**PITUITARY AND ADRENAL DISORDERS OF PREGNANCY**

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**ABSTRACT**

# The pituitary and adrenal glands play an integral role in the endocrine and physiological changes of normal pregnancy. These changes are associated with alterations in the normal ranges of endocrine tests and in the appearance of the glands. It is important for the medical team to be aware of these altered normal ranges in the pregnant population. Some disorders affect women more commonly during pregnancy or the puerperium, e.g., lymphocytic hypophysitis, while other pre-existing disorders such as macroprolactinomas can have worse outcomes in pregnancy. Other conditions may be incidental to pregnancy, but management strategies require modification to ensure safety of the pregnant woman or fetus. This chapter describes the normal physiological alterations in the pituitary and adrenal glands and describes the impact of disorders of these endocrine glands on pregnant women, the fetus, and children of affected women. It also describes the existing data with regard to safety of drugs used to treat pituitary and adrenal disease in pregnancy.

## **PITUITARY DISORDERS IN PREGNANCY**

**Anterior Pituitary Gland Anatomy**

The pituitary gland enlarges in a three-dimensional fashion by approximately 136% throughout pregnancy (1). There is a progressive linear increase in pituitary height of approximately 0.12mm for each gestational week (2), and the gland is thought to reach its peak size in the first 3 days postpartum when it may reach a height of 12mm on magnetic resonance imaging (MRI) (1, 2). The superior aspect of the gland expands to adopt a dome-like contour moving closer to the optic chiasm (3). Despite this enlargement, compressive symptoms are not typically seen during pregnancy.

Pituitary gland enlargement is related to estrogen-stimulated hypertrophy and hyperplasia of the lactotrophs (4). While lactotroph cells make up 20% of anterior pituitary cells in the nonpregnant state, they comprise up to 60% by the third trimester of pregnancy (5). Gonadotrophs decline in number during pregnancy whilst numbers of corticotrophs and thyrotrophs remain constant (5). Somatotrophs are generally suppressed (as a consequence of negative feedback secondary to high levels of insulin like growth factor-1 which is stimulated by placental growth hormone) and may function as lactotrophs (5, 6). After the initial increase in size postpartum there is then a reduction in size back to normal by 6 months postpartum (regardless of breastfeeding status) (2).

An understanding of these anatomical changes is important when investigating suspected pituitary pathology during pregnancy, and also when monitoring pre-existing tumors (1). Investigation should be reserved for those patients with symptoms or signs consistent with tumor or pituitary enlargement, asymmetrical growth, deviation of the stalk, or when the height of the pituitary is larger than expected in pregnancy (7).

The preferred mode of pituitary imaging in pregnancy is non-contrast MRI, which is considered safe due to the absence of ionizing radiation. There is reassuring evidence for its use in all trimesters with no evidence for adverse pregnancy outcomes (8-10). As a precaution, it has been suggested that 1.5-Tesla scanners should be used rather than 3.0-Tesla scanners as the specific absorption rate quadruples when the magnetic field doubles, although the risk of this is theoretical (8, 11).

**Prolactin**

INTRODUCTION

Prolactin (PRL) is secreted by the pituitary and a number of extra pituitary sites including the hypothalamus, lymphocytes, uterus, placenta and lactating mammary gland (12, 13). Extra-pituitary secretion, however, is thought to account for only a small proportion of the overall secretion, as supported by one study which reported that hypophysectomized female rats had 10-20% lactogenic activity in their serum compared to control (14). In combination with other hormones, PRL mediates mammogenesis, lactogenesis, and galactopoiesis, and plays a role in the regulation of humoral and cellular immune responses. Placental estrogen stimulates lactotroph PRL synthesis in the first trimester (15, 16) while progesterone also stimulates prolactin secretion (17, 18). Prolactin levels progressively increase throughout gestation (approximately 10-fold) (19), and then decline postpartum in non-lactating women. Despite increased PRL levels, the normal lactotroph continues to respond to TRH and anti-dopaminergic stimulation. Postpartum, the circadian rhythm of PRL release is enhanced by the effects of suckling.

FERTILITY

Hyperprolactinemia has been reported to account for between 7% and 20% of female infertility (20). It reduces luteinizing hormone (LH) pulse amplitude and frequency through suppression of gonadotrophin-releasing hormone (GnRH) (21), and is associated with diminished positive estrogen feedback on gonadotrophin secretion at mid-cycle (22). Prolactin also has a direct effect on the ovarian granulosa cells and suppresses progesterone and estrogen secretion from the ovaries (23). It can decrease estrogen levels through a direct effect on ovarian aromatase activity and by blocking the stimulatory effects of follicle-stimulating hormone (FSH) (24, 25). At high levels PRL also inhibits progesterone production (26). As a consequence, most hyperprolactinemic women become anovulatory with resultant amenorrhea and infertility (27).

PRECONCEPTION MANAGEMENT AND RESTORATION OF MENSES

Dopamine agonists remain the treatment of choice for the majority of patients with a prolactinoma. Bromocriptine restores ovulatory menses in 70-80% of patients with 50-75% of patients experiencing an over 50% reduction in size of the pituitary tumor (28, 29). Cabergoline is more effective, restoring ovulatory menses in >90% of women and achieving >90% reduction in tumor size (28, 29). Bromocriptine, however, has a larger volume of safety data (although the data are reassuring for both), and this should be discussed during the pre-conception counselling period. In addition, bromocriptine is cheaper, and some clinicians may elect to use it as its use has not been reported to have an association with heart valve disease. However, it should be noted that there are no published reports of cardiac valve abnormalities in cabergoline-treated pregnant women or their fetuses. The disadvantages with bromocriptine include twice-daily dosing (vs twice weekly with cabergoline), although this may not be strictly necessary, a greater side effect profile, and inferior effectiveness at normalizing prolactin concentrations (30, 31). For women who cannot tolerate bromocriptine, cabergoline should be recommended as 70% of patients who have not responded to bromocriptine respond to cabergoline (32). In those who do not achieve restoration of menses, clomiphene citrate or recombinant gonadotrophin may be considered for ovulation induction (33).

Surgical therapy is curative in approximately 70-80% of patients with microadenomas and rarely causes hypopituitarism in expert hands. The cure rate is lower (30%) in patients with macroadenomas, and the risk of hypopituitarism and subsequent infertility is markedly increased (28).

All women with prolactinomas should be counselled in the pre-pregnancy period about their potential fertility and pregnancy outcomes to enable informed decision making (34).

EFFECTS OF DOPAMINE AGONISTS ON THE DEVELOPING FETUS

Bromocriptine has been shown to cross the placenta in human studies (35); cabergoline lacks human data but has been found to do so in animal studies. Current recommendations, therefore, advise that women with prolactinomas discontinue dopamine agonist therapy when they discover that they are pregnant (29). There is a subset of patients in whom this may not apply, e.g., women with macroadenomas, in particular those with an invasive tumor or where it is abutting the optic chiasm. In such cases, the management must be considered on a case-by-case basis.

In the majority of cases, in order to limit the exposure time to the developing fetus it is beneficial to know the timing of the normal menstrual cycle. Use of mechanical contraception may facilitate this if used for the first two to three cycles after starting treatment. As a consequence, women will know when they have missed a period, a pregnancy test can be performed in a timely manner and the dopamine agonist can be stopped in cases where a pregnancy is confirmed. This approach aims to limit the time that the fetus is exposed to bromocriptine to 3-4 weeks and cabergoline to around 5 weeks (as a consequence of its longer half-life (21).

Such short-term exposure to both bromocriptine and cabergoline is unavoidable but reassuringly pregnancy outcomes with respect to spontaneous abortions, terminations, ectopic pregnancies, pre-term births, multiple pregnancies, and malformations do not differ from the normal population Table 1 summarizes outcome data from 6239 pregnancies following bromocriptine treatment and 968 where the mother took cabergoline (21). There was no increased risk demonstrated by either drug but due to the greater wealth of experience with bromocriptine it is the preferred drug of choice for those wishing to become pregnant according to the European guideline (29).

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| --- | --- | --- | --- |
| Table 1. Pregnancy Outcomes While Taking Bromocriptine or Cabergoline Compared to the Normal Population | | | |
|  | **Bromocriptine**  **(*n* (%))** | **Cabergoline**  **(*n* (%))** | **Normal (%)** |
| Pregnancies  Spontaneous abortions  Terminations  Ectopic  Hydatiform moles | 6239 (100)  620 (9.9)  75 (1.2)  31 (0.5)  11 (0.2) | 968 (100)  73 (7.5)  63a (6.5)  3 (0.3)  1 (0.1) | 100  10-15  20  1.0-1.5  0.1-0.15 |
| Deliveries (known duration)  At term (>37 weeks)  Preterm (<37 weeks) | 4139 (100)  3620 (87.5)  519 (12.5) | 705 (100)  634b (89.9)  71 (10.1) | 100  87.3  12.7 |
| Deliveries (known outcome)  Single births  Multiple births | 5120 (100)  5031 (98.3)  89 (1.7) | 629 (100)  614 (97.6)  15 (2.4) | 100  96.8  3.2 |
| Babies (known details)  Normal  With malformations | 5213 (100)  5030 (98.2)  93 (1.8) | 822 (100)  801 (97.4)  21 (2.4) | 100  97  3.0 |

aEleven of these terminations were for malformations

bFive of these births were stillbirths

Long-term follow up studies of children conceived whilst their mothers were taking either bromocriptine or cabergoline are also reassuring, although the numbers are smaller (36-41).

Bromocriptine has been used throughout gestation in just over 100 women with no increase in the rate of abnormalities compared to background rates (33, 36, 42). Of 15 reports of the use of cabergoline throughout gestation (43), 13 healthy infants were delivered at term and another was delivered at 36 weeks’ gestation. There was one intrauterine death at 34 weeks in a pregnancy complicated by severe pre-eclampsia (43). In a study of 25 pregnancies in which cabergoline was continued throughout gestation, the incidence of missed abortion, stillbirth and low birth weight was no different compared to a group of women in whom the cabergoline was not continued. There was also no difference in post-pregnancy recurrence of hyperprolactinemia or tumor remission (44).

