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EDITORIAL

Medical treatment of acromegaly in pregnancy, highlights on new reports

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In this issue of *Endocrine*, van der Lely et al. [1] provided a well-written, extensive review of all reported cases of pegvisomant use in pregnancy, (mother and father) from a large safety database.

Acromegaly is a relatively rare disease, caused by a growth hormone (GH) secreting pituitary adenoma [2]; however, reports now suggest disease incidence might be higher than previously reported, with women and men equally affected [2–4]. Hypogonadism is reported in approximately 70 % of patients with acromegaly [2]. The decreased rate of fertility in women with acromegaly is multifactorial. Gonadotrope reserve can be lower due to mass tumor effect, stalk effect or subsequent to surgery or radiation [5]. The hyperprolactinemia in mixed tumors also plays a role, while GH/insulin-like growth factor 1 (IGF-1) excess per se has been noted to have direct effect on the ovaries. Nevertheless, over the last two decades, more women with acromegaly achieve successful pregnancy [5]. This is due to improved outcomes after transsphenoidal surgery, use of medical therapy as a first line treatment in many patients, and delegation of pituitary radiation to a third line treatment, and of course advances in fertilization techniques.

How to better care for women with acromegaly is complex and not well studied [5]. Management of acromegaly in patients desiring pregnancy should include optimizing biochemical control and maximizing tumor shrinkage before becoming pregnant [5–8]. After becoming pregnant, most reports recommend stopping all medical treatment for acromegaly [5, 9, 10] and restarting only if severe symptoms (headache for example), visual changes, or tumor growth are present. Interestingly, acromegaly symptoms usually improve during pregnancy.

A diagnosis of new onset acromegaly while pregnant is problematic due to the complex issue of measuring GH, which includes placental GH and GH resistance in the presence of high estrogen [5].

The focus of this editorial will be medical treatment of acromegaly during pregnancy, with a review of new data regarding pegvisomant use during pregnancy, published in this issue [1].

Rather than summarizing study-related findings, comments will focus on current, if somewhat limited data on outcomes after acromegaly treatment in pregnancy. For example, do physicians need to treat and if yes, which approach should be pursued?

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 [5, 9]. Tumor enlargement may also be theoretically triggered by somatostatin receptor ligand (SRL) discontinuation at pregnancy onset.

The literature indicates an increased risk of gestational diabetes and gravid hypertension in women with non-controlled GH/IGF-1 hypersecretion before gestation, which must be appropriately and aggressively treated, but in most patients, specific acromegaly therapy can be delayed until after delivery.

Based on experience with dopamine agonists (DAs) in prolactinomas, bromocriptine and cabergoline have constituted the initial treatment of choice for acromegaly in pregnancy; however, efficacy is limited outside of mild cases.

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More experience with SRLs has accumulated over time, but information (one small prospective, a few multicenter retrospective studies, and case reports) remains inadequate. SRLs cross the placenta and as such safety of use during pregnancy has not been fully studied [8]. 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.

To date, use of pegvisomant in pregnancy has been limited to just two case reports [11, 12]. It is reassuring, however, that no transfer of pegvisomant across the placenta or presence in breast milk has been noted.

van der Lely et al. [1], reported in this issue of *Endocrine* the largest aggregate number of patients ($n = 35$) who were taking pegvisomant at the time of conception (27 women and eight men); fetal outcome was not reported in nine of the 35 cases. The data were reported from a global safety database that contains information obtained from various sources: spontaneous reports, health authorities, a post-marketing surveillance program, customer engagement programs, and clinical studies, which are reported regardless of outcome. The study strength lies in the sheer number of acromegaly patients taking pegvisomant followed world-wide, but few cases of pregnancy have been overall reported. Patients who continued treatment during pregnancy were even fewer. Daily pegvisomant dose at conception varied widely (14–40 mg), but mean dose was 15.3 mg/day, which is not very different from that used in most patients in observational studies [10, 13]. Interestingly, a few patients were also taking SRLs at the time of conception. Two women experienced spontaneous abortion, which was deemed unrelated to drug by the investigator. In one case of an ectopic pregnancy, no information was available.

As expected, the majority of patients discontinued pegvisomant immediately after pregnancy was discovered, but three continued therapy, albeit at a lower dose. There are no available IGF-1 data for those patients who continued on pegvisomant throughout pregnancy.

van der Lely et al., present the largest experience with pegvisomant in pregnancy to date. However, there are significant limitations, which are duly and well acknowledged by the authors, including under-reporting (any adverse event reporting is voluntary outside of a clinical study) or incomplete reporting with missing historical data on history. For example, missing concomitant medications and outcomes can make the cause-relationship effect challenging.

Based on limited available data, and in concordance with Endocrine Society Guidelines [3], medical treatment for acromegaly should be stopped at time of conception. The analysis by van der Lely et al., found no link between pegvisomant use up to conception and adverse fetal outcomes. Similarly, DAs and SRLs use up to conception seems also to be safe [5, 7, 8, 11]. Of note, when long-acting SRLs are used, switching to a short-acting SRL for 2–3 months before a planned pregnancy is preferable.

While acromegaly course is uneventful in most women during pregnancy, for the reasons described above, some patients will require treatment. No DAs, SRLs, or GH receptor blockers are approved for use during pregnancy [3]; fortunately more data are being accumulated, albeit from retrospective studies and safety databases.

In conclusion, optimal medical management of a pregnant woman with active acromegaly is far from established. Furthermore, an early acromegaly diagnosis, when tumors are smaller and thus easier to cure with surgery and less comorbidity, will improve fertility chances and outcomes, overall. Most of the reported acromegaly pregnancies in women with pre-existing or newly diagnosed acromegaly progressed without an increased complication rate regarding maternal and fetal outcomes, and with normal delivery of healthy infants.

If clinically needed, SRLs, DAs, or GH receptor antagonists appear, to date, to lack significant adverse effects, but further clinical experience with these particular drugs and use in pregnancy is still required. A concerted effort across all pituitary centers should be made to create a unified patient database to prospectively record all acromegaly patients who desire pregnancy, their treatment, and subsequent maternal and fetal outcome.

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