MANAGEMENT OF ENDOCRINE DISEASE

Acromegaly and pregnancy: a contemporary review

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Abstract

Although fertility is frequently impaired in women with acromegaly, pregnancy is apparently becoming more common due to improvement in acromegaly treatment as well as in fertility therapy. As a result, several studies on pregnancy in patients with acromegaly have been published in recent years adding new and relevant information to the preexisting literature. Also, new GH assays with selective specificities and the knowledge of the expression of the various GH genes have allowed a better understanding of somatotrophic axis function during pregnancy. In this review, we show that pregnancy in women with acromegaly is generally safe, usually with tumoral and hormonal stability. Although the paucity of data limits evidence-based recommendations for preconception counseling and pregnancy surveillance, controlling tumor size and hormonal activity before pregnancy is highly recommended to ensure better outcomes, and surgical control should be attempted when feasible. Treatment interruption at pregnancy confirmation has also proven to be safe, as drugs are not formally allowed to be used during pregnancy. Drug exposure (somatostatin analogs) during early or whole pregnancy might increase the chance of a lower birth weight. Aggressive disease is uncommon and may urge individual decisions such as surgery or drug treatment during pregnancy or lactation.

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Introduction

Acromegaly is usually caused by growth hormone (GH)-secreting pituitary adenomas, mainly macroadenomas. Although fertility is frequently impaired in women with acromegaly, pregnancy is apparently becoming more common, probably due to improvement in acromegaly treatment as well as in fertility therapy (1). As a result,

single-center case series (2) and multicenter retrospective (3, 4) and prospective studies (5) on pregnancy in patients with acromegaly that have been published in recent years have added new and relevant information to the preexisting literature (6, 7). Moreover, the development of GH immunoassays with selective specificities (8, 9) and

Invited Author's profile

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the increasing knowledge of the expression of the various genes (10, 11) have allowed substantial improvement in our understanding of the changes in the somatotrophic axis that take place during pregnancy.

We will review our current understanding of the complex interaction between acromegaly and pregnancy with special emphasis on practical aspects of diagnosis, assessment and treatment.

Growth hormone isoforms

Human growth hormone (GH) is a heterogeneous protein hormone consisting of several isoforms derived from two genes. The genetic locus encoding GH is on chromosome 17q24.2 and contains the two GH genes (*GH-N* or *GH1* and *GH-V* or *GH2*) and another three genes encoding chorionic somatomammotropin (CS), also known as placental lactogen (PL), which is structurally homologous to GH but functionally closer to prolactin. These genes are composed of five exons and four introns and are thought to have arisen by gene duplication (12).

Pituitary GH

GH-N is expressed in somatotrophic cells of the anterior pituitary and yields, through alternative mRNA splicing of its transcript, two main isoforms with different molecular weights: 22K-GH and 20K-GH. The 22K-GH isoform, the prototype pituitary GH, is the main circulating isoform of GH in normal men, nonpregnant women and in patients with acromegaly (13). 22K-GH is also the recombinant GH available for replacement therapies. The 22K-GH has a single polypeptide chain with 191 amino acids and two disulfide bridges. The 20K-GH is a shorter isoform with 176 amino acids that lacks residues 32–46 of 22K-GH and is generated by alternative mRNA splicing at exon 3 (14). Average 20K-GH concentrations correspond to less than 10% of circulating GH in normal subjects of both sexes, across all ages and in various physiological conditions (13), but are slightly increased in acromegaly (15).

Placental GH

GH-V is only expressed in the placenta and its main product is GH-V, a single-chain protein with 191 amino acids, two disulfide bridges and a molecular weight of 22K. Its sequence differs from 22K-GH in 13 amino acids dispersed throughout the peptide chain (16). Unlike 22K-GH, GH-V has a consensus sequence for N-glycosylation

at position 140 and can be found in both nonglycosylated and glycosylated (25K-GH-V) isoforms (17). Other isoforms of GH-V have been identified, but their physiological role remains unknown (10). GH-V is similar to 22K-GH in its half-life, binding affinity to growth hormone-binding protein (GHBP) and also in its somatogenic and metabolic activities, but has a weaker lactogenic action than 22K-GH (18).

