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Endocrine Disorders in Pregnancy Guideline

December 2018

FINAL
V1.0

Document Control

Ownership

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Version control

New	Development commenced by Greater Manchester and Eastern Cheshire Maternal Medicine Group	5/6/18
V0.1	Draft version circulated to Clinical Leads and Heads of Midwifery across GM&EC	5/6/18
V0.2	Comments considered and amendments made by AV. Updated version shared with Clinical Leads and Heads of Midwifery across GM&EC	18/9/18
V0.3	Version updated by AV, formatted in readiness for ratification by GM&EC Maternity Steering Group	26/9/18

Ratification process	Ratified by: Greater Manchester and Eastern Cheshire Maternity Steering Group
Date of Ratification:	14/12/2018
Circulation	17/12/2018
Review	Review Date: 14/12/2020 Responsibility of: GMEC SCN

Acknowledgements

On behalf of the Greater Manchester and Eastern Cheshire and Strategic Clinical Networks, I would like to take this opportunity to thank the contributors for their enthusiasm, motivation and dedication in the development of this **Endocrine Disorders in Pregnancy Guideline and Care Pathway.**

I would also like to acknowledge and thank the members of the Maternal Medicine Group for their passion for the subject and their commitment throughout its development.

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1. Summary of Endocrine disorders in Pregnancy

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Endocrine disease is common in pregnancy. Most pre-existing endocrine conditions, if well controlled, have little impact on maternal or fetal morbidity.

Trans-placental transfer of maternal antibodies can have adverse fetal or neonatal consequences. The initial diagnosis of many conditions is hindered by the overlap of symptoms that occur in normal pregnancy and those that suggest specific endocrine pathologies, and also by the changes in reference ranges for common biochemical measurements that occur as a result of physiological changes in pregnancy.

This guideline summarises the key points from the **Greater Manchester and Eastern/North Cheshire Maternal Medicine Network guideline** which has been developed to promote seamless, multidisciplinary care for women with endocrine disease in pregnancy.

2. Joint obstetric diabetes/endocrine clinic

Services can be contacted as below:

Hospital	Obstetrician	Physician	Frequency
Royal Albert Edward Infirmary, Wigan	Amit Verma/Papa Essilfie (diabetes & endocrine) amit.verma@wwl.nhs.uk papa.essilfie@wwl.nhs.uk	Ian O'Connell / Mohit Kumar	Weekly Mondays & Wednesday am
Stepping Hill Hospital, Stockport	L Tomlinson (diabetes) Lucy.Tomlinson@stockport.nhs.uk Specialist midwife Jane O'Brien (diabetes)	Dr Bell Dr Bell	Tuesday am Friday am
St Mary's Oxford Road, Manchester	Jenny Myers, Melissa Whitworth, Kim MacLeod (Diabetes) Kim MacLeod (Diabetes) Kim.macleod@mft.nhs.uk Sorin Juverdeanu (Endocrine)	Dr Rao-Balakrishna Dr Stevens Dr Stevens	Weekly Tues pm Weekly Friday am Weekly Friday am
Royal Bolton NHS Trust	Dr Neeraja Singh (Diabetes & Endocrine) Neeraja.Singh@boltonft.nhs.uk Mr Andrew Muotune (Gestational Diabetes) Andrew.Muotune@boltonft.nhs.uk	Dr Moulinath Banerjee	Weekly Tuesday pm Monday am
St Marys Wythenshawe,	Dr A Pilkington; Dr A Anbazhagan (diabetes & endocrine)	Dr Issa; Dr Cheer	Weekly Thursday