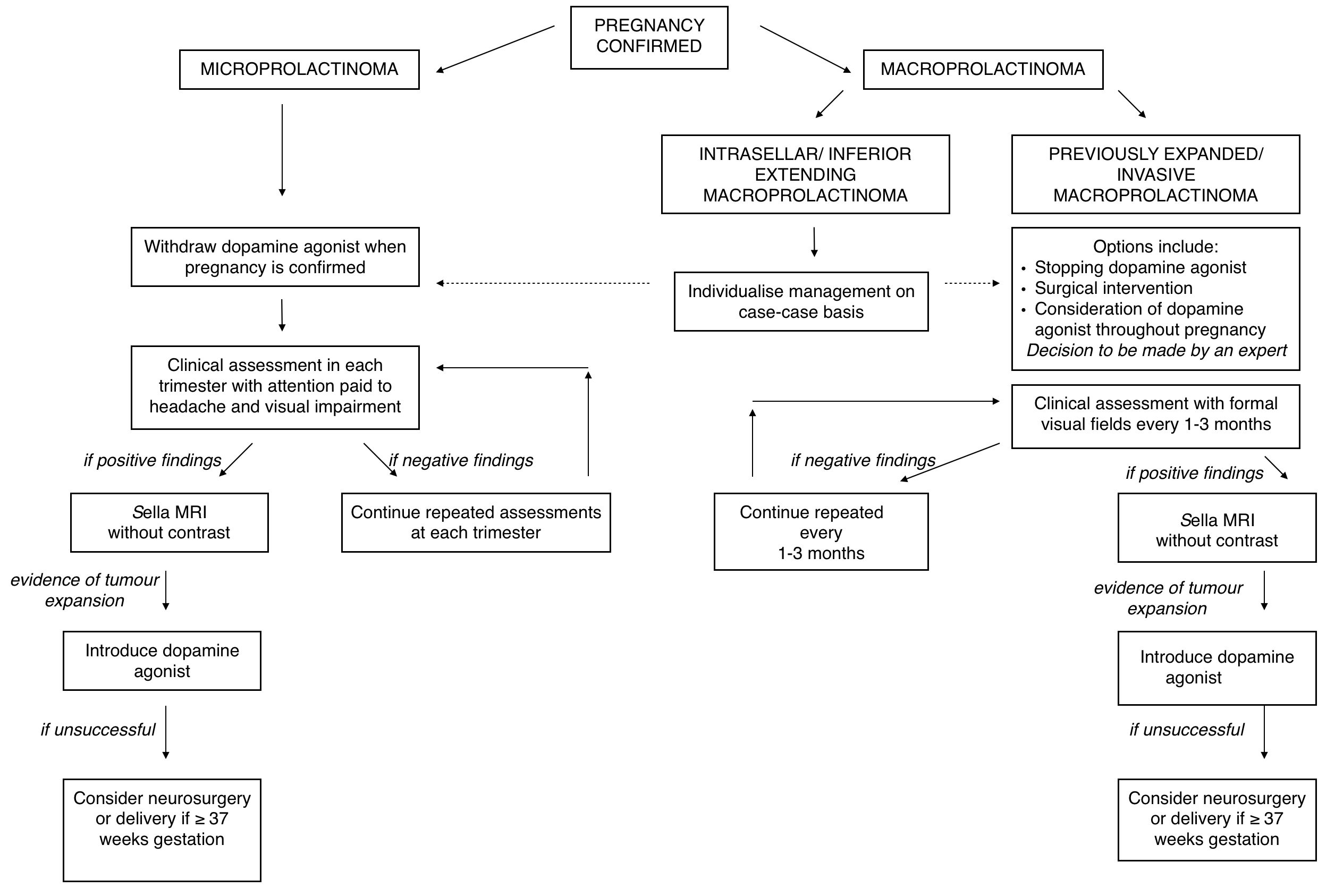
EFFECT OF PREGNANCY ON PROLACTINOMA SIZE

Prolactinomas can enlarge during pregnancy as a consequence of the progressive increase in serum estrogen levels and discontinuation of dopamine agonists (21). This can lead to tumor volume enlargement with the risk of mass effect and visual field loss. In microprolactinomas, the risk of clinically significant tumor growth is less than 5%. In contrast, patients with macroprolactinomas are reported to have a 15-35% risk (33, 45). This risk can be reduced if the patient undergoes surgery or irradiation prior to the pregnancy.

MANAGEMENT FOLLOWING CONCEPTION

The risk of tumor expansion is sufficiently rare for microprolactinomas that dopamine agonists can be withdrawn on confirmation of pregnancy. For patients with a macroprolactinoma decisions about cessation of therapy should be decided on a case-by-case basis. For some women with intrasellar/ inferiorly extending macroprolactinomas there may be less concern than for those where the tumor has close proximity to the optic chiasm. For all women with macroprolactinomas, it is appropriate to undertake a clinical assessment of the patient in each trimester with particular attention to the presence of headache or visual impairment. Where clinical findings are positive it is then pertinent to perform a MRI scan without contrast, and if evidence of tumor expansion either re-introduce a dopamine antagonist or increase the dose (33). If this fails neurosurgery (preferably during the second trimester) or delivery (if the pregnancy is sufficiently advanced, e.g., at >37 weeks’ gestation) may be appropriate (46). If clinical examination or further investigation is reassuring, assessment in each trimester can be re-commenced without changes in treatment. MRI also plays a pertinent role in distinguishing between hemorrhage into a tumor and simple tumor enlargement in those presenting with headache (21).

For patients with previous expansion or an invasive macroprolactinoma, options for management need to be carefully considered by an expert in the field. Options include stopping the dopamine agonist, surgical intervention, or continuing the dopamine agonist throughout pregnancy. Clinical assessment with formal visual fields can be justified every 1-3 months, and if there are positive findings an MRI scan without contrast with a view to addition of dopamine agonist, neurosurgery, or delivery where appropriate should be undertaken (Figure 1).



**Figure 1. Schematic for the Management of Both Micro- and Macroprolactinomas During pregnancy.**

The monitoring of prolactin levels yields no diagnostic benefit in the pregnant woman with a prolactinoma as it bears no correlation to tumor growth. In most cases, serum prolactin concentrations will rise with gestation regardless of the presence of a prolactinoma, and it is also possible for tumor size to increase without a simultaneous rise in prolactin level.

BREASTFEEDING

There are no contraindications to breastfeeding in women with prolactinomas. To date, there is no evidence to suggest a significant increase in prolactin levels or symptoms suggestive of tumor enlargement in lactating women (20). In many women dopamine agonists do not need to be reintroduced during this period. There has even been successful lactation in women with previous surgical resection of a prolactinoma whose prolactin level had not increased during pregnancy. In a study carried out by Narita et al (47), a third of such women whose prolactin levels had not risen above 30ng/mL during pregnancy were still able to lactate.

**Growth Hormone**

INTRODUCTION

Pituitary growth hormone (PGH), expressed by the somatotroph cells of the anterior pituitary, has two main isoforms: 22K-GH and 20K-GH. The 22K-GH isoform is the main circulatory isoform in normal men, nonpregnant women, and in patients with acromegaly (3). In the nonpregnant state the hypothalamus secretes growth hormone releasing hormone (GHRH) which stimulates the production of growth hormone from the pituitary in a pulsatile fashion. PGH subsequently stimulates insulin-like growth factor 1 (IGF-1) release from the liver which is required for metabolism and growth promoting effects. Somatostatin inhibits growth hormone, providing negative feedback and there is also inhibition of PGH production by IGF-1 which prevents the somatotrophs from releasing PGH and encourages the release of somatostatin from the hypothalamus. When too much PGH is secreted by a pituitary adenoma acromegaly is diagnosed. This is confirmed by an elevated age- and sex- corrected serum IGF-1 and failure of PGH to suppress to <0.4ug/L following an oral glucose tolerance test in the presence of a pituitary mass on MRI.

Estrogen blocks the effects of PGH on the liver, which explains why in order to achieve equivalent levels of IGF-1 women need to secrete higher levels of PGH than men (3). During normal pregnancy the rise in estrogen generates a PGH resistant state and, as such, there is an initial drop in IGF-1 levels. As the placenta grows it begins to secrete placental growth hormone (PLGH), a single chain protein that is structurally very similar to the PGH isoform 22K-GH (6). PLGH is initially secreted at 10 weeks (48) eventually overcoming the resistance to growth hormone and resulting in an increase in IGF-1 levels. Eventually, PGH becomes suppressed as a consequence of negative feedback such that by the last week of pregnancy PLGH and IGF-1 levels peak whilst PGH is almost undetectable (49).

DIAGNOSIS OF ACROMEGALY DURING PREGNANCY

The similarities in the structure of PGH and PLGH present challenges for the diagnosis of acromegaly and monitoring of biochemical control in pregnant women with pre-existing acromegaly. Both GH peptides are composed of a single polypeptide chain with 2 disulfide bridges and 191 amino-acids. Conventional assays for GH cannot usually distinguish between the two, and therefore the confident diagnosis of acromegaly is usually reserved until after delivery. When a diagnosis during pregnancy is desired, there are a number of factors that may be considered. The pulsatile nature of PGH may help to establish a true increase in PGH as opposed to PLGH, if pulsatility can be demonstrated. Response to hypoglycemia is enhanced in PGH but decreased in PLGH, and response to arginine is enhanced in PGH and varies in PLGH (6).

A high serum IGF-1 concentration prior to midgestation may also be suggestive of acromegaly as levels are not expected to rise until after this stage of pregnancy. Highly specific assays may also be used to demonstrate raised PGH during the third trimester if raised above the expected 1ug/L, which is expected that that stage of normal pregnancy (3).

If a new diagnosis of acromegaly is suspected, imaging of the pituitary with MRI may be warranted (50).

FERTILITY IN WOMEN WITH ACROMEGALY

It is reported that between 40-84% of acromegalic women suffer with gonadal dysfunction the causes of which are multifactorial (51-55). Mass effect of the adenoma on the gonadotrophic cells may cause gonadotrophin deficiency. In addition, compression of the stalk may reduce levels of GnRH and contribute towards an increase in PRL levels (55). PRL secretion may also be increased in cases of a mixed GH and PRL-secreting tumor. Other contributory features include the effect of GH and IGF-1 on the ovaries (inhibition of GnRH and direct ovarian inhibition) and polycystic ovarian syndrome (54, 55).

EFFECT OF PREGNANCY ON ACROMEGALY

In a recent review of 46 women with acromegaly in pregnancy, 39 received surgical treatment prior to conception, and 21 who were receiving medical treatment and drugs were continued on therapy if the risk of treatment interruption was considered to outweigh the risk of continuation (56). In this and other similar reviews (57-59), this is considered to “reflect the overall improvement in both diagnosis and treatment of patients with acromegaly in the last decades” (3). The adenomatous somatotrophic cells themselves appear to be resistant to the IGF-1 inhibitory feedback demonstrated in pregnancy, as demonstrated by continuous PGH production during pregnancy (using specific placental assays) (3, 55). Despite this, biochemical escape is often witnessed with IGF-1 levels often remaining unchanged or decreasing during pregnancy (60). This is thought to be secondary to reduced IGF-1 generation in the context of hepatic resistance to GH action in a high-estrogen environment (61). However, the degree of hepatic resistance varies from patient to patient, and this most likely explains the variability in clinical course often encountered (59, 62, 63). As might be expected, it is not uncommon for IGF-1 levels to increase rapidly post-delivery (or following termination of pregnancy), and thus vigilance must be exhibited by the clinician at this stage.