GH-V is the main circulating placental GH and only circulates in maternal blood. GH-V is detectable after 8 weeks of pregnancy and rises progressively to reach peak concentrations in the third trimester (mean peak values of 13–25 µg/L, depending on assay) (19, 20). In contrast to GH-N, which is secreted in a pulsatile fashion under hypothalamic control, GH-V secretion is nonpulsatile and is not controlled by the hypothalamus (21). Like GH-N, GH-V secretion is acutely blunted by rising blood glucose levels (22). After midgestation, GH-V progressively replaces pituitary GH through a negative feedback (21, 23).

GH measurements

Several posttranslational modifications in the GH molecules (N-acylation, deamidation and glycosylation of monomeric GH isoforms), circulating GH fragments generated by peripheral metabolism, non-covalent and disulfide-linked oligomerization of GH molecules and the presence of two GHBPs that complex with GH gives rise to the heterogeneous mixture of GH isoforms in blood (24). That heterogeneity and the different crossreactivities of the assay antibodies for each isoform and different reference preparations used in GH assays explain most of the marked disparity among immunoassay results (25, 26, 27).

During pregnancy, measurement of serum GH can lead to spuriously high or low results depending on the crossreactivities of the antibodies with GH-V and the type and design of the assay system (6, 9, 27). GH isoforms cross-react in most immunoassays, but specific assays for 22K-GH, 20K-GH, for both, and for GH-V have been developed (8, 19, 28).

The somatotrophic axis

In normal men and nonpregnant women, pituitary GH secretion is pulsatile and controlled by the hypothalamus, predominantly through the opposing effects of GHRH (stimulatory) and somatostatin (inhibitory) on pituitary

somatotrophic cells. GH-N secretion is enhanced by sleep, fasting, exercise and stress and is inhibited by metabolic signals like glucose and free fatty acids, both of which are influenced directly by GH (insulin antagonism and lipolysis respectively). A negative feedback of GH, predominantly at the hypothalamus and of IGF-1, predominantly at the pituitary, also controls GH release (29).

At physiological levels, nearly 50% of circulating GH is bound to GH-binding protein (GHBP), which is generated by the enzymatic cleavage of GHR. Binding of circulating GH to GHR in liver and several other tissues activates the synthesis and secretion of insulin-like growth factor 1 (IGF-1), which is responsible for the anabolic actions of GH in numerous tissues including bone, cartilage and muscle. Nearly 95% of circulating IGF-1 is bound to binding proteins (IGFBP), mostly to IGFBP-3, forming a ternary complex with an acid-labile subunit (ALS). Synthesis and secretion of IGF-1, IGFBP-3 and ALS are all stimulated by GH and inhibited by starvation and undernutrition and thus require functional integrity of the liver. The ternary complex formed by IGF-1, IGFBP-3 and ALS is responsible for the long half-life of plasma IGF-1 (nearly 18h) and the consequent stability of IGF-1 levels in plasma. Locally produced IGF-1 can also act in a paracrine/autocrine fashion in several tissues, but circulating IGF-1 is mostly generated in the liver through GH stimulation (29, 30).

The somatotrophic axis in nonpregnant women

In pubertal and adult women, the 24-h GH secretion is higher than that in men, but IGF-1 levels are not different. Those observations have been interpreted as a compensatory response of GH-N to counteract the GH-blocking effects of estrogen in the liver. Likewise, women on oral contraceptives containing estrogens usually present increased serum GH levels without increased serum IGF-1, and GH replacement in adult women with GH deficiency requires higher dosages when oral estrogens are being used concomitantly (31, 32).

The somatotrophic axis during normal pregnancy

During pregnancy, circulating estradiol and estrone levels rise progressively. Estradiol can reach peak concentrations up to several hundred times those found in the follicular phase (33). Such high estrogen environment is thought

to induce a state of relative GH resistance, which is key to understand the changes of the somatotrophic axis during normal pregnancy as well as in pregnancy in women with acromegaly (33, 34).

