PREGNANCY MANAGEMENT IN PATIENTS WITH ACROMEGALY

LITERATURE REVIEW

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INTRODUCTION

Pregnancy might be accepted as a new physiological state for the pituitary gland with altered anatomy, modified courses, diagnosis, and treatment of pituitary diseases [1]. Due to physiological changes in the pituitary and target hormone levels, binding globulins, and placental hormones, hormonal evaluation becomes more complex in pregnant women. As a consequence of physiological hormonal changes, the evaluation of pituitary functions in pregnant women is quite different from that done in the prepregnant state [2, 3].

Acromegaly is a rare, chronic, endocrine disorder, usually caused by hypersecretion of growth hormone (GH) for a prolonged period from a somatotroph adenoma [4, 5]. The term "acromegaly" is derived from two Greek words: "akrom", meaning extremity, and "megas", meaning great. The meaning reflects one of the familiar symptoms of the disease, which is abnormal growth of hands and feet [6]. Nowadays acromegaly is diagnosed with increasing frequency and its mean age of onset coincides to a great extent with the child-bearing life of women [7].

Treatments currently available for acromegaly include surgery, drug treatment and, in some cases, radiotherapy. These therapeutic modalities achieve tumor growth control and minimize the clinical consequences of hypersomatotropism in most patients [8]. Despite the positive impact of current treatments on survival and quality of life, pregnancy in acromegaly continues to be an uncommon event and a challenge for clinicians.

FERTILITY AND ACROMEGALY

Infertilily is common in women with acromegaly, as approximately 75% of acromegalic women of child-bearing years have menstrual irregularities [9]. This is attributed either to anatomic compromise of gonadotropin-producing cells (mass effect in the pituitary) or to concurrent hyperprolactinemia. Prolactin hypersecretion may occur from a mass interfering with dopamine action or from cosecretion along with the GH. In addition, prolactin-like effects of GH (specificity spillover) may contribute to the menstrual irregularity observed in acromegaly [9, 10].

Hyperactivity of the somatotropic axis may also alter hormonal cycles leading to ovulation. This, combined with the greater frequency of ovarian functional hyperandrogenism and increased insulin resistance in patients with acromegaly [11], may hinder ovulation and, thus, pregnancy. In addition, hypogonadotropic hypogonadism due to tumor compression or iatrogenic in nature (surgery and radiotherapy) may coexist, and will then require external hormonal induction of ovulation to achieve pregnancy [11, 12].

PHYSIOLOGICAL CHANGES OF PITUITARY GROWTH HORMONE DURING PREGNANCY

Pregnancy is a state of mild physiological acromegaly [5, 13]. The number of somatotrophs is reduced in normal pregnancy and basal and stimulated maternal GH levels are suppressed by the second trimester. However, the placenta produces a variant GH that [14]:

- differs from pituitary GH by 13 amino acids;
- has similar carbohydrate, lipid, and somatogenic properties as pituitary GH, with less lactogenic activity;
- binds to hepatic GH receptor with an affinity that is similar to the affinity with which the receptor binds to GH, and can not be distinguished by conventional radioimmunoassay as different from pituitary GH;
- postpartum disappears from the circulation within 24 hours.

Placental GH is detectable by the fifth week of pregnancy, its levels increase exponentially and peak at 35–37 weeks. The secretion of placental

GH is continuous, and regulated neither by GH-releasing factor nor by ghrelin (an enzyme produced by stomach lining cells) [15]. Placental variant of GH decreases pituitary GH secretion by insulin-like growth factor-1 (IGF1). The both, placental GH and IGF1, have growth-promoting effects on the fetus and placenta [16]. Decreased GH response to insulin-induced hypoglycemia or arginine suggests decreased reserve of GH secretion by the maternal pituitary (Table 1).

Placenta also produces IGF1 which levels are [17, 18]:

- dramatically increase in the second half of pregnancy, contributing to the acromegaloid features of some pregnant women;
- suppresses the pituitary secretion of GH through the normal negative feedback mechanism - pregnancy is a state of physiological GH, IGF1 excess;
- are not useful in the diagnosis of acromegaly in pregnancy, as they elevate in the second half of both normal and acromegalic pregnancies;
- are normal even in patients with pituitary GH deficiency.

DIAGNOSTICS OF ACROMEGALY IN PREGNANCY

Biochemical tests

Diagnosis of new onset acromegaly in pregnancy is problematic due to the complex issue of measuring GH, which includes placental GH and GH resistance in the presence of high estrogen. Standard radioimmune evaluation can not distinguish between normal pituitary GH and the placental variant GH. Because basal levels of placental GH are high results may erroneously indicate acromegaly. Moreover, in acromegaly pituitary GH secretion are autonomous too so both pituitary and placental GH variants persist throughout pregnancy in a high quantity [2, 19].