A multicenter study carried out by Caron *et al.* in 2010 retrospectively studied 59 pregnancies in 46 women with GH-secreting pituitary adenomas. In 3 out of 27 cases in whom adenoma volume was assessed by MRI 6 months post-delivery, there was an increase in size (11.1%), and two affected women had visual complications. Adenoma volume was stable in 22 women (81.5%) and decreased in two cases (7.4%) (56). A number of subsequent published reports have mirrored these figures, demonstrating that the risk of tumor expansion is small (58, 59, 64). In a retrospective analysis of 31 pregnancies in 20 patients with acromegaly, Jallad *et a*l. observed symptomatic pituitary tumor enlargement and subsequent surgical intervention in 3 of 31 (9.6%) pregnancies. It is worth noting, however, that in these cases the patients had visual field impairment at the initiation of pregnancy (61). In a recent series of 17 pregnancies in 12 women with acromegaly no patients developed new visual field abnormalities or symptoms suggestive of tumor expansion (60). In a systematic review including 273 pregnancies in 211 women with acromegaly 9% of women experienced tumour growth (65).

EFFECT OF ACROMEGALY ON THE NEONATE

The presence of elevated PGH levels is not thought to effect the neonate as there is currently no evidence that PGH crosses the placenta or influences placental development (55). Considering the increased risk of the mother developing worsening diabetes or hypertension or gestational diabetes mellitus (GDM) or hypertension, it is important to consider the risk of macrosomia and microsomia respectively (3, 65).

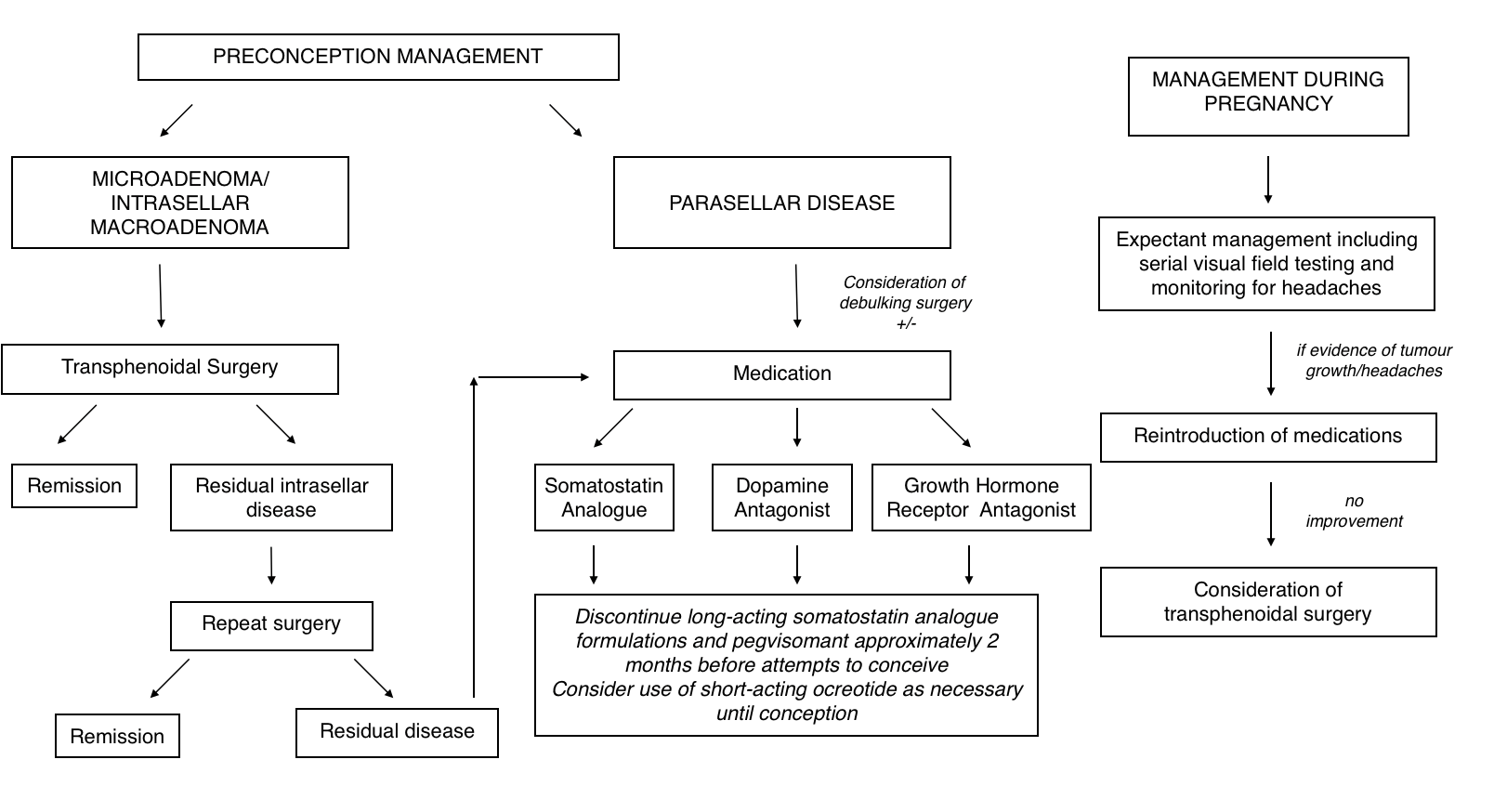
METABOLIC AND CARDIOVASCULAR COMPLICATIONS

Jallad *et al*. described the diabetogenic effects of PLGH and PGH which include hyperinsulinemia, decreased insulin-stimulated glucose uptake and glycogen synthesis, and impairment of the ability of insulin to suppress hepatic gluconeogenesis (61). As a consequence, acromegalic women are at higher risk of developing GDM or suffering worsening control of pre-existing diabetes mellitus (65). The risk of developing GDM in women with acromegaly appears to be in the region of 5.5%-10% (55). This figure is slightly higher than the rate of gestational diabetes in the general UK population, which is reported as 5% (66). The risk of gestational hypertension is also approximately 14% (6, 61). In a retrospective study, this was associated with poor GH/IGF-1 control prior to pregnancy (56).

MANAGEMENT APPROACH

In patients diagnosed prior to pregnancy with microadenomas or intrasellar macroadenomas, transsphenoidal surgery is the most frequent surgical approach and the majority will achieve remission. For those with residual disease repeat surgery can be considered. In cases of persistent residual disease, either a somatostatin analogue, dopamine agonist, or pegvisomant may be used. For those with parasellar disease, debulking surgery +/- introduction of medical management should be considered. It is pertinent for patients taking either a long-acting somatostatin analogue or pegvisomant to aim to stop treatment two months prior to attempting to conceive; short-acting octreotide can be used until conception (67). The advantages and disadvantages of stopping the medication should be discussed with the patient and the ultimate decision be made on a case-by-case basis. In addition, assessment of disease activity, comorbidities and fertility status should be undertaken in the pre-pregnancy period to facilitate informed decision making (34).

For those patients diagnosed in pregnancy, a more conservative approach is advised with introduction of medical management in those patients who require tumor or headache control. When no improvement is seen with medication, transsphenoidal surgery should be considered (Figure 2). Routine measurements of serum concentrations of GH and IGF-1 or routine MRI are not recommended during pregnancy (67).



**Figure 2: Schematic for the Management of Acromegaly During Pregnancy**

MEDICAL THERAPY

*Somatostatin Analogues*

Due to a historic lack of data, awareness that they can cross the placenta, and identification of somatostatin receptors in the placenta and fetal pituitary, somatostatin analogues are typically stopped two months prior to conception. However, due to the long-acting nature of these drugs and the need for some women to continue therapy throughout part of the entirety of gestation, data are starting to accumulate. In a recent study by Vialon et al. 67 pregnancies in 62 women treated with somatostatin analogues during pregnancy were compared with 74 pregnancies in 65 women not treated medically (68). This study included 36 pregnancies in which a somatostatin analogue was taken in the first trimester of pregnancy. Rates of malformation were not reported above the background population and no significant impact on maternal and fetal outcomes were identified. While the paucity of data continues to support withdrawal of this group of medications prior to pregnancy in the majority these data provide reassurance for women who may conceive on these drugs or may require treatment throughout pregnancy or reintroduction during pregnancy.

*Dopamine Agonists*

The considerations regarding the safety use of cabergoline in women with prolactinomas discussed above also apply to those with acromegaly.

*Growth Hormone Receptor Antagonists*

Pegvisomant, a GH receptor antagonist, has only been used in a handful of cases and as such its safety in pregnancy has not been established. Published reports include a woman who had undergone *in vitro* fertilization and intra-cytoplasmic sperm injection following monotherapy with pegvisomant. The drug was discontinued after conception and a healthy neonate was born at 38 weeks by elective cesarean section and remained well at 1 year (69). Another woman treated with pegvisomant throughout gestation gave birth to a healthy girl at 40 weeks by cesarean section after failure to progress following spontaneous labor. In this case there was minimal demonstration of movement of pegvisomant across the placenta, and no evidence of substantial secretion into the breast milk (70). A 2015 review of current safety data compiled in the *Pfizer Global Safety Database* included 27 women exposed to pegvisomant, 3 of whom continued treatment throughout pregnancy. In this report there was no evidence to suggest adverse outcomes, but it was acknowledged that numbers remain too small to provide clear evidence (71). In a more recent series of four pregnancies in three women with pegvisomant used prior to or at the time of conception no significant maternal or fetal complications were reported (72).

**TSH-Secreting Adenomas**

There are only a small number of cases reported of women with TSH-secreting adenomas, four diagnosed prior to pregnancy and two after pregnancy (summarized in Table 2). All cases had positive outcomes with a variety of treatment strategies applied.

