Pregnancy in acromegaly is safe and is associated with improvements in IGF-1 concentrations

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Abstract

Pregnancy is rarely reported in acromegaly. Many patients are diagnosed in later life and younger patients may have subfertility due to hypopituitarism. We present a case series of 17 pregnancies in 12 women with acromegaly. Twelve women with acromegaly who completed pregnancy were identified from centres involved in the Irish Pituitary Study. Eleven women had pituitary macroadenomas and one woman had a microadenoma. Only 5/17 pregnancies had optimal biochemical control of acromegaly preconception, as defined by IGF-1 concentration in the age-related reference level and plasma GH concentration of <2 µg/L. In 6/17 pregnancies, dopamine agonist treatment was continued during pregnancy; all other acromegaly treatments were discontinued during pregnancy.

Effect of pregnancy on acromegaly: No patient developed new visual field abnormalities, or symptoms suggestive of tumour expansion during pregnancy. In 9/12 patients, plasma IGF-1 concentrations that were elevated preconception normalised during pregnancy. There was a reduction in plasma IGF-1 concentrations, though not into the normal range, in a further two pregnancies.

Effect of acromegaly on pregnancy: 15 healthy babies were born at term; one patient underwent emergency C-section at 32 weeks for pre-eclampsia, and one twin pregnancy had an elective C-section at 35 weeks' gestation. Blood pressure remained within normal limits in the remainder of the pregnancies. Gestational diabetes did not develop in any pregnancy.

Our data suggests that pregnancy in women with acromegaly is generally safe, from a maternal and foetal perspective. Furthermore, biochemical control tends to improve despite the withdrawal of somatostatin analogue therapy during pregnancy.

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Introduction

Pregnancy in acromegaly is uncommon. Patients may present with acromegaly later in life after menopause or in younger patients subfertility may be due to hyperprolactinaemia or gonadotrophin deficiency (1). Hypopituitarism may occur due to compressive effects

of the tumour, or may develop secondary to therapeutic interventions such as surgery or radiotherapy. In addition, a significant proportion of GH-secreting adenomas co-secrete prolactin, though this is usually readily reversed by medical therapy with dopamine agonists.

In addition to the potential endocrine compromise of fertility, patients anecdotally report a traditional discouragement of pregnancy, reflecting medical concerns of loss of biochemical control and tumour growth in the mother, or that elevated maternal growth hormone could have detrimental effects on the foetus. As a result, there have been less than 200 cases of pregnancy in acromegaly reported in the literature.

Safety data regarding the use of medical therapy with cabergoline, somatostatin analogues and pegvisomant during pregnancy in acromegaly is lacking. The most recent Endocrine Society guidelines published in 2014 (2), therefore recommend against the use of medical therapy during pregnancy unless there is a specific concern about tumour growth or persistent headaches (2). Before the guidelines were published in 2014, there was no expert guidance for clinicians on the management of acromegaly during pregnancy, therefore clinical practice was based on available case series and available literature from prolactinomas. Reports that plasma IGF-1 concentrations fall during pregnancy suggest that withdrawal of medical therapy should not be detrimental to biochemical control of acromegaly during pregnancy (3, 4).

During the second half of pregnancy, the placenta increasingly produces placental GH, which shares significant homology with pituitary GH (5, 6). Therefore, for interpretation of GH concentrations during pregnancy there is a need to consider the specificity of the assay being used. Furthermore, routine measurement of GH concentrations during pregnancy is not indicated as it will not impact the management of the patient.

There is limited data for outcomes of pregnancy in patients with acromegaly (3, 4, 7, 8); the aim of this study, therefore, was to analyse the data generated from Irish patients with acromegaly who became pregnant and who were enrolled in the Irish Pituitary Study, in order to contribute to the body of knowledge regarding safety and outcomes of pregnancy in acromegalic patients.