Also usual reference ranges for both basal and post glucose GH as well as for IGF1 levels can not be applied to pregnant women, as GH levels decline and IGF1 levels increase during normal pregnancy [20].

In several researchers clinical activity of acromegaly has been variably shown to improve, remain stable, or worsen during pregnancy, but no clear correlation with hormone levels has been established [7, 23]. In conclusion, hormonal assessment of acromegaly during pregnancy is challenging.

Rarely, acromegaly occurs as a result of ectopic tumors producing GH or growth hormone-releasing hormone. When a biochemical diagnosis has been established for acromegaly without any pituitary tumor or diffused pituitary enlargement is detected, ectopic sources should be suspected. Measurement of the plasma growth hormone-releasing hormone level is beneficial in identifying ectopic sources of tumor [7].

Imaging studies

When clinical findings and the limited laboratory examination suggest acromegaly, sella magnetic resonance imaging (MRI) (without gadolinium) is considered to be the most effective imaging technique to locate the pituitary source of excess GH [24]. MRI enables the identification of very small tumors, even smaller than 2 mm, tumor invasiveness, proximity to the optic chiasm, and compression of surrounding structures by the tumor which previously remained undetected. The majority of somatotroph adenomas (75–85%) are macroadenomas (>10 mm in diameter) at the time of diagnosis, which rarely grow into the cavernous sinus [25].

Performing computed tomography scans and coned-down views of the sella is not recommended in pregnancy, due to radiation exposure.

Table 1. Summary of characteristics of pituitary and placental GH

Feature	Pituitary GH	Placental GH
Source	Somatotroph	Syncytiotrophoblast
Maximum levels	Early pregnancy	Late pregnancy
Production	Pulsatile (13–19 pulses per 24 h)	Non pulsatile (tonic)
Effect of gonadotropin-releasing hormone	Positive	No
Paradoxical effect of thyrotropin-releasing hormone	Positive	No
Effect of ghrelin	Positive	No
Inhibition by glucose	Yes	Yes
Response to hypoglycemia	Enhanced	Decreased
Response to arginine	Enhanced	Varies
IGF1 production	Yes	Yes
Measurement by routine tests	Yes	No

CLINICAL COURSE

Clinical course of acromegaly during pregnancy

Acromegalic symptoms may improve during pregnancy from the increased estrogen production inhibiting hepatic IGF1 production. Mostly pregnancy has not been found to change the course of acromegaly, other than, in rare cases of asymptomatic tumor enlargement, which may or may not be related to physiologic pituitary hyperplasia [2].

Recurrence of signs and/or symptoms of acromegaly activity occurred in puerperium and were paralleled by increased IGF1 levels. The overall beneficial effect of pregnancy on both clinical and hormonal activity of acromegaly is transient and usually disappears within a few weeks after delivery [26].

In a large retrospective series, only three of 27 cases (11%) [22] exhibited radiological evidence of tumor growth during pregnancy. Tumor enlargement may also be theoretically triggered by somatostatin receptor ligand discontinuation at pregnancy onset [27]. However, as the pituitary gland enlarges during gestation due to hyperplasia of lactotrophic cells, pregnant patients with macroadenomas may also develop visual symptoms and/or headache as a result of the pituitary enlargement in a restricted sellar space [28].

Tumor enlargement after octreotide withdrawal, tumor apoplexy, aggressive tumors, and untreated acromegaly may determine a less favorable visual outcome during pregnancy [29–31].

The development of gestational diabetes insipidus during late gestation is likely the result from the combined effects of a reduced vasopressin reserve due to previous pituitary surgery and the physiological increase in placental vasopressinase activity in late pregnancy [30, 32].

With worsening of the course of acromegaly acromegaly-associated cardiomyopathy may become symptomatic during pregnancy that can be manifested by hypertension, arrhythmias and congestive heart failure. The rest complications associated with acromegaly include sleep breathing disorders, dolichocolon, arthropathies and metabolic disoders [31, 32].

Breast feeding does not affect the course of acromegaly.

Clinical course of pregnancy in women with acromegaly

The relatively uneventful course of pregnancy and delivery and the healthy newborns is usual. The literature indicates an increased risk of gestational diabetes and gravid hypertension in women with non-controlled GH/IGF1 hypersecretion before gestation [1, 2, 7, 27], which must be appropriately treated, but in most patients, specific acromegaly therapy can be delayed until after delivery.