In 1996 Caron *et al* described a case in which a 31-year-old previously infertile woman was being treated with good biochemical and radiological responses with continuous subcutaneous infusion of octreotide for a TSH-secreting macroadenoma. She was found to be pregnant after four months of treatment, and the octreotide was consequently stopped. During the pregnancy TSH concentrations increased and there was symptomatic and radiological evidence of tumor expansion. Octreotide was restarted with rapid improvement in clinical signs and biochemical markers. Immunoreactive octreotide was detected in the umbilical cord but demonstrated rapidly decreasing concentrations and was undetectable at 40 days. This demonstrated evidence of maternal-fetal transfer of octreotide. Notably, despite this the usual physiological changes in neonatal thyroid parameters were not disturbed (73). In 2002 Blackhust *et al* described the first documented twin pregnancy in a 21-year-old patient with a TSH-secreting adenoma who had been treated with propylthiouracil to control thyrotoxicosis and cabergoline for hyperprolactinemia. She subsequently underwent transsphenoidal surgery due to resistant thyrotoxicosis, followed by long-acting octreotide and postoperative radiotherapy. This patient reported that she was pregnant during the course of radiotherapy and at this stage a decision was made to continue both the octreotide, complete the course of radiotherapy (although it is not documented for how many weeks the radiotherapy was continued it is likely to have been <9 weeks), and substitute cabergoline for bromocriptine (74). In 2003 Chaiamnuay *et al*. described at 39-year-old woman who was treated with propylthiouracil and bromocriptine; on confirmation of pregnancy (after 5 months of treatment) the dose of propylthiouracil was reduced and the bromocriptine was continued. At 27 weeks she developed clinical and radiological signs of tumor expansion and transsphenoidal surgery was performed with subsequent normalization of TSH and prolactin (75). There are two cases described in the literature where the mother was diagnosed during the pregnancy: both declined surgery and were medically managed. Both women had uneventful pregnancies and delivered healthy babies (76, 77).

Perdomo *et al* described a 21-year-old woman who initially underwent transsphenoidal surgery and was subsequently started on octreotide when she relapsed 17 months postoperatively. The octreotide was stopped when she was found to be pregnant (78).

Each pregnancy was uneventful with no congenital abnormalities reported. Although the number of cases is small, previous positive outcomes give some reassurance that pregnancy should not be entirely contraindicated in women with TSH-secreting adenomas. Treatment options include medical management with bromocriptine or octreotide, conservative medical control of thyrotoxicosis using propylthiouracil or carbimazole, or surgical management using the transsphenoidal approach. Emphasis lies on the importance of individualized treatment with the support of the multidisciplinary team. As with all pituitary tumors in pregnancy, close follow-up is paramount with monitoring of visual fields for evidence of tumor expansion.

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| Table 2. Summary of Pregnancies in Women with TSH Adenomas | | | | | | |
| Tumor | **Diagnosis** | **Prior TS** | **Previous medical therapy** | **TS in pregnancy** | **Medical therapy in pregnancy** | **Delivery** |
| TSH-secreting macroadenoma (73) | Prior to pregnancy | No | Oct-CSI (300ug/day) | No | Oct-CSI (300ug/day) -1st month and 3rd trimester | ECS |
| TSH-secreting macroadenoma with hypothalamic disconnection (74) | Prior to pregnancy | Yes | PTU and CBL prior to TS  Oct-LAR post TS  Post-TS RT | No | Br throughout gestation  RT (<9wks)  Oct-LAR- throughout gestation | NA |
| TSH-secreting macroadenoma with hypothalamic disconnection (75) | Prior to pregnancy | No | PTU 50mg TDS and Br 2.5mg OD | Yes | Reduced dose of PTU  Br continued | ECS |
| TSH-secreting microadenoma (76) | 24 weeks gestation | No | N/A | No | PTU 150mg/day in 3 divided doses from 28 wks | NVD |
| TSH-secreting macroadenoma (77) | 20 weeks’ gestation | N/A | N/A | No | PTU 100mg TDS until end of 2nd trimester then carbimazole 30mg/day until delivery | NVD |
| TSH-secreting macroadenoma (78) | Prior to pregnancy | Yes | Octreotide | No | Octreotide stopped | NVD |

Abbreviations: NA- Not available; TS- Transsphenoidal surgery; Oct-CSI- Octreotide Subcutaneous Infusion; CBL- Cabergoline; PTU- Propylthiouracil; Oct-LAR- Octreotide long-acting repeatable formulation; RT- Radiotherapy; Br- Bromocriptine; NVD- Normal vaginal delivery; ESC-Elective caesarean section; OD- once daily

**Non-Functioning Pituitary Adenomas and Gonadotrophin-Secreting Adenomas**

The majority of clinically non-functioning pituitary adenomas (NFPAs) in non-pregnant individuals are demonstrated to be gonadotrophin-cell adenomas when exposed to immunostaining (79). The main concern when a patient with an NFPA becomes pregnant, by virtue of the fact that there is an absence of hormone excess, is the theoretical risk of tumor enlargement causing compressive symptoms or displacement of the tumor causing compressive symptoms secondary to lactotroph hyperplasia. It is thought that in such cases patients may respond to dopamine agonist-mediated reduction of lactotroph hyperplasia. Masding *et al* described such as case in which a pregnant woman developed a visual defect at 18 weeks’ gestation and was demonstrated to have a NFPA which extended into the suprasellar region causing compression of the optic chiasm. This patient responded well to bromocriptine with resolution of the visual field defect (80). A UK national cohort study identified 16 cases of NFPA in pregnancy over a 3-year period, giving an incidence of 0.59 cases/100,000 maternities (45).The numbers were small, but there was no apparent increase in the rate of gestational hypertension or preterm labor in women with NFPA. However, they did have higher rates of operative delivery and induction of labor compared to women without pituitary tumors, a finding that was not reported in women with macroprolactinomas (45).

Gonadotrophin-secreting adenomas in pregnancy are extremely rare, and there are only three cases reported in the literature. The first reports a 29-year-old woman with a microadenoma and ovarian hyperstimulation. She was treated with bromocriptine with subsequent normalization of ovarian size and went onto conceive naturally (81). The second case also had ovarian hyperstimulation secondary to a gonadotrophin-secreting macroadenoma. This patient underwent surgical removal of the tumor with consequent normalization of FSH, LH and estradiol and natural conception (82). Both of these women delivered healthy newborns. The third presented with infertility, during work-up she was found to have an isolated elevated LH, MRI revealed an enlarged sella turcica and intrasellar mass following which she underwent transsphenoidal resection. Menses were restored within 16 days post operation and the patient reported being pregnant three months later. She was still under follow-up at the time the case report, hence, pregnancy outcomes were not reported(83).

**Pituitary Apoplexy**

Pituitary apoplexy is a rare clinical syndrome characterized by headache, visual disturbance, and altered mental status. It is caused by rapid expansion of the contents of the sella turcica as a consequence of hemorrhage or infarction into a pre-existing pituitary adenoma or within a physiologically enlarged gland. Pituitary apoplexy in pregnancy is extremely rare but may present as a medical emergency (due to risk of hormonal insufficiency) and may represent the first presentation of an underlying adenoma. It is therefore pertinent to consider apoplexy as a differential diagnosis for sudden onset headache and/or visual disturbance in pregnancy.

In a recent review of the clinical and biochemical characteristics of male and female patients presenting with pituitary apoplexy, it was found to be the first presentation of pituitary disease in 38/52 (73%) of patients. One quarter of the women (7/27) in this review experienced apoplexy in the peripartum period (84). It is thought that rapid expansion of a pituitary adenoma during pregnancy secondary to increased estradiol may be one explanation for the predisposition to apoplexy in the peripartum period (84).

There are approximately 40 cases of pituitary apoplexy during pregnancy described in the literature. The most common presenting symptoms in these patients are headache (95%) and visual disturbance (63%), comparable to the literature for non-pregnant patients (84-89). Hormonal replacement is required in approximately 60% of women with apoplexy in pregnancy making it important that pituitary hormone profiles are checked (85).

The acute management of apoplexy includes fluid and electrolyte replacement as well as corticosteroid replacement where indicated. The treatment given to the women in the literature ranges from conservative management, the use of dopamine agonists (bromocriptine and cabergoline) as well as surgical intervention. Women have also undergone varying modes of delivery, approximately 64% by vaginal delivery and approximately 36% by caesarean section, demonstrating the importance of an individualized management plan (85, 87-89).

Reassuringly, in the pregnancies described in the literature to date, if apoplexy is promptly diagnosed and managed, there appears to have not been any negative consequences for the fetus.

**Sheehan’s Syndrome**

Sheehan’s syndrome occurs as a consequence of ischemic pituitary necrosis secondary to severe postpartum hemorrhage with hypotension and shock (90). Possible mechanisms include vasospasm, thrombosis, and vascular compression of the hypophyseal arteries. Enlargement of the gland, disseminated intravascular coagulation, and autoimmunity have also been implicated in the pathophysiology of the condition (91). The majority of patients have an empty sella on CT or MRI (90).

Advances in obstetric care and the availability of rapid transfusion has resulted in a significant decline in the incidence of Sheehan’s syndrome in the Western world (91). Although rare, Sheehan’s syndrome may present as a medical emergency, and suspicion should be raised in women that are hypotensive, tachycardic, hypoglycemic, vomiting, or elicit signs of diabetes insipidus despite adequate resuscitation following post-partum hemorrhage (90, 91).

It is thought that the degree of ischemia and necrosis dictates the clinical course, and thus in patients with lesser degrees of ischemia the syndrome may present in a more insidious manner. Such patients may present with failure to lactate, persistent amenorrhea, light-headedness or fatigue, genital and axillary hair loss, dry skin, cold intolerance, and other symptoms of hypopituitarism. In such patients diagnosis may be delayed for over 10 years post-partum (92). In some women only partial hypopituitarism is experienced, and they may therefore go onto have further spontaneous pregnancies.

For those women in whom an acute form of Sheehan’s syndrome is suspected, investigations should include serum electrolytes, cortisol, prolactin, and free thyroid hormones, and possibly ACTH. Thyroxine has a half-life of seven days and so may be normal in the initial period, prolactin levels are usually low, as are ACTH and cortisol levels. Fluid replacement and stress doses of corticosteroids should then be given without delay and additional pituitary testing and subsequent therapy should be delayed until after recovery.

**Hypopituitarism**

The causes of hypopituitarism are vast and include neoplasms, vascular events (pituitary apoplexy, Sheehan’s syndrome, intrasellar carotid artery or subarachnoid hemorrhage), trauma, medications, infiltrative/inflammatory disease, and treatment of sellar/parasellar and hypothalamic disease such as surgery or radiotherapy. The disorder is characterized by the deficiency of one or more of the hormones secreted by the pituitary gland.

In those patients with gonadotrophin deficiency, fertility is often impaired making natural conception rare. Advances in fertility treatment, however, have led to increased pregnancy rates usually with the support of a reproductive endocrinologist. In such cases and with appropriate hormone replacement women can undergo uneventful pregnancies.

An increased demand for thyroid hormones is observed during pregnancy. This is thought to be explained by increased plasma volume and thus volume of distribution, fetal dependence on maternal thyroid hormones, increased human chorionic gonadotropin (hCG) levels (which acts as a weak TSH agonist), increased levels of total binding globulin, and increased thyroid hormone degradation. In patients recognized to have hypopituitarism, an appropriate rise in TSH may not be achieved and so it is recommended that clinicians monitor serum free T4 or total T4 levels every 4-6 weeks so that doses of thyroxine can be adjusted as required to maintain free T4 in the normal range for pregnancy.

