Preconception counselling for women with acromegaly: More questions than answers

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Abstract

Background and aims: Approximately 174 pregnancies in acromegaly have been reported. Our objectives were to identify the key challenges of preconception counselling in this population.

Methods: Case series of three acromegalic women with desire for pregnancy. Issues were identified from chart review and discussion with attending physicians. Literature review of acromegaly and pregnancy was conducted.

Results: Important issues identified included: impact of acromegaly on fertility, management of acromegaly in the peripartum period, screening for associated conditions, risk of progression of acromegaly/tumour growth during pregnancy, impact of acromegaly on pregnancy outcomes, surveillance during pregnancy, method of delivery and impact on neonatal outcomes and breastfeeding.

Conclusions: Pregnancy can be safely achieved in patients with acromegaly. There is little evidence to guide recommendations around conception and pregnancy surveillance. Patients can be reassured that in most situations, pregnancy proceeds without complication and that medical treatment can be used during pregnancy if necessary.

Keywords

Endocrinology, high-risk pregnancy, maternal–fetal medicine, reproductive endocrinology

Introduction

Pregnancy occurrence in a patient with acromegaly although rare, is becoming more common as therapy for acromegaly and fertility improves.^{31,32,34,35} Preconception counselling is important to optimize obstetrical outcomes. Currently there are limited guidelines pertaining to acromegaly and pregnancy; optimal management has not been established. A total of 174 acromegalic pregnancies are reported in the literature thus far; including 33 in a review from literature³³ without any detail to allow analysis. We report three new patients, a total of four pregnancies, each with unique issues to highlight the questions patients and their providers need to address preconception.

Case reports

Patient 1

At age 15 (1992), our patient experienced accelerated growth, coarse facial features and amenorrhea. After two transphenoidal resections (1999, 2000), she was managed with octreotide and one year of pegvisomant (1999–2000). In 2007, when first seen at our institution, she was taking octreotide long acting repeatable (LAR) and had an insulin-like growth factor 1 (IGF-1) level of 242 µg/L (normal range [NR] 131–780) and growth hormone (GH) 1.8 µg/L (NR <0.6). Her MRI showed a 2 × 3 mm left-sided hypointensity in the pituitary gland, likely representing residual tumour. She requested a trial off octreotide. A repeat MRI one year later demonstrated an increase in her residual lesion (1.1 × 0.4 × 0.6 cm) and her IGF-1 levels increased to 415 µg/L. She was restarted on octreotide. In 2012, she inquired about pregnancy. Preconception IGF-1 was 310 µg/L (NR 80–247). She elected to stop her octreotide prior to conception.

During pregnancy, her IGF-1 values decreased (Figure 1). She had an elective caesarean section for breech presentation at 39 weeks of a healthy 3599 g male following an uncomplicated pregnancy. She breastfed successfully and continued off octreotide until four months postpartum when she developed symptoms of diaphoresis and coarsening of her hair, as well an increased IGF-1 level, 561 µg/L (NR 80–247). A repeat MRI postpartum was stable. Octreotide LAR 30 mg monthly was restarted and she stopped breastfeeding. Her IGF-1 level decreased to 222 µg/L (NR 56–257).

Eight months after restarting octreotide, she became pregnant again and discontinued octreotide at pregnancy diagnosis. Preconception IGF-1 level was 247 µg/L (NR 56–257) and again decreased throughout pregnancy (Figure 1). She delivered a healthy female weighing 3630 g at 41 weeks via a vaginal birth complicated by placental abruption requiring transfusion. At her two-month postpartum follow-up, she was doing well off medication and continuing to breastfeed. A repeat MRI demonstrated no change from previous imaging. At six months postpartum, she was experiencing symptoms of drooling and fatigue. Her IGF-1 level was 400 µg/L (NR 56–257), thus she stopped breastfeeding and resumed octreotide.

Patient 2

At age 32 (2012), our patient was diagnosed with acromegaly through an infertility work up. She had amenorrhea and in retrospect increasing shoe and ring sizes. Initial MRI demonstrated a 3 × 2 × 1.5 cm pituitary lesion with extension into the suprasellar region, invasion of right cavernous sinus but no optic chiasm compression. Prolactin (PRL) was 23 µg/L, IGF-1 979 µg/L (NR 56–257), GH 26.3 µg/L luteinizing hormone (LH) 3 IU/L and follicle-stimulating hormone (FSH) 6 IU/L. She had two partial transphenoidal resections.