In the first trimester, GH-N is still the predominant form of GH in maternal blood, does not cross placental barrier and is not essential to normal gestation development as observed in GH-deficient pregnant patients (35, 36). During this period, rising estrogen levels would induce a state of GH resistance as reflected by a significant decline in circulating IGF-1, although a compensatory rise in GH-N levels has not been uniformly observed during this period (37, 38).

Thereafter, placental GH-V levels start to rise and progressively overcome the resistance to GH as reflected by increasing IGF-1 levels. At midgestation, GH-N levels start to decline probably in response to the negative feedback of rising GH-V and IGF-1 concentrations (20).

In the third trimester, GH-V and IGF-1 levels continue to rise, whereas GH-N is further suppressed. In the last weeks of pregnancy, both GH-V and IGF-1 reach peak concentrations, whereas GH-N is markedly suppressed. By the end of pregnancy, average GH-V levels are 13–25 µg/L, depending on assay, with a wide range from <10 to 60 µg/L (19, 20). IGF-1 levels are, in average, nearly two-fold higher than pre-pregnancy levels and also show large inter-individual variability (39, 40). Such increment in IGF-1 levels results from the interaction between the stimulatory effect of the high and sustained concentrations of GH-V in late pregnancy, comparable to the concentrations of GH-N found in active acromegaly, and the relative

Figure 1

Schematic representation of serum concentrations of estrogens, pituitary GH (GH), placental GH (PGH) and IGF-1 in maternal blood during pregnancy.

peripheral resistance (mostly or exclusively at the liver) to GH induced by high estrogen concentrations (31, 32). That interaction can also be understood as a 'shift to the right' of the dose–response curve between GH and IGF-1. In addition, under such high estrogen concentrations, a limiting effect on the maximal response of IGF-1 to GH stimulation might occur (Fig. 1) (34).

The somatotrophic axis during pregnancy in acromegaly

Most of the specific changes in hormone levels that take place in normal pregnancy such as increasing estrogen and GH-V concentrations as well as increased resistance to GH are predictable to occur during pregnancy in women with acromegaly. However, GH-N levels in acromegaly, which is exclusively derived from the adenoma, do not decline as tumoral GH-N secretion is largely autonomous and insensitive to the negative feedback of circulating GH/IGF-1 (5, 6).

As a result of the aforementioned mechanisms, acromegaly would be expected to improve clinically, at least during the first half of pregnancy, when estrogen levels have already induced a state of GH resistance, whereas GH-V levels have not increased appreciably. However, unlike normal pregnancy, both elevated

GH-N and rising GH-V concentrations will coexist after midgestation in patients with acromegaly. Thus, hormonal activity of acromegaly, as reflected by circulating IGF-1 concentrations, will conceivably depend on the interaction of the individual concentrations of both GH-N and GH-V and the degree of estrogen-induced GH resistance, all of which are expected to be highly variable among patients (Fig. 2).

Hormonal assessment of acromegaly during pregnancy

Hormonal assessment of acromegaly during pregnancy is challenging. Interference of circulating placental hormones with homology to pituitary GH can often lead to either falsely elevated (27) or suppressed GH values in GH assays (9). Also, usual reference ranges for both basal and post-glucose GH as well as for IGF-1 levels cannot be applied to pregnant women, as pituitary GH levels decline and IGF-1 levels increase during normal pregnancy (20, 40). If possible, the definite diagnosis of acromegaly should be postponed until puerperium due to the lack of normative data for both GH and IGF-1 levels during gestation. However, as IGF-1 concentrations in normal pregnancy usually rise only after midgestation (41), a high serum IGF-1 before midgestation is suggestive of