Hospital	Obstetrician	Physician	Frequency
	Andrea.Pilkington1@mft.nhs.uk akila.anbazhagan@mft.nhs.uk		
Royal Oldham Hospital	Mr Aziz, Stephy Mathen, Annabel Dieh (diabetes & endocrine) stephy.mathen@pat.nhs.uk	Dr Shiraz, Dr Prakash	Weekly Thursday am Thursday pm Friday am
Warrington	Mustafa Sadiq &Rita Arya (diabetes & endocrine) Mustafa.Sadiq@whh.nhs.uk	Paula Chattington	Weekly Wednesday
North Manchester General Hospital	Caroline Rice (diabetes and endocrine) Caroline.Rice@pat.nhs.uk	Dr Malek	Weekly Thursday
Tameside General hospital	Roopa Krishnamurthy / Purnima Gondane-Sweetman (diabetes & endocrine) Roopa.Krishnamurthy@tgh.nhs.uk	Dr Edward Jude	Weekly Wednesday am
Macclesfield General Hospital	Mandira Hazra (diabetes) mandira.hazra@nhs.net	Dr Basil Issa Dr Devaraj	Weekly Wednesday pm Alternate Wednesday pm (joint clinic with Dr Issa)
Fairfield hospital	Chitra Jain (diabetes & endocrine) chitra.jain@pat.nhs.uk	Helen Smithrust helen.smithrust@pat.nhs.uk	Alternate Tuesday pm
Rochdale Infirmary	Dr Dutta/Dr Mitchel (diabetes and endocrine) Debarati.Dutta@pat.nhs.uk	Dr Prakash	Weekly Friday am

3. Pre-conception

All women of reproductive age with endocrine disease should have access to preconception specialist counselling to empower them to make choices about pregnancy. They should be given advice about contraception and how to access services rapidly when they become pregnant.

In certain conditions such as Congenital adrenal hyperplasia where the fetus is at the risk of virilisation patients should be referred to preconception clinic for counselling and management plan as this may need to be commenced in the preconception period.

4. Termination of pregnancy

Very rarely indicated for endocrine disease but rapid access to termination of pregnancy services should be facilitated, if for whatever reason a woman chooses this. For those terminating due to a high risk endocrinopathy ie. Pheochromocytoma this will need tertiary input and if surgical need to carried out in an experienced centre.

5. Antenatal Care

Many of the endocrine patients mentioned here will already be under the care of a specialist endocrine unit. They should be involved at the earliest stage and personalised care plan should be formulated in close liaison with them even if the management is at local level.

All patients should be seen in the local consultant antenatal clinic ideally a joint obstetric and endocrine clinic. An antenatal plan of care should be made in conjunction with the patient's endocrine team if any.

Following multidisciplinary assessment and risk stratification, appropriate care can be arranged at a district general hospital or tertiary unit according to the complexity of the endocrine disease

- Low risk – care and delivery in local hospital, with escalation if clinical deterioration
- Moderate risk – Liaise with patient's endocrinologist /refer to local joint obstetric endocrine clinic for assessment, but care may be shared with tertiary hospital (St. Mary's)
- High risk – Liaise with patient's endocrinologist / refer to joint obstetric endocrine clinic at St. Mary's hospital (tertiary unit) for further management

Grading:

Low Risk lesions	
No detectable increased risk of maternal mortality and no/mild increase in morbidity. Care and delivery in local hospital, with escalation if clinical deterioration	Pituitary micro adenomas eg Micro-prolactinoma Pituitary insufficiency/lymphocytic-hypophysitis Hypothyroidism Adrenal insufficiency eg. Addison's disease Benign adrenal adenomas /non-functioning tumours

Moderate Risk lesions	
Small increased risk of maternal mortality or moderate increase in morbidity. Refer to local joint obstetric endocrine clinic for assessment, but care may be shared with tertiary hospital	Pituitary macro adenomas eg Macro-prolactinoma Diabetes Insipidus Acromegaly Gestational hyperthyroidism/Grave's thyrotoxicosis Grave's thyrotoxicosis even if euthyroid (if thyroid receptor antibody +ve) Multiple Endocrine Neoplasia (MEN1+2) Hyperparathyroidism/Hypoparathyroidism Adrenal disease Cushing's syndrome Conn's syndrome Congenital adrenal hyperplasia
High Risk lesions	
Extremely high risk of maternal mortality or severe morbidity; pregnancy contraindicated. If pregnancy occurs termination should be discussed. If pregnancy continues refer to joint obstetric endocrine clinic at St. Mary's hospital for further management	Pheochromocytoma

All pregnant women with endocrine disease requiring treatment or care by other specialists should have an integrated care plan developed and agreed between all specialities involved.