Methods

The Irish Pituitary Study has recently been established and at present includes patients with acromegaly managed in four dedicated pituitary centres in Ireland between 1995 and 2017: Beaumont Hospital (Dublin), Tallaght Hospital (Dublin), Cork University Hospital and the Royal Victoria Hospital in Belfast. All patients with acromegaly who had pregnancy after diagnosis were

included in the analysis. Ethical approval for the registry was granted from each local hospital ethics committee and informed consent was obtained from all patients included in the database.

Acromegaly in all patients was diagnosed according to the Endocrine Society guidelines on the basis of raised plasma IGF-1 concentration, in comparison with the reference range for age and sex, together with failure to suppress plasma GH (<1 ng/mL) following an oral glucose load. Serum GH and IGF-1 concentrations were assessed using locally available commercial assays. Before 2013, the laboratories used Diassorin or Siemen's immulite assays, both of which are known to have significant interaction with multiple GH isoforms. After 2013, all included laboratories used the IDS-iSYS method which is specific for pituitary GH ($n=4$ patients in this study) (9). This study included data from 1995 to 2017, therefore both older and newer assays were included for analysis.

As this is a retrospective study, disease control was defined as per the Cortina consensus (an IGF-1 in the age and sex matched reference range and GH <2 μ g/L), as these were the criteria used for control at the time of the majority of the pregnancies (10). Data were retrospectively collected from chart and biochemical review. Demographical details, acromegaly control preconception, and antenatal and pregnancy outcomes were recorded.

Plasma IGF-1 concentrations were reported as % ULN (percentage Upper Limit of Normal) to compare plasma IGF-1 concentrations from different institutions, which used various assays, reference ranges and units. Wilcoxon matched pairs signed rank test was performed on the % ULN IGF-1 to evaluate the statistical significance of the reduction in IGF-1 observed in pregnancy.

Information regarding the pregnancies was obtained from patient recall and chart review. Information regarding conception, complications during pregnancy in particular gravid hypertension, pre-eclampsia, gestational diabetes and mode of delivery was recorded. World Health Organisation (WHO) criteria for birthweight were applied to determine normal birthweight.

Results

Twelve women with acromegaly, who had 17 pregnancies, were identified. Five women had two pregnancies. Eleven women had pituitary macroadenomas, 1 woman had a microadenoma. The age of the women at conception

ranged from 28 to 40 years with a median age of 34 years. A minority of patients had biochemical control of acromegaly preconception (5/17 pregnancies) as defined by plasma IGF-1 concentration in the age-related reference level and plasma GH concentration of $<2\mu\text{g/L}$. Two of 17 pregnancies occurred following in vitro fertilisation, the remainder were unassisted. There were 16 singleton pregnancies and one twin pregnancy. One woman had a carcinoid tumour secreting GHRH. Screening for mutations in AIP gene is not routinely performed in Ireland. Three of 12 women were tested for mutations as part of a research study; one woman had a mutation identified. The patient characteristics are summarised in Table 1.

One further pregnancy was identified that was not included in the analysis. The diagnosis of acromegaly was made during pregnancy, therefore there was no baseline or radiological data available and this pregnancy was not included in analysis.

Effect of pregnancy on acromegaly

(a) Biochemical control

Twelve of the 17 pregnancies had elevated plasma IGF-1 concentrations prior to pregnancy. Nine of these 12 pregnancies had normalisation of plasma IGF-1 concentrations during pregnancy. Plasma IGF-1 concentrations fell despite discontinuation of somatostatin analogue therapy in one further pregnancy, without normalisation into the age-

related reference range. Two pregnancies showed no significant change in plasma IGF-1 concentration. Overall, there was a statistically significant reduction in plasma IGF-1 concentration observed in the first and second trimester of pregnancy ($P<0.005$) compared to preconception levels (Fig. 1A). Five pregnancies had biochemical control preconception with a normal plasma IGF-1 concentration and all 5 remained in the age appropriate normal range throughout pregnancy.