An increase in glucocorticoid dose throughout gestation is not routinely recommended but rather monitoring of clinical symptoms of signs to assess for signs of glucocorticoid deficiency. Additional supplementation is, however, recommended during the active stage of labor and delivery. Current *Endocrine Society* guidelines suggest 50mg intravenous hydrocortisone during the second stage of labor and 100mg every 6-8 hours during caesarean section (93). The NICE guideline on the management of medical disorders in labor recommends slightly less glucocorticoid replacement in those planning a vaginal birth (50mg 6-hourly). For those having a caesarean section, this guideline suggests individualized glucocorticoid replacement strategies that will depend upon whether the woman has received hydrocortisone in labor, i.e., 50mg intravenous hydrocortisone when starting anesthesia if she has and 100mg hydrocortisone if she has not. Hydrocortisone replacement (50mg 6-hourly) is then recommended until 6 hours after birth (94). Mineralocorticoid replacement is not required in these patients.

Hydrocortisone is non-fluorinated glucocorticoid and therefore a good preparation to use for physiological glucocorticoid replacement in pregnancy because it is degraded by the placental enzyme 11beta-hydroxysteroid dehydrogenase-2 and thus limited quantities of the drug cross the placental barrier (95). Prednisolone is also a non-fluorinated glucocorticoid and therefore has limited passage across the placenta (96). Dexamethasone, however, is a fluorinated glucocorticoid and thus poorly metabolized by this enzyme, hence >50% will cross the placental barrier (97). Steroids with low transplacental transfer are favored to reduce the risk of neonatal adrenal suppression and neurocognitive/neurosensory disorders in childhood which have been associated with the fluorinated preparations (98).

Growth hormone is not currently approved for use during conception or pregnancy, and thus the current European Guidelines recommend its discontinuation during pregnancy (93). However, there is ongoing debate as to whether women with GH deficiency may benefit from such treatment. In an observational study of 201 pregnancies of patients with GH deficiency and hypopituitarism, two thirds of the women underwent fertility treatment to achieve pregnancy; 7% stopped GH replacement prior to pregnancy, 40% once the pregnancy was confirmed, and 25% at the end of the second trimester, while 28% continued the treatment throughout pregnancy. A healthy child was delivered in 80% of cases and there was no relationship between the complications and the treatment patterns (99). In a recent study reporting outcomes of 47 women with GH deficiency exposed to growth hormone between conception and delivery no new safety signals relating to GH were identified (100).

**Lymphocytic Hypophysitis**

Lymphocytic Hypophysitis (LH) is characterized by infiltration of the pituitary by lymphocytes and plasma cells which cause destruction of the normal parenchyma (101). The disorder is thought to have an autoimmune basis and is commonly associated with pregnancy or the post-partum period. Most patients present in the last month of pregnancy or within the first 2 weeks post-partum (101). Plausible explanations for the association between LH and pregnancy include, firstly, a change in the pattern of blood flow from predominantly systemic as opposed to portal circulation, and thus increased exposure to the immune system. Secondly, the theory that there are common autoantibodies to both the pituitary and placenta which may be implicated, although it should be noted that conflicting results and poor specificity impair the clinical usefulness of checking anti-pituitary antibodies for diagnostic purposes in the clinical setting(102, 103).

Patients may present with symptoms of mass effects, hypopituitarism, hyperprolactinemia, or diabetes insipidus (101). LH may be mistaken for Sheehan’s syndrome in the postpartum period, and absence of obstetric hemorrhage can be a useful distinguishing feature. A clinical diagnosis can often be made, particularly where there is a temporal relationship with pregnancy, and can be supported by typical appearances on MRI including symmetrical enlargement of the gland, a thickened but rarely displaced stalk, intact sellar floor, and pre-contrast homogeneity of the mass (101). Hypopituitarism disproportionate to the size of the lesion, preferential impairment of ACTH secretion, and the presence of anti-pituitary autoantibodies are also supporting findings (102).

Management is usually symptomatic including hormone replacement and focus on reducing the size of the mass. Due to the risks involved, surgical intervention is reserved for those patients with significant compressive symptoms. Glucocorticoids are favored by some to reduce inflammation, and in some cases their use has led to recovery of pituitary function (102). Other treatment options include azathioprine when pregnant and methotrexate or radiotherapy in non-pregnant individuals.

**Posterior Pituitary Gland Physiology**

The serum osmolality threshold at which arginine vasopressin (AVP) is secreted is reduced in pregnancy by approximately 5-10 mOsm/kg (dropping from 285 to 275 mOsm/kg). Consequently, pregnant women experience thirst and release AVP at lower plasma osmolarities than non-pregnant women (104, 105). These changes are thought to be related to increased levels of human chorionic gonadotrophin (105). The placenta also plays an important role in water homeostasis during pregnancy; vasopressinase, a trophoblast-derived aminopeptidase, is an enzyme produced by the placenta which inactivates endogenous vasopressin (106). Maximum concentrations of vasopressinase are reached in the third trimester, correlate with placental weight, and are higher in multi-fetal pregnancies (107). A compensatory increase in AVP synthesis and secretion is therefore observed (108).

The effect of AVP has been demonstrated to be mediated by one or more of a family of water channels called aquaporins (AQPs). Their discovery has facilitated our understanding of the modes of transport across the renal tubules and collecting ducts (109). Each member of the AQP family has a different sensitivity to AVP. Abnormalities in the AQP2 channel have been implicated in the pathophysiology of nephrogenic DI. An increase in the expression of AQP2 in the renal medulla of pregnant rats has recently been demonstrated (110).

A progressive increase in plasma oxytocin levels is observed during uncomplicated pregnancy. Levels rise dramatically during labor peaking in the second stage (111, 112). A positive feedback loop is executed, oxytocin secretion being stimulated by uterine contraction and the oxytocin then simulating further contractions (111). Uterine sensitivity to oxytocin increases with a rise in oxytocin receptors in the myometrium. Hypophysectomy does not alter onset of labor, indicating that oxytocin provides only a facilitatory role (112). Levels increase further during suckling (113).

**Diabetes Insipidus (DI)**

DI is thought to complicate up to 1 in 30,000 pregnancies and presents with polyuria, polydipsia, and dehydration (114). The presentation may involve exacerbation of previously overt or subclinical cranial or nephrogenic DI (as a consequence of increased clearance of AVP by placental cystine aminopeptidase, lower osmostat for vasopressin release and elevation of vasopressinase levels) or may develop *de novo* in pregnancy.

When investigating pregnant women for diabetes insipidus (DI) one must be aware that sodium levels may be lower than expected (115). Traditional water deprivation testing (requiring 5% weight loss) should be considered on a case-by-case basis due to the risk of hypernatremia, neurological disorders, and fetal harm (116). Providing there is close medical surveillance, a water deprivation test can be performed on women with mild symptoms. It is also reasonable to use a trial of treatment with desmopressin (DDAVP) to establish whether this can correct urinary concentrating ability.

During pregnancy, DI tends to be broadly categorized into 3 main subtypes; central DI, nephrogenic DI and transient DI of pregnancy.

CENTRAL DI

Patients with central DI fail to release AVP from their posterior pituitary. This may occur spontaneously in pregnancy or in the postpartum period secondary to Sheehan’s syndrome, an enlarging pituitary adenoma, pituitary apoplexy, lymphocytic hypophysitis, or with the development of other conditions such as Langerhans cell histiocytosis (110, 116). The most common causes of central DI are listed in Table 3. In a series of 55 cases of central DI described by Takeda et al. there were 19 tumoral lesions; 14 cases of Sheehan’s syndrome; 10 of pituitary apoplexy; and 12 of lymphocytic hypophysitis, infundibuloneurohypophysitis and stalkitis (103).

The use of chlorpropamide (a sulfonylurea) for the treatment of partial central DI is not advised as it may cross the placental barrier and cause hypoglycemia in the fetus. The AVP analogue desmopressin (DDAVP) is the first-line treatment for DI in pregnancy as it is resistant to vasopressinase (116). To date, its use has been demonstrated to be safe for both mother and fetus (104, 106, 117). For women initiated on DDAVP prior to pregnancy it can, therefore, be continued. It should be noted that some women require higher doses during pregnancy and that in such circumstance the dose should be titrated back to pre-pregnancy dose soon after delivery. DDAVP transfers minimally into breast milk and is poorly absorbed from the gastrointestinal tract, and thus should not adversely affect the infant’s water metabolism (115).

|  |  |
| --- | --- |
| **Table 3. Causes of Central Diabetes Insipidus** | |
| **Primary** | |
| Idiopathic | - |
| Genetic | Wolfram syndrome (diabetes insipidus, diabetes mellitus, optic atrophy and deafness  Neurohypophyseal diabetes insipidus |
| Developmental Syndromes | Septic-optic dysplasia |
| **Secondary/ Acquired** | |
| Trauma | Head injury  Post-surgery  Post radiotherapy |
| Vascular | Carotid aneurysm  Cavernous sinus thrombosis |
| Tumor | Craniopharyngioma  Germinoma  Metastases  Pituitary adenomas |
| Inflammatory | Sarcoidosis  Langerhans cell histiocytosis  Meningitis/ Encephalitis  Infundibuloneurohypophysitis  Guillain-Barre Syndrome  Lymphocytic hypophysitis |
| Infection | Tuberculosis  Fungal diseases |
| Post-Partum | Sheehan’s syndrome  Pituitary apoplexy |

NEPHROGENIC DI

Nephrogenic DI is caused by resistance to antidiuretic hormone and water restriction is the first line treatment (118). The risks of using medical therapy must be carefully considered. Thiazide diuretics are not routinely recommended in pregnancy due to the risk of electrolyte imbalance, jaundice, and thrombocytopenia in the neonate. There is also a risk of reducing plasma volume which may pose a challenge in situations where utero-placental insufficiency arises, for example, in pre-eclampsia (110), however, they can be used if the maternal and fetal benefits are thought to outweigh the risks. Non-steroidal anti-inflammatory drugs should not be used in the third trimester of pregnancy (110).

TRANSIENT DI OF PREGNANCY

Transient DI of pregnancy (also called gestational DI) is rare, occurring in between two to four in 100,000 pregnancies (114). It most commonly develops at the end of the second or third trimester and is caused by excessive placental vasopressinase activity. It is more common in multi-fetal pregnancies because the vasopressinase activity is proportional to placental weight. It may also occur in cases of placental abruption which can result in elevated vasopressinase levels (119, 120).