6. Low Risk lesions

6.1 Pituitary disease

6.1.1 Micro Prolactinomas

Prolactinoma is a common cause of infertility in young women and treatment with dopamine agonists (DA) allows restoration of fertility in over 90% of the cases.

Both bromocriptine and cabergoline have shown a good safety profile when administered during early pregnancy. In particular, data on exposure of the fetus or embryo to cabergoline during the first weeks of pregnancy have now been reported in more than 900 cases, and indicate that cabergoline is safe in this context.

There is no increase in the frequency of spontaneous miscarriage, premature delivery, multiple births or neonatal malformations, and follow-up studies of the children for up to 12 years after fetal exposure to cabergoline did not show any physical or developmental abnormalities.

These women should therefore continue DA treatment until pregnancy has been confirmed. Treatment discontinuation is recommended at that time in women with microprolactinomas and should be considered for macroprolactinoma with no evidence of compression of optic chiasm but this should be decided on a case by case basis.

Microprolactionomas (<10mm) rarely expand to encroach on optic chiasma. For microprolactinomas, the risk of symptomatic tumour enlargement during pregnancy is very low (2-3%).

Measurements of prolactin levels should not be done in pregnancy. They are of no value in the diagnosis or management of a prolactinoma as prolactin levels increase in pregnancy.

Triggers for escalation: Pituitary scans are only required in pregnancy if the patient notices a reduction in their lateral visual field. Management is based on symptoms and if there is evidence of tumour enlargement dopaminergic agonists can be used to treat.

There is usually no contra-indication to breast feeding, if they are still on a dopamine agonist specialist advice should be sought as this will inhibit lactation.

6.1.2 Pituitary insufficiency

Pituitary insufficiency can result from previous pituitary surgery or radiotherapy, lesions such as adenomas, infarction or lymphocytic hypophysitis. It can lead to subfertility as the gonadotrophin stimulus to ovulation might be absent, and hence ovulation-induction therapies might be required.

It should be confirmed that adequate hormonal replacement has been achieved prior to pregnancy, if it has; this condition has no effect on maternal or fetal outcome. If the condition is not diagnosed or is inadequately treated, it can be associated with miscarriage, stillbirth and maternal morbidity.

Lymphocytic hypophysitis is rare, annual incidence is estimated to be 1 in 7–9 million but if occurring during pregnancy occurs at increased frequency in late pregnancy and postpartum.

If the patient is cortisol deficient **(please see the section on Addison's disease)**. Current guidance suggesting increase of hydrocortisone therapy in final trimester, in line with increase in adrenal steroid output (25%).

If requiring thyroxine replacement do not rely on TSH levels but adjust medication to keep patient's free thyroxine (FT4) in top 50% of normal non-pregnant range.

6.1.3 Hypothyroidism

Hypothyroidism is present in up to 1% of pregnant women, with the majority having been identified and treated before conception. Many of the common clinical features of hypothyroidism occur in normal pregnancy, including lethargy, weight gain and constipation. More specific features include cold intolerance, bradycardia and delayed relaxation of tendon reflexes.

Diagnosis is based on raised thyroid-stimulating hormone (TSH) and low free thyroxine (FT4) concentrations with gestation adjusted normal ranges.

It is not uncommon for women to require an increase in levothyroxine dose during pregnancy, which may reflect previous inadequate pre-conception treatment plus an increased requirement due to the pregnancy.

Ideally pre-conception thyroxine dose should be adjusted to achieve a TSH levels 0.2 to < 2.5miu/l.

Untreated hypothyroidism is associated with increased rates of miscarriage, anaemia and preeclampsia and with infants of low birth weight and possible long-term cognitive impairment but this has been disputed from a recent cohort study (Pakkila et al).

When pregnant it is recommended that TFTS are checked at booking and then every 4 weeks up to week 12 of the pregnancy and then at weeks 16 and 28 adjusting the thyroxine dose to keep the TSH between the levels outlined above. If your laboratory is able to offer a trimester adjusted normal range refer to that when reviewing results.