Figure 2

In normal pregnancy (mid-panel), placental GH (GH-V) is the major hormone responsible for stimulating the production of maternal IGF-1, and both GH-V and IGF-1 inhibit pituitary GH (GH-N) secretion through a negative feedback action. GH-V replaces GH-N as the predominant form of GH in maternal blood after midgestation. The high estrogen levels during pregnancy inhibit GH-induced IGF-1 generation in liver, but the increasing levels of GH-V after midgestation usually overcome that blockade and IGF-1 levels eventually rise. In pregnant woman with acromegaly, GH-N secretion by the tumor is autonomous and sustained, and both high GH-N and increasing GH-V will drive IGF-1 secretion in opposition to the estrogen blockade (right panel). Modified from Ref. (39).

acromegaly. On the other hand, as pituitary GH levels are expected to decline to less than 1 µg/L (20) during the third trimester in normal pregnancy, higher GH levels by highly specific assays during that period would also be suggestive of acromegaly.

Effect of pregnancy on pituitary structure and function

During pregnancy, all dimensions of the anterior pituitary increase significantly and the gland volume nearly doubles by the third trimester (42). The increase in height is more pronounced than that in other linear dimensions but usually does not exceed 10 mm in the third trimester. The superior part of the gland becomes more convex and dome-shaped and closer to the optic chiasm (42). During the first three days of the puerperal period, pituitary volume shows a further increase, but thereafter, it starts to decrease and returns to pre-pregnancy status within the next six months (42).

Histologically, the gestational enlargement of the pituitary gland reflects a conspicuous increase in both lactotrophic cell size (hypertrophy) and number (hyperplasia). Lactotrophic cells correspond to 20% of the anterior pituitary cells in the nonpregnant state and reach 60% by the third trimester of pregnancy (43, 44). In contrast, the populations of somatotrophs and gonadotrophs decrease, whereas the number of other cell types remains relatively constant. Those changes in cellular composition are associated with changes in circulating pituitary hormone levels as previously discussed for the increasing prolactin and decreasing pituitary growth hormone levels along normal pregnancy.

It is important to note that compressive symptoms are not expected to appear due to the pituitary enlargement in normal pregnancy. However, in women with pituitary tumors, visual impairment during pregnancy may not represent tumor expansion, but the effect of an enlarging pituitary in the limited intrasellar space already occupied by the adenoma (45).

Effect of pregnancy on clinical and hormonal activity of acromegaly

Pregnancy seems to have no major effects on the secretion of GH from the usual somatotrophic adenoma, as shown by measurements of GH concentrations during pregnancy using specific immunoassays that do not cross-react with placental GH (5, 6). On the other hand,

clinical and hormonal activities of acromegaly during pregnancy reflects a temporally dynamic and complex interplay between several factors: tumor-derived GH concentrations, usually stable; placenta-derived GH concentrations, progressively rising after midgestation and increasing estrogen levels and consequent estrogen-induced resistance to GH, all of which are highly variable among patients. Not surprisingly, clinical activity of acromegaly has been variably reported to improve (45, 46), remain stable (2, 5) or worsen during pregnancy (45, 48, 49).

Contemporary experience has usually shown a rather stable clinical course of disease activity during pregnancy in most patients (2, 3, 4, 5, 38, 46, 50, 51). Such favorable outcome is likely to reflect the overall improvement in both diagnosis and treatment of patients with acromegaly in the last decades. At present, pregnancy usually occurs in patients surgically cured or currently under pharmacological treatment with or without a previous pituitary surgery. In most cases, clinical and hormonal disease activity has already been significantly improved (2, 3, 4, 5) before conception. In such patients, prompt interruption of treatment with somatostatin analogs and/or cabergoline once pregnancy is diagnosed has usually been well tolerated or followed by only transient and minor signs of possible disease activity (mostly headache) (5). The usual 'therapeutic' effect of pregnancy on acromegaly is well illustrated by IGF-1 levels throughout pregnancy being similar to those obtained with pharmacological treatment before pregnancy as well as by the sharp rebound of both IGF-1 concentrations and clinical symptoms after delivery (5, 52).

The relative stability of IGF-1 levels often observed during pregnancy seems to reflect the dynamic interplay among several factors as pregnancy advances: (I) lack of influence of pregnancy and/or of its relatively short duration in changing the secretory activity of most GH-secreting adenomas; (II) persisting effects of previous medications for weeks/months after their interruption and (III) blocking effects of increasing estrogen levels on IGF-1 generation induced by GH.

