhibits the GH activation of the signal transduction (Jak/STAT) pathway, resulting in GH resistance.³⁸

If acromegaly is left untreated for the duration of the pregnancy, the pregnancy and lactation are thought not to have any adverse effects on the natural history of the acromegaly, which otherwise is a chronic disease that can be addressed after delivery. Consequently, the benefits of achieving control or establishing a new diagnosis of acromegaly in

pregnancy are most likely limited to reducing the risk of complications associated with insulin resistance—which, if present, should be closely monitored and treated.

Conclusions

Most pregnancies occurring in women with pre-existing or newly diagnosed acromegaly progress without an increased complication rate regarding maternal and fetal outcomes, with the normal delivery of healthy infants. Due to the chronic nature of acromegaly, the diagnosis of suspected new cases during pregnancy may be delayed until after

delivery. If clinically indicated, continuation or introduction of medical therapy with somatostatin agonists, dopamine agonists or GH receptor antagonists appear, to date, to be without adverse effects. Greater clinical experience with these agents in pregnancy is still required. In patients with symptomatic tumor enlargement during pregnancy or with severely symptomatic acromegaly, dopamine agonist therapy is an appropriate initial treatment option. Somatostatin analogs may also be considered. When considering transsphenoidal surgery in pregnancy, the patient needs to be carefully selected, as this procedure is associated with an increased risk of premature delivery and fetal loss. ■