A repeat level at 6 weeks post-partum to allow for any readjustment in medication after the pregnancy.

Subclinical hypothyroidism (TSH concentration >97.5th centile and normal T4) can be seen in 5% of the population and there is some evidence that this is associated with increased rates of preterm delivery and placental abruption.

Levothyroxine (LT4) is safe and appropriate for use in pregnancy and can be started in patients diagnosed with subclinical hypothyroidism preconception and in pregnancy aiming to achieve TSH levels 0.2 to <2.5 mIU/l. American thyroid Association Guidelines 2017 recommend measurement of TPO antibodies in women with subclinical hypothyroidism to help inform decisions regarding starting T4, particularly if the TSH is very slightly raised above trimester specific range.

It is advisable to change the treatment for women on other forms of thyroid replacement, such as liothyronine (T3) or animal thyroid products to LT4 as T3 does not cross the placenta. This is important as the fetus is dependent on maternal thyroid hormone until approximately 12 weeks of gestation.

Levothyroxine is excreted into breast milk, but not at levels sufficient to affect neonatal thyroid function and so breastfeeding can be undertaken as normal.

6.1.4 Adrenal insufficiency

First diagnosis of adrenal insufficiency in pregnancy is challenging as many of the clinical features of hypo-adrenalism occur in pregnancy, such as nausea, vomiting, weakness and hyponatraemia. Nevertheless, weight loss, hyperpigmentation in skin folds, hyponatraemia of greater magnitude than that expected in pregnancy (>5 mmol/l reduction) or hypoglycaemia are not features of normal pregnancy and should be investigated further. Collapse episodes with a finding of postural hypotension would also be an indication to investigate cortisol reserves. A referral to an endocrinologist should be done in such cases.

In patients with known adrenal insufficiency due to **Addison's disease** or **anterior pituitary failure**, glucocorticoid and mineralocorticoid replacement can be continued in pregnancy. Current guidance suggests an increase of hydrocortisone therapy in final trimester, in line with increase in adrenal steroid output (25%). Stress dose of steroids are vital at the onset of labour and for the next 48 hours after delivery, or if patient needs a caesarean section, to reduce the risk of an Addisonian crisis. (Usually 50-100 mg hydrocortisone IV 6 hourly until eating and drinking again).

The usual sick day rules apply for patients who are experiencing stress such as vomiting, concurrent infection or significant psychological distress, who require an increased glucocorticoid dose. The usual advice is to double their normal dose until recovered. If they vomit within 30 minutes of ingesting their steroids they should try within the hour to retake double that dose. If they are still being sick they require either intramuscular or intravenous steroids and possibly iv fluids**. Sick day rules should be re-iterated to the woman and their partner with written information provided as they are very important.**

Management should be outlined clearly by the joint clinic before delivery. Referral to the anaesthetist should be considered. Breast feeding is not contra indicated.

6.1.5 Benign Adrenal adenomas/ Non-functioning tumours:

When adrenal adenoma /pituitary tumour has been assessed and designated benign this should not usually cause any risk of harm to mother or baby. An individualised management plan should be made by the obstetrician and endocrinologist looking after the patient as sometimes due to their size or compression they can cause symptoms or other issues.

7. Moderate risk lesions

7.1 Pituitary Macro adenomas

Pituitary macroprolactinoma (>10mm):

The risk of tumour expansion is higher for macroprolactinomas (about 20-30%) and careful follow-up is advised. If a symptomatic tumour enlargement does occur, re-initiation of the dopamine agonist is indicated rather than surgery. Breast-feeding has no harmful effect on tumour growth and DA treatment, if still needed, may be postponed as long as breast-feeding is desired.

Dopamine receptor agonists can be continued in patients who have macroprolactinomas and who are at risk of symptomatic tumour expansion.

Threshold for escalation: Formal ophthalmology based visual field testing should be performed in each trimester. If patient reports visual field changes particularly in the temporal area, pituitary imaging including MRI without contrast injection should be performed. This may need discussion in Pituitary MDT.