GH and IGF1 levels during pregnancy and puerperium in women with acromegaly

Previous studies showed that in most cases tumor secretion of GH is autonomous [2, 3, 14]. Thus in pregnant acromegalic patients, pituitary GH levels are initially increased. However, most researches indicate that pregnancy does not further stimulate the secretory activity of somatotrophic adenomas [19, 21, 22].

Clues to the presence of a true increase in pituitary GH include a documentation of pulsatility, which is characteristic of acromegaly, while placental GH secretion is apulsatile [19].

The effect of pregnancy on IGF1 levels is likely to reflect the blockade of IGF1 generation by the strikingly high estrogen levels of pregnancy [34, 35] which can lead to some improvement in the clinical features of acromegaly during pregnancy [2]. IGF1 levels in patients are increased during the first trimester (as tumoral GH secretion is not progressively suppressed), but remained stable thereafter. The apparent paradox of increasing placental GH with no further increases in IGF1 levels after midgestation in acromegalic patients may reflect that the tumoral GH levels (range 3.7–8.4 mg/l in second trimester) can not be significant to add somatogenic effect to much higher placental GH concentrations (range 2.1–69.8 mg/l in third trimester) in a situation of blunted maximal response of hepatic IGF1 generation [2, 7, 14].

IGF1 levels increase markedly when the influences of both placental GH and estrogen have completely ceased after delivery [34, 36]. Thus estrogen-induced GH resistance is likely to be a major factor keeping IGF1 levels stable in spite of increasing placental GH and unrestrained tumor GH secretion during pregnancy [36, 37].

Effect of acromegaly on fetus

GH does not cross the placenta, and maternal acromegaly has little direct impact on the fetus. While initial reports suggested fetus growth retardation due to hemodynamic changes in materno-fetal barrier, further studies failed to confirm an association with small babies for gestational age and suggested no apparent adverse effects [8, 20, 23].

Macrosomia in such pregnancies is likely secondary to maternal glucose intolerance [20].

ACROMEGALY THERAPY

Somatostatin analogs, dopamine agonists and GH receptor ligands are used in acromegaly. Pharmacological treatment with somatostatin analogs has been associated with decreased length in newborns and small-for-gestational-age babies [16, 39]. Nevertheless, octreotide, a short-acting somatostatin analog, can be successfully used to treat tumor enlargement symptoms (has a dramatic analgesic effect on acromegaly-associated headache) [41, 42].

Initial reports on the use of pegvisomant (GH receptor antagonist) in pregnancy have been encouraging, but data are insufficient to support the usage of this agent in anything but an exceptional situation [38]. No transfer across the placenta or entering of the breast milk has been noted. Because of the lack of many case reports and no controlled studies, this agent is best avoided during pregnancy other than in clinically indicated situations.

Use of dopamine agonists (cabergoline, bromocriptine) during pregnancy in some cases has been associated with fetal macrosomia [21]; otherwise use of these drugs throughout pregnancy has not been associated with any fetal malformation or any adverse postnatal development [40]. In patients with significant tumor enlargement during pregnancy or with severely symptomatic acromegaly, bromocriptine therapy or transsphenoidal surgery is an appropriate treatment option.

A Practice Guideline on Acromegaly by the US Endocrine Society (2014) included the following recommendations on pregnancy:

- In pregnancy long-acting somatostatin receptor ligands formulations and pegvisomant should be discontinued approximately 2 months before attempts to conceive, with use of short-acting octreotide as necessary until conception [43].
- Dopamine agonists (bromocriptine or cabergoline) or somatostatin analogs (octreotide or lanreotide) can be instituted in patients with symptomatic (headache) tumor enlargement during pregnancy or with severely symptomatic acromegaly [44].
- Transsphenoidal surgery can be performed during the second trimester if there is no relief [45].
- Women with tumor expansion during pregnancy should be advised against breast feeding [6].

Drugs for acromegaly therapy in pregnant women presented at Table 2.

PREGNANCY MANAGEMENT IN ACROMEGALIC PATIENTS

Optimal management of acromegaly during pregnancy has not been established. With the widespread use of pharmacological treatment to control disease activity, a consensus on acromegaly management has recently stated the need to encourage reporting of outcomes in medically treated pregnant patients.