Plasma GH concentrations were available for 15/17 pregnancies; there was no clearly discernible pattern during pregnancy. Five of 17 pregnancies had controlled random GH concentrations ($<2\mu\text{g/L}$) preconception. GH measurements pre-2013 used non-specific assays; after 2013 the IDS-iSYS assay was used and this is specific for pituitary GH (9). Figure 2 depicts the GH concentrations throughout pregnancy in both specific (bold line) and non-specific (dashed line) assays.

(b) Medical therapy

All four women who were receiving treatment with somatostatin analogues pre-pregnancy had discontinuation of therapy with the first positive pregnancy test. No woman continued somatostatin analogue treatment during pregnancy. All four of these pregnancies had normalisation of the plasma IGF-1 concentration during pregnancy in spite of the withdrawal of somatostatin analogue therapy, and these results are depicted in Fig. 1C. One of these

Table 1 Patient characteristics and treatment modalities prior to conception in patients with acromegaly who became pregnancy.

Patient	Adenoma	Surgery before pregnancy	Radiotherapy before pregnancy	Medical therapy before pregnancy	Hypopituitarism	Acromegaly control before pregnancy	Acromegaly control during pregnancy
A1	Micro	Yes	No	Nil	No	No	Yes
A2	Micro	Yes	No	Octreotide	No	No	Yes
B	Macro	Yes	No	Octreotide	No	Yes	Yes
C1	Macro	Yes	No	Nil	No	No	Yes
C2	Macro	Yes	No	Nil	No	No	Yes
D	Macro	Yes	No	Octreotide	No	Yes	Yes
E	Macro	Yes	Yes	Cabergoline	Yes	Yes	Yes
F1	Macro	Yes	No	Cabergoline	TSH def	No	Yes
F2	Macro	Yes	No	Cabergoline	TSH def	No	No
G	Macro	No	No	Cabergoline Octreotide	ACTH def	No	Yes
H	Macro	No	No	Bromocriptine	No	No	Yes
I1	Macro	Yes	No	Cabergoline	ACTH, TSH def	No	Yes
I2	Macro	Yes	No	Cabergoline	ACTH TSH def	Yes	Yes
J1	Macro	Yes	Yes	Cabergoline	No	No	Yes
J2	Macro	Yes	No	Cabergoline	TSH def	No	No
K	Macro	Yes	Yes	Cabergoline	No	No	Yes
L	Macro	Yes	No	Cabergoline	TSH def	No	No

Figure 1

Graphs depicting %ULN IGF-1 pattern during pregnancy. (A) Boxplot of median %ULN IGF-1 (range) in each trimester, median and range. (B) % ULN IGF-1 in pregnancies with no treatment. (C) % ULN IGF-1 in pregnancies with withdrawal of somatostatin analogue therapy, (D) % ULN IGF-1 in pregnancies with dopamine agonist therapy. Data was analysed using Wilcoxon matched matched-pairs signed rank test.

four pregnancies continued cabergoline therapy throughout pregnancy.

Eleven pregnancies were taking dopamine agonist (DA) therapy preconception. Five pregnancies stopped DA therapy with the first positive pregnancy test. One patient continued DA therapy until 11 weeks' gestation. The remaining 5 pregnancies continued dopamine agonist therapy throughout the entire pregnancy (4 cabergoline, 1 bromocriptine). There were no adverse maternal or foetal events in any of these 5 pregnancies. None of these 5 pregnancies had controlled plasma IGF-1 concentration at conception: 3 normalised their plasma IGF-1 concentration during pregnancy, 2 pregnancies had a reduction in plasma IGF-1 concentration without normalisation; these results are depicted in Fig. 1D. No patient received

Pegvisomant therapy pre-pregnancy or during pregnancy.

(c) Tumour size during pregnancy

MRI imaging of the pituitary gland was not routinely performed in pregnancy and is not indicated in pregnancy unless there are clinical symptoms of tumour expansion (2). Fifteen of the 17 pregnancies occurred following surgical intervention. None of the women had a clinically relevant increase in tumour size as evidenced by a deterioration in visual fields or development of suggestive symptoms, such as progressive headaches. All women were examined by an experienced neuro-ophthalmologist with formal perimetry testing performed in each trimester as per best international practice.