If there is confirmed evidence of tumour enlargement, dopamine agonists can be restarted and continued by lactating mothers with no detrimental effect on the neonate, but they can interfere with breastfeeding

A referral to the anaesthetist should be done to evaluate the option of regional analgesia and anaesthesia for delivery.

7.2 Diabetes insipidus (DI)

Diabetes insipidus can complicate up to 1 in 30,000 pregnancies. Diabetes insipidus during pregnancy has a variety of causes, some that predate the pregnancy and others that begin during gestation. Polyuria and polydipsia can occur or be exacerbated in women with overt or subclinical central or nephrogenic diabetes insipidus

The symptoms of DI can worsen in pregnancy as a result of placental vasopressinase production and an associated reduction in antidiuretic hormone (ADH) levels.

Transient DI can occur in pregnancy secondary to placental vasopressinase production and will usually resolve by 6 weeks post-partum. Pregnancy induced DI can be a feature of significant hepatic pathology, such as acute fatty liver of pregnancy. In this condition, the hepatic breakdown of placental vasopressinase is reduced. It is therefore important to exclude liver disease as well as other pituitary disorders that can precipitate DI in pregnancy.

ADH analogues such as desmopressin (DDAVP) can be continued and no adverse effects on the fetus have been reported, but a higher-than-normal dose might be required by pregnant women.

A clear individualised care plan should be there for antenatal and postnatal care by the professionals looking after these patients.

Management of central diabetes insipidus can be achieved with desmopressin. Nephrogenic diabetes insipidus is typically resistant to both DDAVP and vasopressin and underlying causes should be addressed.

As DI is a disorder of the posterior pituitary, it can be associated with reduced oxytocin production. This can have important consequences at delivery, as labour may not progress and there is an increased rate of uterine atony.

7.3 Acromegaly

Pregnancy in patients with acromegaly (a pituitary adenoma with over secretion of growth hormone) is uncommon because the majority undergo surgery soon after diagnosis; they typically have problems conceiving as a result of hyperprolactinaemia from pituitary stalk compression.

Most diagnostic assays cannot distinguish between pituitary and placental growth hormone, so confirmation of a diagnosis of acromegaly might have to wait until after delivery, when levels of placental growth hormone fall rapidly.

Insulin-like growth factor is also present in greater concentrations in normal pregnancy. Acromegaly can increase the risk of gestational diabetes and pregnancy-induced hypertension. The associated cardiac conditions, including coronary artery disease and cardiomyopathy, can manifest for the first time in pregnancy.

Women taking long-acting Somatostatin analogues when not pregnant need to use a short-acting analogue before planning a pregnancy and all the drugs need to be stopped upon confirmation of pregnancy.

Three classes of drugs (somatostatin analogs, dopamine agonists and growth hormone receptor ligands) have been used in acromegaly. Although dopamine agonists, SST analogs and GH receptor ligands cross the placenta, no major adverse effects have been reported in mother and fetus.

Patients with acromegaly need to be carefully followed during pregnancy. Only a small number of women with acromegaly have been reported to have had this condition worsen in pregnancy, but there have been a few reports of tumour growth and one case of pituitary apoplexy. An individualized management plan should be made by the wider joint MDT (multi-disciplinary team).

The advice given for macroprolactinomas relating to tumour sizing and monitoring should also be followed for pregnant women with acromegaly. If the tumor has increased in size, dopamine agonists such as bromocriptine or cabergoline can be instituted. Use of drugs during pregnancy is only limited to controlling an expanding mass and headache [Katznelson *et al*. 2014]. If there is no relief, trans-sephenoidal surgery can be performed during the second trimester.

Women with tumor expansion during pregnancy should be advised against breast feeding.

7.4 Hyperthyroidism

Gestational hyperthyroidism (GTT): Gestational transient thyrotoxicosis is a transient, mild hyperthyroidism that occurs early in pregnancy and is due to human chorionic gonadotropin. There is no clear information about why only some pregnant women develop this condition though.

The signs and symptoms of thyrotoxicosis in pregnancy are the same as those in non-pregnant patients and can include anxiety, tremor, heat intolerance, palpitations, weight loss or lack of weight gain, goiter, tachycardia, and hyperreflexia.