An MRI after the second surgery demonstrated residual tumour (2.1 × 1.3 cm) around the right internal carotid artery. After discussion with the patient, bromocriptine was trialed because of its known safety in pregnancy and effectiveness in some patients with acromegaly. Her

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Figure 1. IGF-I levels (µg/L), compared to prepregnancy and baseline, and in each trimester for each pregnancy.

Figure 2. Patient 2 postpartum MRI. One week postpartum. The lesion has slightly increased in size to 34.4 × 23.2 × 20.8 mm. No compression of the optic chiasm.

IGF-1 levels increased to 945 µg/L (NR 56–257) thus she was switched to octreotide LAR. She became pregnant one year after surgery, seven months after starting octreotide, despite a continued elevated IGF-1 level prior to conception of 758 µg/L (NR 56–257). Her octreotide was discontinued at diagnosis of pregnancy. She was restarted on octreotide LAR 10 mg monthly at 12 weeks gestation due to known tumour burden and development of headaches and diaphoresis. Octreotide was continued to term. Her IGF-1 levels decreased in pregnancy (Figure 1). Pregnancy was uncomplicated and visual field testing was normal. She delivered a healthy 4746 g male infant vaginally following induction at 41 + 4 weeks. A postpartum, MRI demonstrated slight increase in size to 3.4 × 2.3 × 2.1 cm (Figure 2) from 3.2 × 2.2 × 1.8 cm on a prepartum MRI (Figure 3). Six weeks postpartum her IGF-1 level increased to 1004 µg/L (NR 65–238) and thus her octreotide LAR was increased from 10 to 20 mg monthly. She continues to breastfeed successfully on octreotide.

Patient 3

Our third patient was diagnosed with acromegaly at age 23 (2003) with a 2 × 2 × 1.5 cm macroadenoma. She was initially managed with

Figure 3. Patient 2 prepartum MRI. Residual right-sided tumor, 32 × 21.5 × 18.3 mm, with invasion of the right cavernous sinus and encasing of the right cavernous ICA. Leftward stalk deviation. No compression of the optic chiasm.

Table 1. Issues to discuss with women with acromegaly prior to pregnancy.

How does acromegaly affect fertility?
What should be done to optimize acromegaly prior to pregnancy?
Should medications used to treat acromegaly be stopped prior to pregnancy?
Should medications used to treat acromegaly be stopped/changed during pregnancy?
What monitoring is needed in pregnancy? Is it reliable?
Is there a risk of progression of acromegaly during or after pregnancy?
Is the patient at increased risk of obstetrical complications?
Are there potential risks to the fetus if growth hormone levels high?

octreotide LAR and then transphenoidal surgery six months later. She continued on octreotide LAR and had a stable lesion. She frequently inquired about pregnancy planning and specifically asked about management during pregnancy, use of octreotide in the peripartum period, risk of fetal malformation and safety of delivery.

At age 33, she decided to actively pursue pregnancy. She conceived two months after discontinuing her oral contraceptive and discontinued her octreotide. Her IGF-1 level prior to conception was 379 µg/L and decreased throughout pregnancy (Figure 1). She had a spontaneous vaginal delivery at 41 + 2 weeks of a 3377 g healthy girl with no complications. Postpartum MRI was stable, with no evidence of a definite adenoma. She remained off octreotide for five months postpartum when she became symptomatic and had an IGF-1 level of 469 µg/L (65–238). She discontinued breastfeeding and restarted octreotide.

Discussion

In our experience, women with acromegaly had many questions regarding impact of acromegaly and its management on fertility, risks in pregnancy and impact on breastfeeding. We used each case, together with a literature review to identify the key issues important to address in prepregnancy counselling (Table 1).

Figure 4. GH-IGF1 axis during pregnancy: the placenta secretes a variant of GH, which replaces pituitary GH for stimulating IGF1 production from the liver. GH-IGF1 axis during pregnancy: the placenta secretes a variant of GH, which replaces pituitary GH for stimulating IGF1 production from the liver. Increased IGF1 inhibits pituitary GH secretion. —: stimulation; - - -: inhibition; GH-V: GH variant; IGF1: insulin-like growth factor I.