In addition, as the upper reference limits of IGF-1 during normal pregnancy raise progressively after midgestation, reflecting increasing placental GH concentrations overcoming estrogen blockade, even patients with relatively high but stable IGF-1 levels will eventually be considered hormonally controlled in relation to IGF-1 concentrations as pregnancy advances. Interestingly, unlike normal pregnancy, the effect of increasing placental GH concentrations on IGF-1

Figure 3

IGF-1 levels (ULN) in ten pregnancies in patients with acromegaly. Bars (after surgery, before pregnancy and puerperium) represent the ranges of normal IGF-1 values in the Brazilian population or the ranges of IGF-1 values obtained in our pregnant controls. Horizontal lines represent mean values from patients. * $P < 0.05$ vs after surgery (repeated measured ANOVA, Bonferroni's post test for multiple comparisons) (from Ref. (5)).

concentrations after midgestation does not seem to occur in a substantial degree in most patients with acromegaly, as their IGF-1 levels in late gestation were not different from early and midgestation levels (Fig. 3). The most plausible explanations for those observations include the well-known nonlinear relationship between GH and IGF-1 levels, a shift to the right in the GH vs IGF-1 dose-response curve and a decrease in the maximal response of IGF-1 to GH stimulation in a high estrogen milieu (42). Nevertheless, the overall somatogenic activity in serum from pregnant women with acromegaly differ considerably among patients due to the variations in tumoral GH-N as well as in GH-V concentrations, and some patients may eventually overcome the estrogen blockade after midgestation.

Less commonly, patients are diagnosed with acromegaly during pregnancy (3, 53, 54, 55, 56, 57, 58, 59, 60) or they become pregnant before treatment has been effective (6, 61). In such cases, clinical and hormonal activity of acromegaly may also improve due to the protective effects of estrogens. However, as discussed previously, it may as well deteriorate later on as the

combined effects of an excessively high GH and increasing placental GH may eventually overcome estrogen-induced peripheral GH resistance.

Effect of pregnancy on acromegaly-associated comorbidities

The development of diabetes and hypertension during pregnancy would be expected to increase markedly in acromegaly due to the known effects of excess GH and pregnancy on insulin resistance and sodium retention. Surprisingly, the prevalence of both conditions has been shown to be only slightly increased (3, 5) and those complications have been correlated with hormonal control before pregnancy (3).

Effect of pregnancy on tumor growth in acromegaly

Pregnancy is not considered to stimulate the usual GH-secreting adenoma to grow. In effect, no changes in tumor volume were detected by magnetic resonance imaging (MRI) in two multicentric studies on acromegaly and pregnancy, one prospective with 10 pregnancies and one retrospective with 13 pregnancies (4, 5). On the other hand, asymptomatic tumor growth was detected by postpartum MRI in 3 of 27 pregnancies in the largest retrospective study (3) and in two of six cases by routine MRI performed at 6 months of pregnancy. Interestingly, the tumors in those two cases were mixed GH/PRL-secreting adenomas (38).

Symptomatic tumor enlargement during pregnancy in acromegaly is even less common than asymptomatic tumor growth. In nearly 180 cases reported (excluding a historical review with 34 cases with scarce data to be properly analyzed) (62), only six patients with acromegaly required surgery during pregnancy. Of note, four of them had acromegaly diagnosed during gestation, and the reasons for surgery were increased intracranial pressure (48), apoplexy (53) and visual loss (3, 58, 60, 63). A few other cases with mass effect symptoms during pregnancy were medically managed with bromocriptine, octreotide or glucocorticoid (3, 54, 55, 56, 64).