Thus an analysis of the literature [6, 16, 22, 23, 33] and our own clinical experience have allowed to include the following recommendations for pregnancy management in acromegalic patients:

- Discontinue long-acting somatostatin receptor ligands formulations and pegvisomant approximately 8 weeks before conception, with use of short-acting octreotide.
- Acromegaly medical therapy should be withheld and administered only for tumor growth and headache control during pregnancy.

Table 2. Drugs for acromegaly therapy in pregnant women

Drug	Dosage	Comments
Bromocriptine (dopamine agonists) Category B*	2.5–20 mg orally two times per day.	Cross the human placenta. Maternal and fetal prolactine levels are suppressed.
Cabergoline (dopamine agonists) Category B*	0.5 mg orally two times per week.	Second-line therapy. Useful in women who are resistant or can not tolerate bromocriptine.
Octreotide (somatostatin analogs) Category B*	20 mg subcutaneously every 4 weeks for 3 months; titrate up or down to 10–30 mg; not to exceed 40 mg.	Risk of fetal growth retardation.
Lanreotide (somatostatin analogs) Category C*	60–90 mg subcutaneously every 4 weeks for 3 months; not to exceed 120 mg.	Risk of fetal growth retardation. Decreased fetal survival and increased fetal skeletal/soft tissue abnormalities (in rats).

* U.S. Food and Drug Administration pregnancy categories

- Monitoring of GH and/or IGF1 levels during pregnancy is not necessary in patients without clinical symptoms.
- Clinical and biochemical evaluation at least one time per trimester and at least one time after delivery (between 3 and 6 weeks) in patients with registered symptoms.
- Screening for diabetes mellitus between 24 and 28 weeks.
- Screening for pregnancy-induced hypertension.
- Visual field testing monthly in women with macroadenoma, in women with microadenoma every 3 months.
- Sellar MRI without contrast can be performed after the first trimester in case of symptoms and visual field abnormalities.
- Lactation is allowed except for women with tumor expansion during pregnancy.
- The decision to resume drug treatment and stop lactation should be individualized according to clinical judgment.

CONCLUSIONS

Pregnancy in acromegalic patients usually improves disease control and does not stimulate tumor growth, even after drug treatment withdrawal, and newborns are usually healthy. Women with pre-existing acromegaly who have had their drug therapy withdrawn usually have an uneventful pregnancy. Biochemical monitoring is of less value during pregnancy, and clinical data are more difficult to interpret, because the typical changes of pregnancy may be very similar. Patient should be monitored closely for gestational diabetes, pregnancy-induced hypertension and tumor growth during pregnancy.

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Literature review

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Acromegaly is a rare, chronic, endocrine disorder, usually caused by hypersecretion of growth hormone (GH) for a prolonged period from a somatotroph adenoma. Hormonal evaluation becomes more complex in pregnant women due to physiological changes in the pituitary and target hormone levels, binding globulins, and placental hormones. Evaluation of pituitary functions in pregnant women is quite different from nonpregnant women because of physiological hormonal changes. Pregnancy in acromegaly continues to be an uncommon event and a challenge for clinicians despite the positive impact of current treatments on survival and quality of life. Diagnosis of acromegaly during pregnancy is difficult because of changes in GH and insulin like growth factor 1 (IGF 1) levels, GH production by placenta, and the inability of routine methods to distinguish the pituitary GH from placental GH.

In the majority of patients with acromegaly pregnancy does not have an adverse effect on mother or fetus and pituitary mass does not increase in size. Tumor enlargement may theoretically occur if pre-existing therapies such as somatostatin analogues are discontinued with the onset of pregnancy. Acromegalic symptoms may improve during pregnancy, possibly from the increased estrogen production inhibiting hepatic IGF 1 production. Pregnancy course is mostly uneventful but the literature indicates an increased risk of gestational diabetes and gravid hypertension in women with non-controlled GH/IGF 1 hypersecretion before gestation.

In case of tumor enlargement frequent monitoring is required, surgery can be considered in the second trimester. Dopamine agonists and somatostatin analogs can be used without any adverse consequences on mother or fetus. In pregnancy acromegaly medical therapy should be withheld and administered only for tumor growth and headache control during pregnancy. Breast feeding does not affect the course of acromegaly. Postpartum pituitary imaging demonstrates no increased tumor growth after pregnancy.

Keywords: acromegaly, pregnancy, growth hormone, insulin like growth factor-1, dopamine agonists, somatostatin analogs.