Source: Karaca et al.⁴²

Acromegaly and fertility

Fertility impairment in patients with acromegaly is multifactorial:¹⁻⁴ (1) stalk compression from the mass, which may reduce GnRH and increase PRL, (2) PRL co-secretion in some adenomas, (3) mass effect on gonadotrophic cells resulting reduced LH and FSH production and (4) direct effect from excess GH and IGF-1 (inhibition of GnRH and direct ovarian inhibition) independent of mass effect.¹⁻⁴ Grynberg et al.'s⁹ review of 55 females with acromegaly reported 17 (31%) were eugonadal and 38 (69%) were anovulatory. Compared with anovulatory women, eugonadal patients were significantly more likely to have microadenomas (2/26 vs. 5/17; $P=0.04$) and trended towards lower serum PRL levels. Of the 38 anovulatory women, 11 (28.9%) were due to hyperprolactinemia, 6 (15.7%) due to mass effect, 7 (18.4%) secondary to increased GH/IGF-1. The remaining 14 (36.8%) were considered mixed etiology or unclassifiable. After treating the determined cause, 25/38 (65.8%) had resumption of menses. Cases where regular menses did not occur were due to menopause (2/38), persistent gonadotrophic insufficiency after radiation therapy (6/38) or unstated causes (5/38). With treatment of acromegaly, there is hope for recovery of ovulation and successful pregnancy. Conversely, contraception is required for women not wanting pregnancy.

GH physiology in pregnancy

In normal pregnancy, GH is mainly secreted by the maternal pituitary in a pulsatile manner during the first trimester. Around 15 weeks, gestation placental GH variant (GH-V) becomes the main component of circulating GH.^{2,3} This stimulates maternal liver production of IGF-1 which in healthy women inhibits pituitary production of

GH (Figure 4). GH-V production rises exponentially until 37 weeks⁷ and pituitary GH gradually drops to undetectable levels.⁷ Thus in normal pregnancies, there is a modest reduction of IGF-1 in the first trimester then increases during second half of pregnancy to two to three times upper limit of normal, peaking at 37 weeks.^{2,3,7} The majority of laboratory GH assays cannot distinguish between pituitary GH and the placental GH-V. These normal changes limit the usefulness of continued monitoring levels during pregnancy.

Effect of pregnancy on acromegaly

During pregnancy, IGF-1 levels or adenoma size rarely increase to the point of becoming a concern in regards to the safety of the mother or fetus. In acromegaly, adenomatous somatotroph cells are resistant to IGF-1 inhibitory feedback; thus pituitary production of GH continues.^{3,5,6} Interestingly, in the majority of cases, including our patients (Figure 1), IGF-1 levels often decrease compared to preconception levels. One theory is that the increased estrogen levels of pregnancy increase GH binding protein and inhibit GH activation of signal transduction, thus producing a state of GH resistance.^{6,23,24} Postpartum, IGF-1 levels will quickly rise to preconception levels and often surpass baseline values.^{5,6} This is important as reintroducing medical management may result in some women electing to discontinue breastfeeding early as in our case.

In normal pregnancy, the pituitary gland enlarges up to 45% in the first trimester due to hyperplasia of lactotroph cells and reduced gonadotroph cells.³ Thus during pregnancy in patients with acromegaly, there is a theoretical risk of tumour enlargement and optic chiasm compression.^{3,4} There is concern with vaginal delivery that increasing valsalva pressure may translate to increasing intracranial pressure and pituitary apoplexy or hemorrhage during delivery.