Accordingly, the overall risk of tumor growth during pregnancy is relatively low, around 10% (3), and the risk of a clinically relevant growth is even smaller. Obviously, patients with larger tumors close to the optic chiasm are at a higher risk for visual impairment than those with small tumors or even large tumors distant from the optic

chiasm (45). Visual field assessments are recommended throughout pregnancy in patients with macroadenomas and suprasellar extension, and visual changes should be further evaluated by an MRI of the sellar region. The rare case of a GH-secreting adenoma aggressively growing during pregnancy has been recently reported (65).

It should be noted that visual and/or ocular symptoms denoting compression of the optic chiasm and/or cranial nerves within the cavernous sinus during pregnancy may not reflect proliferative growth of the tumor. Those symptoms may also be caused by tumor enlargement due to bleeding/infarction (apoplexy) (53), 'expansion after shrinkage' of the tumor after the withdrawal of somatostatin analogs (2, 38) and even by the physiological enlargement of the pituitary gland during pregnancy (56). The distinction among true proliferative growth of the tumor, tumor enlargement due to bleeding/infarction and pregnancy-induced pituitary enlargement should be well established through patient's history and pituitary imaging for proper therapeutic management. Thus, in pituitary apoplexy, management can be either conservative, with glucocorticoid, or surgical, according to the extension of visual impairment and/or degree of coma (66). In the other two situations, a trial of dopaminergic agonists can alleviate chiasm compression, either by reverting lactotrophic hyperplasia or, less likely, by decreasing tumor size. In the absence of any significant improvement soon after initiating dopamine agonists, octreotide should be attempted. Surgical intervention should be individually evaluated, restricted to the most severe cases that failed to respond to drug intervention.

Treatment of acromegaly during pregnancy

The general approach for the treatment of acromegaly during pregnancy should strictly follow the principle *primum non nocere* (first, do no harm), taking into account the risks and benefits of treatment against no treatment for both mother and fetus. The effects of drugs used in acromegaly treatment on fetal development are not sufficiently known to recommend their liberal use throughout pregnancy. On the other hand, surgery during pregnancy increases the risks for hypopituitarism, abortion in the first trimester and fetal loss in the last trimester. Therefore, surgery should be avoided or postponed as much as possible (67) and preferably performed in centers with large experience.

As previously discussed, pregnancy has a transient therapeutic effect in clinical activity of acromegaly that

can last until delivery, and pregnancy *per se* does not seem to stimulate tumor growth. Accordingly, pharmacological treatment can be safely interrupted in most patients (2, 3, 4, 5). Occasional patients, however, may show worsening of disease activity (mostly persistent headache) and/or visual impairment that will require medical therapy to be reconsidered and, more rarely, even surgical intervention. Although the overall risks of metabolic and/or visual deterioration are usually acceptable, they are highest among patients with poor pre-pregnancy control of disease (3), with acromegaly diagnosed during pregnancy (59, 68), and in those with pituitary adenomas closer to the optic chiasm (45). Tumor expansion, usually asymptomatic, has been observed after interruption of treatment in patients with recent shrinkage of the tumor with somatostatin analogs (2, 50).

Women with acromegaly who wish pregnancy should be counseled about the risks of maternal and fetal complications, mainly if the disease is not under control. That should encourage both patient and physician to control both disease activity and tumor growth before pregnancy occurs. In cases with large adenomas in close proximity to the optic chiasm, pituitary surgery before conception can be considered in order to decrease the risk of visual impairment during pregnancy. In patients requiring medical therapy for tumor and/or disease control before pregnancy, the advantages and relative safety of discontinuing treatment during pregnancy should be discussed along with the probability of developing metabolic complications and/or visual impairment that will require medical treatment and, less frequently, pituitary surgery.

Accordingly, a recent guideline from The Endocrine Society (69) suggests that discontinuation of long-acting somatostatin analogs or pegvisomant two months before attempts to conceive, with the use of short-acting octreotide is necessary until conception. During pregnancy, it also recommended that medical therapy of acromegaly should be withheld and administered only for tumor and/or headache control (69). Although the first recommendation was proposed to reduce embryo exposure to drug in relation to the residual exposure with the long-acting analog, it requires more meticulous conception planning that is often difficult to implement in clinical practice. On the other hand, the following recommendation to reintroduce the medication for headache control, as stated, might lead to more and unnecessary fetal exposure to octreotide as headache after withdrawal of short-acting octreotide is more frequent and more severe than that after withdrawal of

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long-acting octreotide (70), which is usually responsive to safer analgesics (5).