Figure 2

GH concentrations throughout pregnancy. Dashed line = non-specific GH assay, block line = GH assay specific for pituitary derived 22 kDa GH.

Effect of acromegaly on obstetric outcomes

(a) Blood pressure

One pregnancy was complicated by pre-eclampsia, and required emergency caesarean section at 32 weeks' gestation. The patient's blood pressure remained normal throughout her second pregnancy and she had an uncomplicated elective caesarean section at term. The remainder of the pregnancies were uncomplicated by hypertension. There was no discernible increase in blood pressure observed throughout pregnancy in the overall group.

(b) Gestational diabetes

A standard 75 g glucose tolerance test was performed in all 17 pregnancies in the second trimester. There were no cases of gestational diabetes.

(c) Delivery method

Eleven of the 17 babies were delivered by caesarean section, and the remainder were born by spontaneous vaginal delivery. The reason for the high rate of caesarean section is unclear as there was no increase in macrosomia or other complications. One woman was pregnant with twins by assisted fertility. She had elective caesarean section at 35 weeks' gestation. Although she was a high-risk pregnancy, her blood pressure and glucose levels remained normal throughout pregnancy. The babies of 6/17 patients were breast fed, with no post-natal complications reported.

(d) Neonatal outcome

The WHO define normal singleton birthweight as 2500–4200 g (11). One pregnancy had a small for gestational age baby; patient A developed

pre-eclampsia and had an emergency caesarean section at 32 weeks' gestation, with delivery of a low birthweight infant at 1200 g. The neonate recovered well and had no long-term sequelae. A second patient had a twin pregnancy, and both infants had low birthweight of 2450 and 2200 g at delivery when compared to singleton pregnancies. However, in twin pregnancies, normal birthweights are lower and both neonates would be considered of normal birthweight for a twin pregnancy (12). There was one case of foetal macrosomia which was just over the threshold at 4260 g. This woman was screened for gestational diabetes and had normal glucose metabolism during pregnancy; her IGF-1 was within the age matched reference range both before and during pregnancy. No other neonatal complications were detected.

All neonates were examined by an experienced neonatologist; no congenital malformations were identified in any of the pregnancies. The pregnancy outcomes from this case series are summarised in Table 2.

Discussion

This series of cases describes the outcomes of 17 cases of pregnancy in acromegaly. The results from our series suggest that pregnancy in acromegaly is generally safe, with no indication that maternal or foetal well-being is threatened by pregnancy in patients with acromegaly.

The Endocrine Society guidelines recommend the withdrawal of somatostatin analogue and pegvisomant therapy two months before conception (2). Medical treatment should only be considered in patients with significant headache or tumour growth (2). Withdrawal of somatostatin analogue therapy may potentially cause an increase in tumour size, due to removal of the tumour-shrinking properties of these agents (13). However, no patients in our cohort exhibited features of headaches or visual disturbances, which might have suggested clinically significant tumour growth, when reviewed in each trimester. Although routine MRI scanning was not conducted to confirm this (this would be routine clinical practice for pituitary lesions), formal visual field assessment in each trimester showed no evidence of hemianopia in any patient. Therefore, if tumour growth did occur, it did not do so to the extent that it was clinically significant. These findings are similar to the report from Dias *et al.* which described 10 prospectively followed pregnancies in acromegaly; medical therapy was withdrawn in all patients once pregnancy was confirmed and there were no reported cases of tumour growth (3).

Table 2 Pregnancy outcomes in patients with acromegaly.