In reviewing the available data, most studies did not report postpartum imaging. However, in the 47 cases where it was available, a small proportion of patients, 6/47 (13%) experienced tumour growth, especially in patients with baseline macroadenoma.^{2,8,21,23,36,37} In our review, 5/145 (3%) reported tumour growth during pregnancy necessitating surgery. Three of these patients were diagnosed with acromegaly during pregnancy.^{2,17,18,20,25} Indications for surgery were visual loss (3),^{2,17,18} apoplexy (1)²⁰ and increased intracranial pressure (1).²⁵ Fifteen patients out of the 145 reviewed (10%) experienced symptoms of tumour growth managed medically.^{2,11,14,22,28} In our cases, one patient demonstrated postpartum tumour growth (uncontrolled IGF-1 and macroadenoma prior to pregnancy). Formal visual field examinations are recommended every six weeks, especially in patients with macroadenoma.⁶

Effect of acromegaly on pregnancy

Elevated GH levels may put the pregnant woman at increased risk of glucose intolerance, gestational diabetes mellitus (GDM), hypertension (HTN) and preeclampsia. Based on a combined review of 145 cases reported, 5.5% developed GDM, 5.5% developed gestational HTN and there was a 2.8% rate of preeclampsia.^{2,4,5,8,11,19,20–22,24} None of our cases developed metabolic complications.

In Caron et al.'s² study of 59 acromegalic pregnancies, 6.8% developed GDM compared to an incidence of <6% in healthy French women. Furthermore, 13.6% developed new HTN, compared to an incidence of 5–15% in healthy French women.² When comparing women with controlled IGF-1/GH levels preconception, 4% of controlled patients developed GDM compared to 9% of uncontrolled. Dias et al.⁵ reported 10 pregnancies in women with acromegaly, 10% developed GDM and 10% developed preeclampsia/HTN. Similarly, the prevalence of HTN and GDM during pregnancy was felt to be comparable to the normal Brazilian population, 7.4% for HTN and 7.6% for GDM.⁵ Thus, both studies support a hypothesis that uncontrolled preconception IGF-1 levels may be related to an increased risk of metabolic complications.

Women with glucose intolerance/diabetes and HTN should be optimized preconception with medications that can be used throughout pregnancy.⁴¹ No studies have reported impact of pregnancy on the other complications of acromegaly such as compression neuropathies and sleep apnea.

Treatment during pregnancy

Acromegaly may be treated with one or more of transsphenoidal surgery, medical treatment (somatostatin receptor agonists [SA], dopamine agonists [DA] and GH receptor antagonists [GHRAs]) and radiation.⁴² Transsphenoidal surgery is generally the first treatment option if diagnosed prior to pregnancy. For young women, there is risk of LH/FSH deficiency from surgery and thus infertility must be discussed. Regardless it should remain the first option. Surgery is often noncurative and postoperative long-term medical therapy is frequently required.

Long-acting SAs are the medical therapy of choice. Most recommend discontinuation of medical therapy prior to a planned conception or at the diagnosis of pregnancy.^{2,4,5,8,42} The Endocrine Society recommends changing from long-acting to short-acting SA to limit duration of exposure when pregnancy confirmed. There is a theoretical concern regarding use of SA during pregnancy since octreotide can cross the placenta and there are placental somatostatin receptors. However, octreotide has a minimal effect on GH-V production.¹² Ability for SA to bind to fetal somatostatin receptors and their functionality is unclear since IGF-1 levels were normal in newborns exposed to octreotide in-utero.^{8,12} The effect of octreotide on uterine artery blood flow has been studied in one patient. Within five minutes after octreotide injections, a statistically significant reduction in blood

flow was observed, 45% in systole and 25% in diastole. However this was fully reversible and only lasted 10 min.¹² Thus, there is evidence of fetal exposure to somatostatin receptor agonists and potential effect on uterine blood flow with no clear documentation of a clinically significant effect. Review of the data for SA for acromegaly during pregnancy identified 27 pregnancies. Of the 27, there were 6 small for gestational age (SGA) births (two women were also taking DA) and 4 large for gestational age (LGA) infants.^{2,4,13,15,27,30} and one case of preeclampsia (this patient was also on DA). Two case reports with three and six-year follow-up demonstrated normal growth parameters.^{12,19} Given the paucity of data, most would suggest discontinuing octreotide prior to pregnancy and only reinstituting if symptoms occur.