Vasopressinase is metabolized in the liver and thus higher concentrations of the enzyme are observed in women with hepatic dysfunction. Both transient liver disease (acute fatty liver of pregnancy, hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome and preeclampsia) and chronic liver diseases may result in increased circulating vasopressin. It is therefore important to check for liver dysfunction in women with a new diagnosis of DI during pregnancy (121). In a series of 50 patients described by Takeda et al of pregnancy-associated DI due to liver pathologies just over half (n=27) developed DI during pregnancy associated with pre-existing liver or coincidental diseases; 15 developed DI associated with acute fatty liver of pregnancy, and 8 with HELLP syndrome (103). DDAVP is the treatment of choice.

In patients with idiopathic or central DI, oxytocin levels are normal and labor may begin spontaneously (122). The oxytocinergic pathways, however, may be affected in DI which occurs secondary to trauma, infiltrative disease, or neoplasm, and this may result in poor progression of labor and uterine atony.

**Syndrome of Inappropriate Antidiuretic Hormone (SIADH)**

SIADH is rare in pregnancy. In a series of 18 cases of hyponatremia in pregnancy, seven fit the criteria for SIADH (123). SIADH has been reported in a small number of cases with pre-eclampsia but the mechanism remains unclear (124).

# ADRENAL DISORDERS IN PREGNANCY

The maternal hypothalamo-pituitary-adrenal axis undergoes significant changes in pregnancy. A rise in cortisol is observed partly due to estrogen-stimulated elevation corticosteroid-binding globulin, and also because the placenta releases corticotropin-releasing hormone (CRH) during the second and third trimester which stimulates both the maternal pituitary and adrenal glands (125, 126). A positive feedback mechanism is then initiated as maternal cortisol stimulates placental CRH synthesis leading to a further increase in cortisol levels (127). The diurnal secretion is maintained during pregnancy despite these changes. The fetus is protected from excess glucocorticoid exposure by the action of placental 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2) which inactivates 80-90% of cortisol into cortisone (126).

The renin-angiotensin-aldosterone system (RAAS) also undergoes changes in pregnancy. Renin levels rise early in pregnancy as a consequence of extrarenal release from the ovaries and maternal decidua (128). In addition, estrogen simulates angiotensinogen synthesis in the liver resulting in increased levels of angiotensin II (129). Angiotensin-converting enzyme (ACE) levels decline in pregnancy (130). Aldosterone levels rise up to 10-fold by term (131). Despite these changes, blood pressure is often decreased for most of pregnancy, returning to baseline by delivery. This is thought to be the result of reduced responsiveness to angiotensin II in the pregnant state (130, 132). Other theories include increased progesterone and prostacyclin concentrations during pregnancy which may decrease angiotensin II sensitivity, and the monomeric state of the angiotensin receptor (AT1) in pregnancy which renders it less active (133, 134).

**Cushing’s Syndrome During Pregnancy**

Cushing’s syndrome (CS) during pregnancy is rare, with fewer than 200 cases reported in the literature (135). However, it is associated with high maternal and fetal morbidity and so an understanding of its management is important. Fertility is generally reduced in women with CS as a result of suppression of gonadotrophin secretion (136). This is one explanation for the fact that adrenal adenomas are more commonly found to be the cause of CS in pregnancy than in non-pregnant women (40-60% vs 10-15% of cases, respectively), although a more favored theory is that adrenal adenomas associated with Cushing’s syndrome may express the LH receptor which then responds to pregnancy-induced hCG secretion. In pregnancy Cushing’s Disease (CD) accounts for 15-40% of cases in comparison to non-pregnant patients where the figure is closer to 70% (137). Adrenal carcinomas and ectopic ACTH secretion are rare causes of CS in pregnancy, accounting for less than 10% of cases (137).

INVESTIGATIONS

Clinical diagnosis is more challenging in pregnancy because some of the signs of hypercortisolism overlap with clinical signs observed in a normal pregnancy. These include central weight gain, fatigue, emotional lability, glucose intolerance, hypertension, and edema. Useful differentiating features may include muscular weakness, purple striae, and osteoporosis, i.e., the more catabolic features of Cushing’s syndrome (136).

Laboratory investigations of CS are also altered in pregnancy. Serum and urinary cortisol concentrations are frequently high in normal pregnancies and the cortisol may fail to suppress during an overnight dexamethasone suppression test (138). Urinary free cortisol can only be relied upon to distinguish between CS and normal pregnancy if it is more than three times the upper range of normal, particularly in the second and third trimesters (139, 140). In contrast to a normal pregnancy, however, the circadian rhythm is lost in CS and this can be useful when confirming a diagnosis. Changes in salivary cortisol during pregnancy are less marked and night time salivary cortisol has been proposed as a potential diagnostic tool. Trimester-specific ranges have been defined with high sensitivity and specificity (141). However, this test is not available in some locations.

Placental secretion of ACTH and CRH may prevent the expected suppression of ACTH in women with adrenal CS, adding to the diagnostic challenge (138). High-dose dexamethasone suppression tests, CRH testing, desmopressin testing, and petrosal vein sampling have not been performed in sufficient numbers during pregnancy to be able to draw firm conclusions regarding their reliability (135). CRH has been used in a small number of cases of pregnant women with no ill effects. However, in late gestation it has the potential risk of inducing premature labor as CRH has been demonstrated to enhance the contractile response of the myometrium to oxytocin in the pregnant woman, and has been implicated as a contributory factor in the process of parturition (138, 142, 143). There are a small number of cases in whom inferior petrosal sinus corticotropin sampling has been performed with CRH stimulation (138, 143). One must balance the risk of possible thrombotic events and radiation when considering such sampling.

Radiological imaging may be required following initial investigations. When an adrenal cause is suspected, ultrasound may be sufficient, particularly in cases of adrenal carcinoma (144, 145). Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) appear to be equally sensitive. However, MRI is the investigation of choice due to its superior safety profile (144). Expert bodies do not advocate the use of contrast MRI as the effects on the fetus are currently unknown. Investigation of suspected pituitary CS requires an appreciation of the normal anatomical changes of the pituitary in pregnancy (discussed at the beginning of the chapter) in order to avoid false-positive findings. Enlargement of the normal pituitary makes the assessment of microadenomas particularly difficult (145). Similar to adrenal imaging, the modality of choice is non-contrast MRI.

COMPLICATIONS

Untreated CS (in particular) may pose a risk to both mother and fetus. Maternal complications include hypertension (68%), diabetes mellitus or glucose intolerance (25%), preeclampsia (14%), osteoporosis and fractures (5%), cardiac failure (3%), psychiatric disorders (4%), wound infection (2%), and maternal death (2%) (138). Complications for the newborn include preterm delivery (43% of pregnancies), intrauterine growth restriction (21%), stillbirth (6%), spontaneous abortion or intrauterine death (5%), and hypoadrenalism (2%) (138).

TREATMENT

A review of 136 cases of CD in pregnancy demonstrated a 13% increase in the frequency of live birth rate in patients who underwent active treatment instituted prior to 20 weeks’ gestation and thus treatment is advocated during pregnancy (138). In another review the live birth rate was 15% higher and global fetal morbidity was reduced by 28% (146).

Surgical intervention (pituitary or adrenal) may be performed during pregnancy, ideally during the second trimester due to lower rates of maternal and fetal complications (138, 143, 147-149). Medical therapy is also an option. Metyrapone, a steroidogenesis inhibitor, is the most frequently reported option (136). It has been demonstrated to provide good control of the hypercortisolism, although there are reports of adrenal insufficiency, worsened systemic hypertension, and risk of preeclampsia due to deoxycorticosterone accumulation (138, 150-153). Ketoconazole, another steroidogenesis also inhibitor, while effective in controlling hypercortisolism, is avoided because of its potential teratogenicity and increased abortion rate in animal studies (152, 154-157). Cyproheptadine, a nonselective 5-hydroxytryptamine, is not recommended due to lack of efficacy (138, 158). In a review of four children exposed to mitotane, an adrenal steroidogenesis blocker, during fetal life no clear teratogenic effects were observed; however, the concentrations measured were sub-therapeutic and long-term data do not exist (159). Furthermore, the number of cases was very small. In a previous report it was demonstrated to be teratogenic and thus remains contraindicated (160). Aminoglutethimide, another adrenal steroidogenesis blocker previously in use is also contraindicated as it may cause fetal masculinization (161). There are no reported cases using Pasireotide, a somatostatin analogue, during pregnancy. There are only two reported cases of cabergoline being used for the treatment of CD in pregnancy. The first in a woman who conceived one year after the therapy was initiated and was maintained on high-dose cabergoline throughout gestation undergoing an uneventful pregnancy and delivering a heathy baby (162). The other, being treated for the management of recurrent CD during pregnancy and again a healthy infant was born, on this occasion by caesarean section at term (163).

**Adrenal Insufficiency**

Adrenal insufficiency (AI) is relatively rare in pregnancy with an estimated incidence of 1:3000 (164). In cases of primary AI, direct destruction of the adrenal gland occurs and both deficiency in glucocorticoids and mineralocorticoids is observed. In developed countries autoimmune adrenalitis is the most common cause of primary AI which may occur in isolation or as part of an autoimmune polyglandular syndrome (APS). APS type 2 constitutes the most common form and presents as a combination of Addison’s disease, thyroid autoimmune disease, type 1 diabetes, and/or premature ovarian failure (165). This association between primary AI and the other autoimmune disease goes some way towards explaining the reduced fertility rates observed in these women (166). Fertility rates are also reduced in women with AI and no coexisting autoimmune disorders. This has been attributed to lack of libido and the reduced sense of well-being associated with androgen depletion (165). In low income countries, tuberculosis is the most common cause of primary AI (167).

Secondary AI occurs is most commonly caused by prolonged exogenous suppression of the hypothalamo-pituitary-adrenal axis as a result of administration of glucocorticoids to treat pre-existing conditions such as asthma. It can also be caused by decreased stimulation of ACTH as a consequence of pituitary or hypothalamic tumors and their associated treatments, resulting in atrophy of the adrenal cortex. Pregnancy-related causes of secondary AI include Sheehan’s syndrome and lymphocytic hypophysitis. In such women decline in other pituitary hormones is frequently observed (168, 169).

Regardless of the cause of the AI, with appropriate hormonal substitution and, if necessary, artificial ovulation techniques, affected women are able to undergo pregnancy. Although considered high risk these women can still achieve favorable outcomes (164, 170).

Only a few cases of AI detected during pregnancy have been reported in the literature [40–43], and in this relatively small proportion of women with AI the diagnosis may be challenging as many of the symptoms mimic those of normal pregnancy (165). Common symptoms include weakness, light-headedness, syncope, fatigue, nausea and vomiting, hyponatremia, and increased pigmentation. One must therefore be vigilant for the possibility of a diagnosis of AI, particularly in those with excessive fatigue, weight loss, hypoglycemia, and vomiting, or in those craving salt in order to establish a timely diagnosis. Similarly, one should consider AI in those patients with persistent unexplained orthostasis or hypotension particularly following acute illness or obstetric hemorrhage. Features which may heighten clinical suspicion include hyperpigmentation on the mucous membranes, extensor surfaces, and non-exposed areas, hyponatremia, and a personal or family history of autoimmune diseases.