ВЕДЕННЯ ВАГІТНОСТІ В ПАЦІЄНТОК ІЗ АКРОМЕГАЛІЄЮ

Огляд літератури

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Акромегалія – рідкісне хронічне ендокринне захворювання, яке зазвичай викликається гіперсекрецією гормону росту (ГР) соматотрофною аденомою протягом тривалого періоду часу. Через фізіологічні зміни рівнів гіпофізарних гормонів, зв'язуючих глобулінів і плацентарних гормонів гормональна оцінка стає більш складною у вагітних жінок. Внаслідок фізіологічних гормональних змін оцінка функцій гіпофіза у вагітних жінок дуже відрізняється від такої у невагітних. Незважаючи на позитивний вплив сучасних методів лікування на виживання та якість життя, вагітність при акромегалії продовжує залишатися нечастою подією та проблемою для клініцистів. Діагностика акромегалії під час вагітності утруднена через зміни рівнів гіпофізарного ГР та інсуліноподібного фактора росту-1 (ІФР-1), вироблення ГР плацентою та нездатність рутинних методів відрізнити гіпофізарний ГР від плацентарного.

У більшості пацієнток з акромегалією вагітність не чинить несприятливого впливу на матір або плід, а маса гіпофіза не збільшується в розмірах. Збільшення пухлини теоретично може відбутися, якщо лікування, наприклад, аналогами соматостатину було припинено з настанням вагітності. Під час вагітності симптоми акромегалії зменшуються внаслідок збільшення синтезу естрогену, що інгібує вироблення ІФР-1 в печінці. Перебіг вагітності здебільшого неускладнений, однак у літературі є дані про підвищений ризик гестаційного діабету та гіпертензії в жінок із неконтрольованою до вагітності гіперсекрецією ГР/ІФР-1.

При збільшенні пухлини необхідним є частий моніторинг, хірургічне втручання може бути проведене у другому триместрі. Агоністи дофаміну та аналоги соматостатину можна застосовувати без шкідливих наслідків для матері чи плода. Під час вагітності медикаментозну терапію акромегалії слід відмінити та призначати лише при збільшенні пухлини та появі головного болю. Грудне вигодовування не впливає на перебіг акромегалії. У більшості випадків томографія гіпофіза не демонструє збільшення росту пухлини після вагітності.

Ключові слова: акромегалія, вагітність, гормон росту, інсуліноподібний фактор росту-1, агоністи дофаміну, аналоги соматостатину.

ВЕДЕНИЕ БЕРЕМЕННОСТИ У ПАЦИЕНТОК С АКРОМЕГАЛИЕЙ

Обзор литературы

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Акромегалия – редкое хроническое эндокринное заболевание, обычно вызываемое гиперсекрецией гормона роста (ГР) соматотрофной аденомой в течение длительного периода. Из-за физиологических изменений уровней гипофизарных гормонов, связывающих глобулинов и плацентарных гормонов, гормональная оценка становится более сложной у беременных женщин. Как следствие физиологических гормональных изменений оценка функций гипофиза у беременных женщин весьма отличается от оценки у небеременных. Несмотря на положительное влияние современных методов лечения на выживаемость и качество жизни, беременность при акромегалии продолжает оставаться редким явлением и проблемой для клиницистов. Диагностика акромегалии во время беременности затруднена из-за изменений уровней гормона роста (ГР) и инсулиноподобного фактора роста-1 (ИФР-1), выработки ГР плацентой и неспособности рутинных методов отличить гипофизарный ГР от плацентарного.

У большинства пациенток с акромегалией беременность не оказывает неблагоприятного воздействия на мать или плод, а масса гипофиза не увеличивается в размерах. Увеличение опухоли теоретически может произойти, если лечение, например, аналогами соматостатина было прекращено с наступлением беременности. Во время беременности симптомы акромегалии могут уменьшиться вследствие увеличения синтеза эстрогена, ингибирующего выработку ИФР-1 в печени. Беременность в основном протекает без осложнений, однако в литературе есть данные про повышенный риск гестационного диабета и гипертензии у женщин с неконтролируемой до беременности гиперсекрецией ГР/ИФР-1.

При увеличении опухоли необходим частый мониторинг, оперативное вмешательство может быть проведено во втором триместре. Агонисты дофамина и аналоги соматостатина могут быть использованы без каких-либо неблагоприятных последствий для матери или плода. При беременности медикаментозную терапию акромегалии необходимо отменить и назначать только при росте опухоли и возникновении головной боли. Грудное вскармливание не влияет на течение акромегалии. В большинстве случаев томография гипофиза не демонстрирует увеличения роста опухоли после беременности.

Ключевые слова: акромегалия, беременность, гормон роста, инсулиноподобный фактор роста-1, агонисты дофамина, аналоги соматостатина.