GHRAs (pegvisomant) are a second-line medical therapy for acromegaly.²⁶ Animal studies have not demonstrated teratogenicity from GHRA. A case series of 21 pregnancies with pegvisomant exposure resulting in 13 live births was recently reported and did not suggest any adverse consequences, however this does not prove safety.⁴³ In another study, low levels of pegvisomant were detected in cord blood suggesting minimal placental transfer or potentially maternal blood contamination.¹⁶ Similarly, despite the maternal pegvisomant level being in therapeutic range, the fetal pegvisomant levels were minimal. Pegvisomant levels in breast milk were undetectable. The longest follow-up after use of pegvisomant was six months and showed normal growth parameters.¹⁶ However, the small sample prohibits any reliable conclusions regarding the safety of GHRAs in pregnancy.

A large amount of data of use of DA in pregnant patients with prolactinomas are reassuring for use in acromegaly as well.³ There is evidence that bromocriptine crosses the placenta and affects the fetal pituitary from a case study in an acromegalic woman treated with bromocriptine 10 mg daily throughout gestation. At birth, the infant's plasma GH levels were normal, but PRL was very low and increased in the following days. The amniotic fluid levels of PRL were high.¹⁰ Our review of the data for DA specifically for acromegaly in pregnancy identified 28 pregnancies.^{2,10,11,29,38} Of the 28, there were 2 SGA births (these women were also on SA), 2 LGA births, 2 cases of preeclampsia (one of which the woman was also on SA).^{2,10,11,29}

In all studies reviewed, with or without exposure to acromegaly-targeted medications, there have been no reports of congenital malformations or teratogenicity. Surgical management and control of IGF-1 levels prior to pregnancy should be targeted. Growth of tumour is possible therefore monitoring for mass effect symptoms and visual fields is advised. If need for treatment manifests or if patient has a baseline macroadenoma with risk of visual compromise and continuation of treatment is desired, a thorough discussion with the patient is required. Although there is more evidence to support the safety of DA in pregnancy, they are less effective. SA is likely safe. At this point, GHRAs have an unknown risk due to lack of evidence. If medication is continued, close monitoring of fetal development is necessary. Surgery is reserved for emergencies such as visual loss and pituitary apoplexy.

Effect of acromegaly on neonates

Pituitary GH does not cross the placenta and thus has no effect on fetal development.³⁹ With discontinuation of medical therapy, there does not appear to be any risk to the fetus. Although there is a theoretical potential indirect effect of elevated GH/IGF-1 levels on development of the placenta, there has not been any documented clinically relevant effect. Long-term data are lacking.

Postpartum issues

Postpartum the major issues are risk of exacerbation, need for imaging and when to reinstate medical therapy especially in breastfeeding women. A postpartum MRI seems prudent, given the risk of tumour growth as described above.

The reductions in IGF-1 during pregnancy are often followed by a rise postpartum, often to levels higher than preconception^{3,4,8} as exhibited in our cases. GH-V levels drop on the first day postpartum³ and so GH levels within a few weeks postpartum should reflect pituitary source. IGF-1 levels have a longer half-life, thus should be measured 12 weeks postpartum unless there is clinical evidence of progression.

Use of DA would limit breastfeeding since lactation is inhibited. SAs are excreted in breast milk but the risk is unclear; given that these agents are ineffective when taken orally, there is unlikely a risk to the newborn. GHRA has unknown secretion in breast milk and thus risk cannot be ruled out. Breastfeeding can be safely attempted in patients with a no signs of tumour growth during pregnancy, but appreciating that if maintained off medical therapy, there is an increased risk of elevated IGF-1 levels and disease activity.

Conclusion

Pregnancy in acromegaly is rare, and there are multiple mechanisms that contribute to infertility. However, as treatment of acromegaly and infertility advances, pregnancy is becoming more common. Preconception counselling is important to optimize a successful pregnancy and neonatal outcome. Women with acromegaly will want information on the potential risks during pregnancy, delivery and postpartum. Additionally management of acromegaly during pregnancy and the need for increased monitoring should be discussed. Women will want to be informed about neonatal outcomes and any potential effects to the fetus.

The scarcity of data limits the ability to provide evidenced-based recommendations to women around conception and pregnancy surveillance. However, the accumulated reported experience is encouraging and patients can be reassured that in most situations pregnancy proceeds without complications and that medical treatment can be used during pregnancy if necessary.