In the more usual cases, patients conceive during treatment with long-acting somatostatin analogs and/or cabergoline and/or pegvisomant, and treatment should be promptly discontinued once pregnancy is confirmed. In this scenario, fetal exposure to long-acting octreotide could be further minimized by screening patients at risk for pregnancy through a serum beta-hCG measurement before each injection, which should detect pregnancy as soon as 7–10 days after conception (71). Thereafter, all patients should be regularly monitored for the control or development of complications such as diabetes, hypertension, hypopituitarism and visual field disturbances. Routine measurements of GH and IGF-1 levels and MRI of pituitary are not recommended in uneventful cases, but are mandatory when metabolic and/or visual complications appear and management decisions have to be made (69). Also, MRI during pregnancy should be performed without contrast (72).

Effect of acromegaly and its treatment on fetal development

Data regarding fetal outcomes are scarce, but acromegaly *per se* does not seem to affect fetal development. Newborns from women who interrupted medical treatment before or at the beginning of pregnancy have been typically normal (2, 3, 4, 5, 38). Also, children born from women with acromegaly who discontinued treatment during pregnancy have been shown to have normal general health status at 2, 3 and 6 years of age (73, 74, 75), as well as IQ scores similar to those born from normal women or from women with prolactinoma (76). However, as some patients with acromegaly may have or develop impaired glucose tolerance/diabetes mellitus and hypertension during pregnancy, their newborns should also be considered at a higher risk for macrosomia and microsomia (77) respectively.

Although octreotide crosses placental barrier and placenta has somatostatin receptors that bind octreotide (78), no serious adverse fetal outcomes have been detected in nearly 50 (2, 3, 4, 5, 7, 36, 38, 47, 48, 50, 51, 55, 57, 63, 79, 80, 81, 82, 83, 84) cases of transient exposure (mostly in first trimester) nor in a much smaller number of continuous exposure to somatostatin analogs (SA) and/or dopaminergic agonists (4, 64, 73, 75, 78, 85, 86, 87). Notwithstanding, concerns about low birth weight associated to fetal exposure to SA either alone or, as

more often reported, in combination with dopaminergic agonists (DA) have been raised by a large retrospective study and by few case reports (3, 4, 85, 88). However, fetal exposure to DA in patients with prolactinomas has not been associated with altered birth weight (89). A suggested mechanism for that low birth weight with SA is decreased blood flow in uterine artery, which has been demonstrated to occur transiently after short-acting octreotide injection in a single case report (75).

Finally, it should be noted that the reported experience of fetal exposure to SA during pregnancy is even more limited with lanreotide than with octreotide (3, 4, 38, 80, 84, 90). No reports of pasireotide in pregnancy were found in PubMed up to December 2016 and that drug should not be used in women at risk for pregnancy. Although both octreotide and lanreotide are therapeutically similar, it is not known whether lanreotide would have the same degree of maternal–fetal transfer and placental binding as octreotide. Also, FDA risk classification for their use during pregnancy is not the same. Animal reproduction studies have shown serious adverse effects to the fetus with lanreotide (and pasireotide) exposure (Class C), but not with octreotide (Class B) (Drugs leaflet, available at: <http://www.fda.gov>, accessed in December 12th, 2016) (Table 1).

Transient (4, 91) and total (92) exposure to pegvisomant during pregnancy has been reported. One patient who used pegvisomant throughout pregnancy delivered a healthy and normal-sized baby (92). In that case, pegvisomant was found in very low concentrations in cord blood in spite of its therapeutic levels in maternal blood. Also, pegvisomant did not suppress placental GH and was undetectable in breast milk. More recently, safety data on pegvisomant use during pregnancy was reported in a compilation of Pfizer's Global Safety Database (93). Twenty-seven cases of maternal exposure and eight cases of paternal exposure to pegvisomant during conception were reported. Most patients stopped pegvisomant when pregnancy was confirmed and only three maintained it throughout pregnancy. Although no fetal malformations were reported, a higher rate of premature birth (94) was associated with both maternal and paternal exposure to pegvisomant. However, many cases had incomplete data to be properly analyzed for confounding factors.