Patient	Medical therapy during pregnancy	Gravid hypertension	Gestational diabetes	Delivery	Gestation	Birthweight (g)	Visual field change	Breast feeding
A1	No	Yes	No	Emerg C/S	32/40	1300	No	No
A2	No	No	No	C/S	40/40	3570	No	No
B	No	No	No	C/S	39/40	3170	No	Yes
C1	No	No	No	C/S	42/40	3402	No	Yes
C2	No	No	No	C/S	41/40	3033	No	Yes
D	No	No	No	SVD	39/40	3120	No	Yes
E	No	No	No	SVD	40/40	3670	No	No
F1	No	No	No	SVD	38/40	3990	No	No
F2	No	No	No	SVD	39+5/40	4110	No	No
G	Cabergoline	No	No	C/S	39+3/40	3530	No	No
H	Bromocriptine	No	No	C/S	38+6/40	2770	No	No
I1	No	No	No	SVD	40/40	3300	No	Yes
I2	No	No	No	SVD	38/40	4260	No	Yes
J1	Cabergoline	No	No	C/S	40/40	3760	No	No
J2	Cabergoline	No	No	C/S	35/40	2450, 2200 (twins)	No	No
K	Cabergoline	No	No	C/S	41/40	2746	No	n/a
L	Cabergoline	No	No	C/S	39/40	3510	No	No

C/S, caesarean section; emerg C/S, emergency caesarean section; SVD, spontaneous vaginal delivery.

Withdrawal of somatostatin analogues and pegvisomant may be hypothesised to have adverse effects on complications of pregnancy such as gestational diabetes and hypertension, due to the potential elevation in plasma GH/IGF-1 concentrations. In our series, withdrawal of medical therapy was not associated with elevation of IGF-1 concentrations. In the majority of patients, plasma IGF-1 concentrations fell after treatment withdrawal. There were no cases of gestational diabetes in 17 pregnancies, including one twin pregnancy, and there was no rise in blood pressure.

Two previous case series reported similar reductions in plasma IGF-1 concentrations in pregnancy (3, 7). In spite of the withdrawal of therapy, mean plasma IGF-1 concentrations fell during pregnancy and increased again in the puerperium, similar to the report from Diaz *et al.* (3). Caron and colleagues reported similar data, with a statistically significant reduction in plasma IGF-1 concentrations ($P=0.02$ – 1st trimester, $P\leq 0.01$ – 2nd trimester) in pregnancy ($n=20$) (7). Our data concurs with this, as 9/12 plasma IGF-1 concentrations that were elevated preconception normalised during pregnancy, with a reduction in IGF-1 reported in a further pregnancy in spite of discontinuation of somatostatin analogue therapy.

Our data is in agreement with the data derived from the French Acromegaly Registry. Caron and colleagues published a series of 59 pregnancies in 46 women, which showed low rates of gestational diabetes or gravid

hypertension in acromegalic pregnancies (7). The rates of gestational diabetes and hypertension described were marginally higher than those defined in the general French population (gravid hypertension 5–15% in general population vs 13.6% acromegaly population, gestational diabetes <6% in general population vs 6.8% in acromegaly population). The analysis of the French data did not adjust for other risk factors of gestational diabetes and hypertension such as age and BMI, and neither the Caron study data, nor our data raises concern for gestational diabetes or hypertension, even in patients with uncontrolled acromegaly (7).

A recent review article by Acbucham *et al.* described the changes in GH and IGF-1 physiology in normal pregnancy and patients with acromegaly (14). In normal pregnancy, increased plasma oestrogen and progesterone concentrations produce a relative state of GH resistance, leading to decreased IGF-1 generation from the liver (14). In the first trimester of normal pregnancy, pituitary GH (predominantly 22kDa GH) is the predominant GH isoform observed in maternal blood and rising plasma oestrogen levels cause GH resistance, with a resultant decrease in IGF-1 (15). However, as the pregnancy progresses there are increasing plasma concentrations of placental GH, which eventually overcomes the resistance to GH, with increasing plasma IGF-1 levels observed towards the end of pregnancy (16).

This theory is further supported when one considers the studies that evaluated oestrogen therapy in acromegaly

(17). These studies demonstrated a reduction in plasma IGF-1 concentrations (18) with a paradoxical rise in GH (19, 20), indicating a loss of negative feedback inhibition to the pituitary. This data suggests that reduction in plasma IGF-1 does not occur through a hypothalmo-pituitary derived mechanism but rather an effect of oestrogen in the hepatic circulation suppressing hepatic derived IGF-1 (18). The mechanism of this action is thought to be mediated through the JAK-STAT pathway which inhibits the transcriptional action of GH (18, 21).