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Author contributions

Dr. Assal is the lead author of this publication. She developed the study protocol, performed the literature review and summarized the evidence. She collected patient data from the chart and described the patient cases. She wrote and edited the manuscript. Dr. Keely is the attending supervisor for this project. She assisted in generating the research question and directed the study protocol. She assisted in data collection and reviewing the results. She assisted in writing and editing the manuscript. Dr. Malcolm assisted in study protocol development, collection of data and review of the evidence. She assisted in editing the manuscript. Dr. Lochnan assisted in study protocol development, collection of data and review of the evidence. She assisted in editing the manuscript.

References

- Caron P. Acromegaly and pregnancy. *Ann Endocrinol* 2011; 72(4): 282–6.
- 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(10): 4680–4687.
- Cheng V, Faiman C, Kennedy L, et al. Pregnancy and acromegaly: a review. *Pituitary* 2012; 15: 59–63.
- Cheng S, Grasso L, Martinez-Orozco JA, et al. Pregnancy in acromegaly: experience from two referral centers and systematic review of the literature. *Clinical Endocrinology* 2012; 76: 264–271.
- Dias M, Boguszewski C, Gadelha M, et al. Acromegaly and pregnancy: a prospective study. *Eur J Endocrinol* 2014; 170: 301–310.
- Valassi E. Acromegaly and pregnancy. *Endocrinol Nutr* 2013; 60(1): 1–3.
- Verhaeghe J. Does the physiological acromegaly of pregnancy benefit the fetus? *Gynecol Obstet Invest* 2008; 66(4): 217–226.
- Cozzi R, Attanasio R and Barausse M. Pregnancy in acromegaly: a one-center experience. *Eur J Endocrinol* 2006; 155(2): 279–284.
- Grynberg M, Salenave S, Young J, et al. Female Gonadal Function before and after Treatment of Acromegaly. *J Clin Endocrinol Metab* 2010; 95(10): 4518–4525.
- Bigazzi M, Rogna R, Lancranjan I, et al. A pregnancy in an acromegalic woman during bromocriptine treatment: effects on growth hormone and prolactin in the maternal, fetal, and amniotic compartments. *J Clin Endocrinol Metab* 1979; 48(1): 9–12.
- Hisano M, Sakata M, Watanabe N, et al. An acromegalic woman first diagnosed in pregnancy. *Arch Gynecol Obstet* 2006; 274(3): 171–173.
- Maffei P, Tamagno G, Nardelli G, et al. Effects of octreotide exposure during pregnancy in acromegaly. *Clin Endocrinol (Oxf)* 2010; 72(5): 668–677.
- Fassnacht M, Capeller B, Arlt W, et al. Octreotide LAR treatment throughout pregnancy in an acromegalic woman. *Clin Endocrinol (Oxf)* 2001; 55(3): 411–415.
- Neal JM. Successful pregnancy in a woman with acromegaly treated with octreotide. *Endocr Pract* 2000; 6(2): 148–150.
- Mozas J, Ocon E, Lopez de la Torre M, et al. Successful pregnancy in a woman with acromegaly treated with somatostatin analog (octreotide) prior to surgical resection. *Int J Gynaecol Obstet* 1999; 65(1): 71–73.
- Brian SR, Bidlingmaier M, Wajnrajch MP, et al. Treatment of acromegaly with pegvisomant during pregnancy: maternal and fetal effects. *J Clin Endocrinol Metab* 2007; 92(9): 3374–3377.
- Güven S, Durukan T, Berker M, et al. A case of acromegaly in pregnancy: concomitant transphenoidal adenomectomy and cesarean section. *J Matern Fetal Neonatal Med* 2006; 19(1): 69–71.
- Sahli R and Christ E. Pregnancy in active acromegaly. *Dtsch Med Wochenschr* 2008; 133(45): 2328–2331.
- Takano T, Saito J, Soyama A, et al. Normal delivery following an uneventful pregnancy in a Japanese acromegalic patient after discontinuation of octreotide long acting release formulation at an early phase of pregnancy. *Endocr J* 2006; 53(2): 209–212.
- Atmaca A, Dagdelen S and Erbas T. Follow-up of pregnancy in acromegalic women: different presentations and outcomes. *Exp Clin Endocrinol Diabetes* 2006; 114(3): 135–139.
- Persechini ML, Gennaro I, Grunenwald S, et al. Acromegaly and pregnancy: Report of six new cases. *J Gynecol Obstet Biol Reprod (Paris)* 2013; 43(9): 704–712.
- Edo AE and Eregie A. Pregnancy associated with recurrent acromegaly: a case report. *West Afr J Med* 2010; 29(2): 120–122.
- Shimatsu A, Usui T, Tagami T, et al. Suppressed levels of growth hormone and insulin-like growth factor-I during successful pregnancy in persistent acromegaly. *Endocr J* 2010; 57(6): 551–553.