Breastfeeding

Breastfeeding during active acromegaly seems safe to neonates and does not seem to induce further rebound

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Table 1 Pharmacological treatment of acromegaly during pregnancy: drug characteristics and compilation of maternal/fetal outcomes associated to their use during pregnancy (PubMed, from 1990 to 2016).

Drug	Mean half-life	Presence in cord blood	Presence in breast milk	FDA class for pregnancy ^a	Drug use during lactation	Cases exposed during pregnancy		Maternal/fetal outcomes
						Partial ^b	Total	
Pegvisomant	6 days	Minimal	Minimal	B	Not recommended	25	4	Spontaneous abortions (two), premature births (three), ectopic pregnancy (one) (92)
Lanreotide Autogel (Depot)	23–30 days	Unknown	Unknown	C	Not recommended	7 ⁺	0	No in 7 cases; small size newborns in 0–4 cases (not specified in Ref. (3))
Prolonged release (LA)	3–7 days	Unknown	Unknown	C	Not recommended	0	0	Not applicable
Octreotide		Yes ^c	Yes (humans)	B	Not recommended	50 ⁺	5	
Long acting (LAR)	35–42 days							Reduced newborn size, small for gestational age ^d , usually with DA Ref. (3)
Short acting Pasireotide	1.7 h 12 h	Unknown	Yes (rats)	C	Not recommended	0	0	Not applicable
Cabergoline	63–109 h	Yes	Impaired lactation	B	Impaired lactation	19	0 ^e	Usually uneventful
Bromocriptine	4.8 h	Yes	Impaired lactation	B	Impaired lactation	22	1	Usually uneventful

^aLeaflet recommendation. B, no proven risk in humans; C, risk cannot be ruled out. ^bPartial exposure includes patients in which long-acting drugs (cabergoline, lanreotide and octreotide LAR) were suspended at the time of pregnancy diagnosis. ^cAlso present in amniotic fluid and child serum.

^dUsually in combination with dopamine agonists. ^eCabergoline use throughout pregnancy was observed in patients with prolactinoma.

*And a few more cases that do not specify which SSA or DA was used Ref. (3).

of acromegaly activity or tumor growth (5). However, breastfeeding under acromegaly treatment is still controversial. Data on children breastfed by women on octreotide or lanreotide treatment are extremely limited. Somatostatin analogs are excreted in breast milk (75), but their biological activity and gastrointestinal absorption might not be relevant through the oral route. Pegvisomant is probably safer in the breastfeeding period as it has only a negligible transfer to breast milk (92).

Conclusion

Pregnancy in women with acromegaly is generally safe, usually with tumoral and hormonal stability. The paucity of data limits evidence-based recommendations for preconception counseling and pregnancy surveillance, but controlling tumor size and hormonal activity before

pregnancy is highly recommended to ensure better outcomes, and surgical control should be attempted when feasible. Treatment interruption at pregnancy confirmation has also proven to be safe, as drugs are not formally allowed to be used during pregnancy. Drug exposure (somatostatin analogs) during early or whole pregnancy might increase the chance of a lower birth weight. Aggressive disease in some patients may urge individual decisions such as surgery or drug treatment during pregnancy or lactation.

Declaration of interest

Julio Abucham (J A) is a principal investigator on clinical trials for Novartis and Ipsen and a speaker and advisory board member for Novartis and Ipsen. Marcello Delano Bronstein (M D B) is a consultant and a member of the Steering Committees for Chiasma, Novartis and Ipsen. M D B is a speaker for Novartis and Ipsen and a principal investigator on clinical trials for Pfizer, Novartis and Ipsen. Monike Lourenço Dias (M L D) has nothing to declare.

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