- Bengtsson BA, Edén S, Ernest I, et al., Epidemiology and long-term survival in acromegaly. A study of 166 cases diagnosed between 1955 and 1984, *Acta Med Scand*, 1988;223:327–35.
- Gonzalez JG, Elizondo G, Saldivar D, et al., Pituitary gland growth during normal pregnancy: an in vivo study using magnetic resonance imaging, *Am J Med*, 1988;85:217–20.
- Diñç J, Esen F, Demirci A, et al., Pituitary dimensions and volume measurements in pregnancy and postpartum. MR assessment, *Acta Radiol*, 1998;39:64–9.
- Heald AH, Hughes D, King A, Buckler H, Pregnancy related pituitary enlargement mimicking macroadenoma, *Br J Neurosurg*, 2004;18:524–6.
- Herman-Bonert V, Seliverstov M, Melmed S, Pregnancy in acromegaly: successful therapeutic outcome, *J Clin Endocrinol Metab*, 1998;83:727–31.
- Grynberg M, Salenave S, Young J, Chanson P, Female gonadal function before and after treatment of acromegaly, *J Clin Endocrinol Metab*, 2010;95:4518–25.
- Kaltsas GA, Androulakis II, Tziveriotis K, et al., Polycystic ovaries and the polycystic ovary syndrome phenotype in women with active acromegaly, *Clin Endocrinol (Oxf)*, 2007;67:917–22.
- Scippo ML, Frankenne F, Hooghe-Peeters EL, et al., Syncytiotrophoblastic localization of the human growth hormone variant mRNA in the placenta, *Mol Cell Endocrinol*, 1993;92:R7–13.
- Igout A, Van Beeumen J, Frankenne F, et al., Purification and biochemical characterization of recombinant human placental growth hormone produced in *Escherichia coli*, *Biochem J*, 1993;295:719–24.
- Frankenne F, Closset J, Gomez ML, et al., The physiology of growth hormones (GHs) in pregnant women and partial characterization of the placental GH variant, *J Clin Endocrinol Metab*, 1988;66:1171–80.
- Lønberg U, Damm P, Andersson AM, et al., Increase in maternal placental growth hormone during pregnancy and disappearance during parturition in normal and growth hormone-deficient pregnancies, *Am J Obstet Gynecol*, 2003;188:247–51.
- Chellakootty M, Vangsgaard K, Larsen T, et al., A longitudinal study of intrauterine growth and the placental growth hormone (GH)-insulin-like growth factor I axis in maternal circulation: association between placental GH and fetal growth, *J Clin Endocrinol Metab*, 2004;89:384–91.
- Fuglsang J, Skjaerbaek C, Espelund U, et al., Ghrelin and its relationship to growth hormones during normal pregnancy, *Clin Endocrinol (Oxf)*, 2005;62:554–9.
- Fuglsang J, Sandager P, Møller N, et al., Kinetics and secretion of placental growth hormone around parturition, *Eur J Endocrinol*, 2006;154:449–57.
- Beckers A, Stevenaert A, Foidart JM, et al., Placental and pituitary growth hormone secretion during pregnancy in acromegalic women, *J Clin Endocrinol Metab*, 1990;71:725–31.
- McIntyre HD, Russel A, Serek R, et al., Placental growth hormone is not suppressed by oral glucose loading in normal human pregnancy, *Horm Metab Res*, 2002;34:250–3.
- Barkan AL, Stred SE, Reno K, et al., Increased growth hormone pulse frequency in acromegaly, *J Clin Endocrinol Metab*, 1989;69:1225–33.
- Wang PI, Chong ST, Kielar AZ, et al., Imaging of pregnant and lactating patients: part 1, evidence-based review and recommendations, *AJR Am J Roentgenol*, 2012;198:778–84.
- Chen MM, Coakley FV, Kaimal A, Laros RK Jr, Guidelines for computed tomography and magnetic resonance imaging use during pregnancy and lactation, *Obstet Gynecol*, 2008;112:333–40.
- Evain-Brion D, Alsat E, Igout A, et al., Placental growth hormone variant: assay and clinical aspects, *Acta Paediatr Suppl*, 1994;399:49–51.
- Davenport ML, Clemmons DR, Miles MV, et al., Regulation of serum insulin-like growth factor-I (IGF-I) and IGF binding proteins during rat pregnancy, *Endocrinology*, 1990;127:1278–86.
- Verhaeghe J, Does the physiological acromegaly of pregnancy benefit the fetus? *Gynecol Obstet Invest*, 2008;66:217–26.
- Caron P, Broussaud S, Bertherat J, et al., Acromegaly and pregnancy: a retrospective multicenter study of 59 pregnancies in 46 women, *J Clin Endocrinol Metab*, 2010;95:4680–7.
- Cheng S, Grasso L, Martinez-Orozco JA, et al., Pregnancy in acromegaly: experience from two referral centers and systematic review of the literature, *Clin Endocrinol (Oxf)*, 2012;72:264–71.
- Ono M, Miki N, Amano K, et al., Individualized high-dose cabergoline therapy for hyperprolactinemic infertility in women with micro- and macroprolactinomas, *J Clin Endocrinol Metab*, 2010;95:2672–9.
- DeMenis E, Billeci D, Marton E, Gussoni G, Uneventful pregnancy in an acromegalic patient treated with slow-release lanreotide: a case report, *J Clin Endocrinol Metab*, 1999;84:1489.
- Neal JM, Successful pregnancy in a woman with acromegaly treated with octreotide, *Endocr Pract*, 2000;6:148–50.
- Fassnacht M, Capeller B, Arlt W, et al., Octreotide LAR treatment throughout pregnancy in an acromegalic woman, *Clin Endocrinol (Oxf)*, 2001;55:411–5.
- Mikhail N, Octreotide treatment of acromegaly during pregnancy, *Mayo Clin Proc*, 2002;77:297–8.
- Maffei P, Tamagno G, Nardelli GB, et al., Effects of octreotide exposure during pregnancy in acromegaly, *Clin Endocrinol (Oxf)*, 2010;72:668–77.
- Qureshi A, Kalu E, Ramanathan G, et al., IVF/CSI in a woman with active acromegaly: successful outcome following treatment with pegvisomant, *J Assist Reprod Genet*, 2006;23:439–42.
- Brian SR, Bidlingmaier M, Wajnaich MP, et al., Treatment of acromegaly with pegvisomant during pregnancy: maternal and fetal effects, *J Clin Endocrinol Metab*, 2007;92:3374–7.
- Cozzi R, Attanasio R, Barausse M, Pregnancy in acromegaly: a one-center experience, *Eur J Endocrinol*, 2006;155:279–84.
- Kasuki L, Vieira Neto L, Takiya CM, Gadelha MR, Growth of an aggressive tumor during pregnancy in an acromegalic patient, *Endocr J*, 2012;59:313–9.
- Güven S, Durukan T, Berker M, et al., A case of acromegaly in pregnancy: concomitant transsphenoidal adenectomy and cesarean section, *J Matern Fetal Neonatal Med*, 2006;19:69–71.
- Lau SL, McGrath S, Evain-Brion D, Smith R, Clinical and biochemical improvement in acromegaly during pregnancy, *J Endocrinol Invest*, 2008;31:255–61.
- Wiesli P, Zwimpfer C, Zapf J, Schmid C, Pregnancy-induced changes in insulin-like growth factor I (IGF-I), insulin-like growth factor binding protein 3 (IGFBP-3), and acid-labile subunit (ALS) in patients with growth hormone (GH) deficiency and excess, *Acta Obstet Gynecol Scand*, 2006;85:900–5.
- Leung KC, Johannsson G, Leong GM, Ho KK, Estrogen regulation of growth hormone action, *Endocr Rev*, 2004;25:693–721.