AI may present with an adrenal crisis during pregnancy. Scenarios where this may occur include hyperemesis gravidarum-associated AI in early pregnancy, or presentation secondary to infection at any stage of gestation (164, 171). Some women may present in the postpartum period as transplacental transfer of cortisol from the fetus to the mother can conceal AI until the postpartum period when it is unveiled (172).

COMPLICATIONS

Pregnancies in which AI is untreated may be complicated both for the mother and neonate. Intrauterine growth restriction, low birth weight, fetal distress, oligohydramnios, and intrauterine death have all been described. Most adverse pregnancy outcomes occur in women in whom the AI was either untreated or undiagnosed (172-176). The fetus receives glucocorticoids from the placenta and thus maternal AI tends not to interfere with fetal development (137). In addition, maternal adrenal antibodies, although capable of crossing the placental barrier, are not thought to be transferred in sufficient quantities to cause fetal/neonatal insufficiency (177).

INVESTIGATIONS

Interpretation of the investigations to confirm AI present a challenge during pregnancy. Laboratory findings may include hyponatremia, hypoglycemia, eosinophilia, and lymphocytosis. Hyperkalemia may not be present in pregnancy due to gestational effects on the RAAS system (described above).

Both serum cortisol and ACTH are increased during pregnancy making them unreliable markers. However, where clinical suspicion is high a low morning cortisol <5 ug/dL (181 nmol/L) in the setting of typical symptoms may be enough to confirm a diagnosis. If this finding is accompanied by a raised ACTH (>2-fold the upper limit of the reference range) a diagnosis of primary AI may be made (178). If both serum cortisol and ACTH are low the patient has secondary AI.

The gold standard investigation, and that advocated in the Endocrine Society guidelines, is the cosyntropin stimulation test, also called the short *Synacthen* test (179). Higher diagnostic cortisol cut-offs are recommended, i.e. 25 ug/dL (700 nmol/L), 29 ug/dL (800 nmol/L) and 32 ug/dL (900 nmol/L) for the first, second and third trimesters respectively (180). Some investigators have proposed the use of the 1 ug cosyntropin test as it is more physiological and may be of value in diagnosing secondary adrenal insufficiency. However, it remains controversial as to whether it improves sensitivity, and is cumbersome to use (181-183).

The overnight single-dose metyrapone test may be used to assess adrenal responsiveness but is not recommended in pregnancy as it may precipitate a crisis (167, 184). When used with 750mg every 4 hours for 6 doses in pregnancy 75% of normal pregnant subjects showed a diminished response whereas 25% had a normal response and thus the test did not appear to be valid in pregnancy (185). Cortisol and ACTH responses to CRH are blunted in normal pregnancy (159). As such, the CRH stimulation test is unhelpful in differentiating secondary and tertiary AI in pregnancy. The insulin tolerance test is not used in pregnancy due to the risk of the effect of hypoglycemia on the fetus.

Adrenal antibodies remain helpful in pregnancy and, if positive, should prompt consideration of other autoimmune endocrine deficiencies which may co-exist.

In cases where radiological imaging is required MRI without gadolinium is the recommended option (145).

MANAGEMENT

Despite the normal increase in plasma cortisol during pregnancy, an increase in maternal replacement doses of glucocorticoids is not routinely advised. Rather, with the primary aim of avoiding either under or over replacement it is currently recommended that patients are monitored clinically (at least once per trimester) and dose adjustments be made on an individualized basis if required (179). Glucocorticoid preparations that may be used in pregnancy include hydrocortisone, cortisone acetate, prednisolone, or prednisone (179). These glucocorticoids are safe and suppression of neonatal adrenal function is not reported when used for replacement (186). Hydrocortisone is recommended as the glucocorticoid substitution of choice due to its safety profile (167). Dexamethasone is not recommended because it is not inactivated by placental 11β-hydroxysteroid dehydrogenase type 2 and therefore may cross the placenta, this is of concern as this may result in neurocognitive and neurosensory disorders in childhood(98). Higher doses are required during periods of stress such as hyperemesis gravidarum or infection. Additional supplementation is also recommended during the active stage of labor and delivery. Current Endocrine Society guidelines suggest 50mg intravenous hydrocortisone during the second stage of labor and 100mg every 6-8 hours during caesarean section (93). The NICE guideline on management of medical disorders in labor recommends slightly less glucocorticoid replacement in those planning a vaginal birth (50mg 6-hourly). For those having a caesarean section, this guideline suggests individualized glucocorticoid replacement strategies that will depend upon whether the woman has received hydrocortisone in labor, i.e., 50mg intravenous hydrocortisone when starting anesthesia if she has and 100mg hydrocortisone if she has not. Hydrocortisone replacement (50mg 6-hourly) is then recommended until 6 hours after birth (94). The hydrocortisone dose can then be rapidly tapered down following delivery. Physiological doses are safe while breastfeeding as only very minimal quantities are transferred into the milk (187).

Progesterone exerts an anti-mineralocorticoid effect, and as a result mineralocorticoid requirement may increase in the third trimester. Serum sodium and potassium and evidence of orthostatic hypotension may be used to for monitoring, but plasma renin is not useful as it increases in pregnancy. If the patient develops hypertension or hypokalemia the dose of the mineralocorticoid should be reduced and if pre-eclampsia occurs it must be stopped (188).

Adrenal crisis may occur secondary to infection, hyperemesis gravidarum, or during the stress of labor. In such cases the priorities of treatment include fluid replacement and parenteral administration of glucocorticoid replacement (165). Women should be advised to wear a medic-alert bracelet, or equivalent, and to carry a “steroid card”.

Patient and partner/family education plays a key role in the management of adrenal insufficiency both in and outside of pregnancy. Education should include the basic principles of glucocorticoid replacements, sick day rules, vigilance for symptoms suggestive of glucocorticoid deficiency, and how to self-administer intra-muscular preparations when required. If diagnosed prior to pregnancy this should be included as part of the pre-conception counselling.

**Congenital Adrenal Hyperplasia**

Congenital adrenal hyperplasia (CAH) encompasses a group of inherited autosomal recessive (AR) disorders that arise from defective steroidogenesis and result from a deficiency of one or more of the enzymes required for cortisol biosynthesis (189). The most common form of CAH is 21-hydroxylase (CYP21 gene) deficiency, which accounts for 90% of cases (190). CAH due to 21-hydroxylase deficiency can be classified as either classical or non-classical CAH. In classic, severe 21-hydroxylase deficiency females are exposed to excess androgens prenatally and are born with virialized external genitalia (190). Other associations include inadequate vaginal introitus, premature adrenarche, advanced somatic development, central precocious puberty, menstrual irregularity, and possibly salt wasting. Women with the non-classical form present with pubertal and post pubertal hirsutism and menstrual irregularity.

Fertility is reduced in these women (191). In women with 21-hydroxylase deficiency a number of rationales for this exist, including the role of progesterone in regulating GnRH, the impact of elevated androgen concentrations on the GnRH/LH pulse generator and on the ovaries (suppressing later stages of follicular development and compromising ovulation) (192). Additionally, an unfavorable anatomical structure may play a role, sometimes complicated by reconstruction surgery. Psychosexual factors may also play a role with reduced sexual desire or orientation reported in some women (192, 193). However, pregnancy is possible in women with CAH (194), and may occur spontaneously once good hormonal control has been achieved with optimized glucocorticoid and mineralocorticoid regimens (189).

Fetal risk depends on the carrier status of the father and thus CYP21 genotyping should be performed (195). If the father is a carrier the female fetus is at risk of virilization in cases of classic 21-hyrdoxylase deficiency in the absence of adequate adrenal androgen suppression. In this context, some advocate the use of prenatal dexamethasone which, if used to suppress ACTH and reduce androgen excess, may block the virilization of external genitalia in female fetuses. However, this is an area of ongoing debate as in order to be effective the treatment must be implemented in early pregnancy (prior to the stage of pregnancy when clinicians were previously able to establish fetal sex) thus risking unnecessary exposure in some pregnancies (196). However, the use of newer tests to establish early prenatal diagnosis is an area which will be of great value. Current options include establishing the sex of the fetus using sex determining region Y (SRY) gene testing as early as four weeks of gestation (197). Trophoblast retrieval and isolation from the cervix has also been recently proven to non-invasively and correctly identify male fetal DNA in fetuses at risk of CAH as early as five weeks gestation (189, 198). Alternative options include measurement of cell-free fetal DNA in maternal plasma as early as six weeks, or alternatively chorionic villi sampling at 14 weeks gestation (but this would be associated with a more prolonged period of exposure to glucocorticoids) (199, 200).

In pregnancies in which the fetus is thought to be at risk of having CAH and prenatal treatment is desired to reduce androgen excess, dexamethasone is the treatment of choice. Dexamethasone, unlike hydrocortisone, is not inactivated by the placental 11-hydroxysteroid dehydrogenase type 2 and thus may cross the placenta. The aim of this treatment is to reduce virilization, the need for reconstructive surgery, and the emotional distress associated with ambiguous genitalia. However, it does not negate the need for lifelong hormonal replacement (201). The current recommended dose of dexamethasone is 20ug/kg maternal body weight (preconception weight) per day, divided into 2-3 daily doses without exceeding 1.5mg/day (199, 202). This is ideally initiated before seven weeks’ gestation and should be maintained for the entire pregnancy if there is a female fetus (189). Lower doses may, however, be used when poorly tolerated by the mother (197, 203). Maternal plasma or urinary estriol reflect adrenal synthesis and are monitored to assess efficiency. Therapy must be discontinued as soon as possible if a male or unaffected fetus is identified. Glucocorticoids will need to be increased to cover the stress of labor and delivery.

In cases where the fetus is not expected to be affected, hydrocortisone is the maternal glucocorticoid replacement of choice to avoid unnecessary transplacental passage to the fetus.

**Primary Hyperaldosteronism During Pregnancy**

The physiological changes observed in the renin angiotensin aldosterone system (RAAS) make the diagnosis of primary hyperaldosteronism (PA) in pregnancy difficult. Thus, despite hypertensive disorders affecting 6-8% of all pregnant women and PA being assumed to account for 10% of all hypertensive disorders, the number of cases reported in the literature is small (204). In a review of 32 pregnancies in women diagnosed with PA during pregnancy, 81% were diagnosed with hypertension during the pregnancy and 19% had been previously diagnosed with hypertension but not screened for PA (205). Of these cases, hypertension was controlled in 19% (two on diuretics), Hypertension was uncontrolled despite medical treatment in 32% of cases and 16% of cases required adrenalectomy during the pregnancy: 23% developed preeclampsia, 61% had induced labor, and the prevalence of caesarean section was 44% (205).