24. Lau SL, McGrath S, Evain-Brion D and Smith R. Clinical and biochemical improvement in acromegaly during pregnancy. *J Endocrinol Invest* 2008; 31(3): 255–261.
25. Montini M, Pagani C, Gionala D, et al. Acromegaly and primary amenorrhea: ovulation and pregnancy induced by SMS 201-995 and bromocriptine (letter). *J Endocrinol Invest* 1990; 13: 193.
26. Qureshi A, Kalu E, Ramanathan G, et al. IVF/ICSI in a woman with active acromegaly: successful outcome following treatment with pegvisomant. *J Assist Reprod Genet* 2006; 23: 439–442.
27. de Menis E, Billeci D, Marton E, et al. Uneventful pregnancy in an acromegalic patient treated with slow-release lanreotide: a case report. *J Clin Endocrinol Metab* 1999; 84: 1489.
28. Takeuchi K, Funakoshi T, Oomori S, et al. Successful pregnancy in an acromegalic women treated with octreotide. *Obstetr Gynecol* 1999; 93: 848.
29. Sanchez R, Boix E, del Pino Navarro M, et al. Pregnancy in an acromegalic patient treated with lanreotide and bromocryptin. *Medicina clinica* 1999; 113: 198.
30. Mikhail N. Octreotide treatment of acromegaly during pregnancy. *Mayo Clinic Proceeding* 2002; 77: 297–298.
31. Hierl T, Ziegler R and Kasperk C. Pregnancy in persistent acromegaly. *Clin Endocrinol (Oxf)* 2000; 53: 262–263.
32. Herman-Bonert V, Seliverstov M and Melmed S. Pregnancy in acromegaly: successful therapeutic outcome. *J Clin Endocrinol Metab* 1998; 83: 727–731.
33. Abelow WA, Rupp JJ and Paschkis KE. Acromegaly and pregnancy. *J Clin Endocrinol Metab* 1954; 14: 32.
34. Colao A, Merola B, Ferone D, et al. Acromegaly. *J Clin Endocrinol Metab* 1997; 82: 2777–2781.
35. Landolt AM, Schmid J, Wimpfheimer C, et al. Successful pregnancy in a previously infertile woman treated with SMS-201-995 for acromegaly. *N Engl J Med* 1989; 320: 671–672.
36. Kasuki L, Neto LV, Takiya CM and Gadelha MR. Growth of an aggressive tumor during pregnancy in an acromegalic patient. *Endocr J* 2012; 59(4): 313–319.
37. Ben Salem Hachmi L, Kammoun I, Bouzid C, et al. Management of acromegaly in pregnant woman. *Ann Endocrinol (Paris)* 2010; 71(1): 60–63.
38. Luboshitzky R. Bromocriptine-induced pregnancy in an acromegalic patient. *JAMA* 1980; 8;244(6): 584–586.
39. Koshy G, Rajaratnam S, Mathews JE, et al. Acromegaly in pregnancy. *Indian J of Endocrinol Metab* 2012; 16(6): 1029–1031.
40. Karaca Z, Tanriverdi F, Unluhizarci K and Kelestimur F. Pregnancy and pituitary disorders. *Eur J Endo* 2010; 162(3): 453–475.
41. Melmed S, Casanueva FF, Klibanski A, et al. A Consensus on the Diagnosis and Treatment of Acromegaly Complications. *Pituitary* 2013; 16(3): 294–302.
42. Katznelson L, Laws E, et al. Acromegaly: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2001; 99: 3933–3951.
43. Van der Lely AJ, Gomez R, Heissler JF, et al. Pregnancy in acromegaly patients treated with pegvisomant. *Endocrine* 2015; 49(3): 769–773.