Women who become pregnant with acromegaly will also experience oestrogen-induced GH resistance. Therefore, physiologically one would predict an improvement in IGF-1 levels in the first trimester of pregnancy. However, after the second trimester both pituitary GH and rising placental GH concentrations will coexist in patients with acromegaly. Circulating plasma IGF-1 concentrations, will therefore depend on the interaction of placental and pituitary GH and the degree of oestrogen-induced GH resistance, all of which are highly variable amongst patients (14).

The breast feeding rate observed in our cohort is low at 6/17. However, this should be taken in the context of low rates of breast feeding in the general population in Ireland. Ireland has one of the lowest rates of breast feeding worldwide, with 42.3% of mothers exclusively breast feeding their baby on discharge, in comparison to 79.8% for the remainder of the EU (22). The primary reason for not breast feeding was patient choice, although two women were unable to produce adequate breast milk (one woman was receiving DA therapy).

The observed rate of caesarean section is high in this cohort; 11/17 pregnancies were delivered by caesarean section. One of these caesarean sections was an emergency caesarean section for the treatment of pre-eclampsia, the remainder were elective. The rate of caesarean sections in our cohort was higher than the background caesarean section rate in Ireland of 25.6% (23). This may reflect a perception amongst obstetricians that patients with acromegaly are more complex patients with a potential risk of peri-partum apoplexy, leading to a delivery by caesarean section.

Although all somatostatin therapy was discontinued with the first pregnancy test, dopamine agonists (DA) were continued in 6/17 pregnancies. This is a historic cohort of patients and reflects practice before the 2014 Endocrine Society guidelines for acromegaly were available. DA may have been continued due the theoretical risk of tumour expansion, which has been described in case reports (13, 24). Furthermore, the

prevalence of hyperprolactinaemia in this cohort is not available; previous studies have observed 23% of patients with macroprolactinomas (without prior ablative treatment) had a significant increase in tumour size during pregnancy, therefore DA therapy may also have been continued to offset this risk (25). Whilst dopamine agonists are known to cross the placenta (26), published case series have not shown to have any adverse maternal or foetal outcomes (27, 28). The majority of data supporting the safety of dopamine agonists in pregnancy is derived from treatment of prolactinomas. The largest series to date ($n=6239$) found that bromocriptine use for management of prolactinomas in the early stages of the first trimester of pregnancy was not associated with an increased risk of congenital malformations (29). Similarly, Colao *et al.* reported that cabergoline use in 329 patients with hyperprolactinaemia during pregnancy was not associated with miscarriage or congenital malformations (28).

Somatostatin analogues have also been shown to cross the placenta (30) and there have case reports of intra-uterine growth restriction in mothers taking somatostatin analogue therapy during pregnancy (7). There are only isolated case reports of women taking pegvisomant during pregnancy, therefore there is insufficient data to recommend their use during pregnancy. None of the above agents are licenced for use during pregnancy. When one considers the generally positive foetal and maternal outcomes observed in this case series and others (3, 7), medical therapy in acromegaly is required and indicated only in exceptional circumstances for symptom management or tumour growth during pregnancy.

Conclusion

Our data supports the previously published data that pregnancy in women with acromegaly is generally safe, from a maternal and foetal perspective. Furthermore, biochemical control tends to improve in spite of the withdrawal of somatostatin analogue treatment for acromegaly during pregnancy. The lack of data for clinical outcomes of pregnancy in acromegaly limits the development of evidence-based guidelines. Whilst controlling tumour size and hormonal activity preconception is advised to ensure optimum outcomes, these data support that pregnancy is generally safe even in women without biochemical control. As therapeutic interventions such as surgery and radiotherapy may have a detrimental effect on fertility, this is an important

observation and suggests that even women without biochemical control should not be dissuaded from becoming pregnant.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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