The physiological elevation of plasma aldosterone observed in healthy pregnant women is similar to the elevation observed in those with PA, and thus plasma aldosterone levels are not useful for diagnosis in pregnancy. Plasma renin, however, is usually elevated in normal pregnancy, whereas in women with PA it is often found to be suppressed during pregnancy this making an aldosterone-to-renin ratio a more useful test (204, 206, 207). Confirmatory tests such as the saline infusion test or captopril tests are not recommended during pregnancy due to the risk of volume expansion or teratogenicity respectively (204, 208). MRI is the first line imaging modality during pregnancy. Further subtyping including adrenal vein sampling is not recommended until after the pregnancy (137, 207).

The optimal management for PA in pregnancy is unclear due to the condition being rare. Medical management has historically been advocated provided that hypertension and hypokalemia can be adequately managed. However, laparoscopic adrenalectomy during the second trimester has been suggested where an adrenal adenoma can be demonstrated (204, 207, 209).

Spironolactone, a mineralocorticoid receptor antagonist (MRA), crosses the placenta, and may have anti-androgenic effects on the male fetus, particularly in the first trimester (the most sensitive period for sex differentiation) (210). Eplerenone, a selective MRA, to date, has not been demonstrated to cause teratogenic effects and is therefore favored in pregnancy (211, 212). Amiloride has also been demonstrated to be effective and safe in a small number of cases (206, 213, 214). Women with primary aldosteronism in pregnancy have higher rates of stillbirth and preterm labor than controls with uncomplicated pregnancy (214).

Glucocorticosteroid-remediable aldosteronism (GRA), is a rare hereditary form of primary hyperaldosteronism that is characterized by severe hypertension, hypokalemia, volume expansion, and suppressed plasma renin activity (215). It is a monogenic form of inherited hypertension caused by a chimeric gene originating from an unequal cross-over between the 11β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11 B2) gene (216). In a review of 35 pregnancies in 16 women with GRA there was no increased risk of preeclampsia observed: however, in women with chronic hypertension 39% experienced pregnancy-induced hypertension. In such women with pregnancy-induced hypertension the birth weight of the infants was lower than in those women without. The cesarean section rate was approximately double that seen in the general population (215).

**Pheochromocytoma and Paraganglioma in Pregnancy**Pheochromocytomas and paraganglioma, collectively known as PPGL, are catecholamine-secreting neuroendocrine tumors which are rare in pregnancy (217). Early recognition of these tumors is important as they are associated with high rates of maternal and fetal complications if undiagnosed. Untreated, the estimated maternal and fetal mortality is estimated at approximately 40-50% (218) whereas when treated maternal and fetal mortality can be reduced to less than 5% and 15%, respectively (219). In a multi-center retrospective study Bancos et al. identified 232 patients with a total of 249 pregnancies in women with PPGL; 78% had a single PPGL (pheochromocytoma in 142 and paraganglioma in 41); 13% had multiple primary PPGL and 9% had metastatic PPGL(220).

Symptoms related to episodic catecholamine excess reflect those outside of pregnancy and include paroxysmal headaches, sweating, palpitations, dyspnea, dizziness, and most commonly paroxysmal or sustained hypertension (221). In patients presenting with hypertension, a rare diagnosis such as a PPGL may be missed, as other causes of hypertension (pregnancy-induced hypertension or preeclampsia) are much more common. It is therefore important to be able to distinguish between the different causes. Pregnancy-induced hypertension characteristically presents after 20 weeks’ gestation and pre-eclampsia typically in the last trimester (218, 222). In addition, hypertension associated with pre-eclampsia tends to be consistent throughout whereas when associated with pheochromocytoma there is a tendency towards both paroxysmal and postural changes. The proteinuria and edema associated with pre-eclampsia is not in keeping with a diagnosis of PPGL (223).

In some patients, symptoms may be vague and extremely periodic, in which case initial suspicion may only arise when an enlarging uterus causes compression of the neoplasm or during the stress of labor, anesthesia, or surgery. Where a diagnosis is made during such periods of stress and where the diagnosis remains unrecognized, maternal complications such as severe hypertension, hemorrhage into the neoplasm, hemodynamic collapse, myocardial infarction, cardiac arrhythmia, heart failure, or cerebral hemorrhage may occur contributing to the high mortality rate (218, 224).

Paraganglioma are often located at the organ of Zuckerkandl, at the bifurcation of the aorta, a region where compression may occur in the context of an enlarging/contracting uterus or during fetal movement (225). In a review of the literature maternal and fetal mortality was lower in women with paragangliomas, 3.6% and 12% respectively compared to 9.8% and 16% in women with pheochromocytomas, but rates were considerably higher than the general obstetric population (226). In the study by Bancos et al. unrecognized PPGL (OR 26.0; 95% CI 3.5-3128.0), abdominal/pelvic locations (OR 11.3; 95% CI 1.5-1441.0), and catecholamine levels of ≥10 times the upper limit of normal (OR 4.7; 95% CI 1.8-13.8) were associated with adverse outcomes. For patients in which a diagnosis was made antepartum alpha-adrenergic blockage was protective in terms of adverse outcomes (OR 3.6; 95% CI 1.1-13.2).

First-line investigations include measurement of plasma or 24-hour urinary fractionated metanephrines. Levels in pregnancy are comparable to outside pregnancy and have a sensitivity of 98-99% (221, 227). False positive results may occur in the context of medications such as methyldopa, labetalol, tricyclic antidepressants, ethanol, clonidine, acetaminophen (paracetamol), and phenoxybenzamines, and in other situations that may increase adrenergic activity such as surgery, myocardial infarction, ketoacidosis, obstructive sleep apnea, stroke, and severe heart disease (228). As such, it is recommended that patients stop taking any medication that might interfere with the measurements at least two weeks prior to testing (228). Catecholamine production is not observed to rise in patients with preeclampsia; however, it may rise two-four-fold in the 24-hours following a seizure in eclamptic patients (229, 230).

Where the clinical picture and biochemical findings are suggestive of a pheochromocytoma, it is important to establish the location of the tumor. In pregnancy, ultrasound and MRI are the preferred imaging modalities, and if not definitive a multi-detector CT or nuclear scanning may be required (145).

After diagnosis, genetic counselling should be considered in the follow-up period as approximately 30% of cases are found to be related to a hereditary syndrome (231). These include multiple endocrine neoplasia type 2 (MEN2), von Hippel-Lindau syndrome, neurofibromatosis, or succinate dehydrogenase subunit gene mutations (218, 219, 232-236). Malignant pheochromocytoma has only been very rarely reported in the literature during pregnancy (237-239).

Fetal complications can occur as a consequence of the vasoconstrictive effect of the maternal catecholamines on the uteroplacental circulation which may lead to spontaneous abortion, fetal growth restriction, preterm delivery, fetal distress, and stillbirth (214, 240). Minimal placental transfer of the catecholamines is observed, and this is likely due to high placental concentrations of catechol-O-methyltransferase and monoamine oxidase (240-242).

The management of patients with pheochromocytoma and paraganglioma relies on α-adrenergic receptor blockade prior to surgical removal of the tumor. In pregnancy it is important to maintain adequate uteroplacental circulation which is entirely under the influence of maternal blood pressure. Therefore, a balance must be achieved between reducing excess catecholamines and avoiding severe hypotension (231). The most commonly used α-adrenergic receptor blockers include phenoxybenzamine, doxazosin, and prazosin. Phenoxybenzamine is favored due to its long acting, stable, non-competitive blockade and has been used in a number of pregnant women with pheochromocytoma with good outcomes (243). It does, however, cross the placental barrier and neonatal hypotension and respiratory distress have been reported in babies whose mothers were treated with phenoxybenzamine; thus, careful monitoring is required with the involvement of neonatologists at the time of delivery (244). Maternal tachycardia may occur with phenoxybenzamine, and in such cases prazosin or doxazosin may have a role as they produce less tachycardia (218). Prazosin has been used in the management of hypertension in pregnancy (245) but should be used with caution as, when compared to nifedipine for control of severe hypertension in pregnancy, a greater number of intrauterine deaths occurred in the prazosin group (246). Doxazosin has also been used with good outcomes (247).

administered following α-blockade. Beta-blockers have been associated with fetal bradycardia and intrauterine growth restriction when used in high doses, but clearly the advantages in women with pheochromocytoma should be weighed against the relatively uncommon fetal risks (248, 249). Labetalol is a combined alpha and beta blocker but is not recommended as the α-blockade is relatively weak, and thus paroxysmal hypertension may occur. Methyldopa is also not recommended as it has been suggested that it might worsen hypertension (231). In case of a hypertensive emergency, phentolamine is advised due to its prompt onset of action. Beta-adrenoceptor blockers may be added if tachyarrhythmia occurs but must only be

Drugs that should be avoided in women with pheochromocytoma include corticosteroids, opioids, pethidine, metoclopramide and certain anesthetic drugs such as thiopental, ketamine, ephedrine and mivacurium, as they may induce crisis by promoting the release of catecholamines (231).

Adequate α-adrenergic blockade +/- the addition of beta-blockade is the first priority in managing women with pheochromocytoma, but surgery is the definitive treatment. The optimal timing of surgery remains a topic of debate and depends on gestational age, the success of medical management, and the location of the tumor. In patients in whom the diagnosis is made within the first 24 weeks and adequate α-adrenergic blockade has been achieved, the current recommendation is that the tumor be removed in the second trimester. In patients with pheochromocytoma identified in the third trimester and/or in whom medical management is adequate it is often advised to delay surgery until following delivery (218, 250). Where possible, a laparoscopic approach in now preferred (231, 235).

Historically, a vaginal delivery was avoided in women with pheochromocytoma due to concerns about a catecholamine surge during labor and delivery. However, this theoretical risk should be mitigated with adequate α-adrenergic blockade. Several vaginal deliveries with good outcomes have now been reported in the literature, with careful consideration of medical management during the labor and good analgesia with avoidance of medications which may trigger a crisis (218, 251-253). Ideally an individualized, patient-centered, and multidisciplinary approach is required to decide the best mode of delivery for the individual patient.

**SUMMARY**

In summary, the management of both pituitary and adrenal diseases in pregnancy relies on a good understanding of the physiological changes during gestation. Increasing evidence is becoming available regarding the drugs that are available for management of these conditions, giving more confidence to those managing affected pregnant women and providing additional information to share with patients. As with other medical problems encountered in pregnancy, it is important to provide women with evidence-based pre-conception counselling to enable informed shared decision making. Multidisciplinary team and individualized care are essential to ensure prompt diagnosis and effective management of potentially high-risk pituitary and adrenal disease in pregnancy to ensure the best outcomes for both mother and child.

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