There is some evidence that Vitamin D deficiency plays a role. It doesn't need any treatment but just needs monitoring of thyroid function tests as it usually comes back to normal when vomiting settles.

Hyperthyroidism complicates approximately 1 in 500 pregnancies. Pre-existing disease can lead to infertility if inadequately treated. If appropriate treatment is started with normalisation of thyroid function, then the occurrence of miscarriage, preterm labour and fetal growth restriction that are associated with uncontrolled disease are reduced. Patients should be advised to try and delay a pregnancy until their thyrotoxicosis is stabilised and the dosage of anti-thyroid drugs minimised.

Thyroid surgery is an option pre-conception and very occasionally in the second trimester. Radio-iodine should be avoided in the 6 months pre-conception and during pregnancy or breast feeding due to the risk of inducing fetal hypothyroidism.

Autoimmune thyrotoxicosis often improves during pregnancy because of the occurrence of a degree of immunosuppression, but after delivery there is a risk of a flare.

Patients should be managed in conjunction with an endocrinologist. Anti-thyroid drugs such as Propylthiouracil (PTU) and carbimazole can be used in pregnancy. Both cross the placenta, but PTU to a lesser extent, both have some degree of teratogenicity which seems to be dose related.

Carbimazole is associated with fetal teratogenicity in 2-4% cases of exposure in weeks 6-12: aplasia cutis, choanal/oesophageal atresia and carbimazole/methimazole embryopathy (abnormal facies, developmental delay, VSD).

PTU is associated with developmental problems in about 2-3% where there is early exposure: renal tract abnormalities, malformations in the head and neck regions (peri-auricular and branchial sinuses/cysts) and problems with cilary dysfunction (situs invertus)

PTU is usually the medication of choice for hyperthyroidism diagnosed pre-conception or in the first trimester. If a woman has been able to control her hyperthyroidism with low dose carbimazole prior to pregnancy, however, she could remain on this drug so as to maintain good control. PTU can cause idiosyncratic hepatic reactions including fulminant hepatitis and liver failure requiring monitoring of liver function. For this reason, carbimazole is often preferred in the second and third trimesters.

Anti-thyroid medication crosses the placenta and there is a risk of fetal hypothyroidism when treating the mother's thyrotoxicosis. Therefore, it is recommended that the mother is treated with the lowest dose of anti-thyroid medication aiming for a T4 levels at or just above the reference range and a TSH 0.1-0.3.

Never use block and replace regimes in pregnancy. The anti-thyroid medication will cross the placenta but very small amount of thyroxine will cross thus rendering the fetus hypothyroid.

Both PTU and carbimazole can be used by breastfeeding mothers, but carbimazole at high doses (over 20 mg) can result in neonatal thyroid dysfunction and therefore neonatal monitoring is required. Less PTU is excreted in breast milk.

Fetal thyrotoxicosis:

TSH receptor antibodies (TRAB) can cross the placenta and cause transient fetal and neonatal thyrotoxicosis in about 2.6% of cases even in euthyroid or hypothyroid mothers who have been treated by partial thyroidectomy or radio iodine in the past**.**

TRAB should be measured at the beginning of pregnancy and at the end of 2nd trimester (20-22 weeks). A level of 2-3 times the normal suggests risk of fetal hyperthyroidism.
There should be an individualised plan by the obstetrician and endocrinologist if raised titres are present. Weekly monitoring of fetal heart rate to identify tachycardia from 20 weeks gestation should be arranged. Serial growth scans in third trimester are recommended to identify hydrops, fetal goitre and growth restriction

Once fetal thyrotoxicosis is identified, treatment can be started with ant thyroid drugs such as propylthiouracil 50-200mg daily and dose adjusted to titrate against fetal heart rate. The mother will need levothyroxine cover to stop her becoming hypothyroid; this requires close working between the endocrine and the obstetric teams. Untreated fetal hyperthyroidism as a result of trans placental passage of antibodies is associated with a mortality rate of up to 15%.

Cord and neonatal blood should be taken for assessment of thyroid function. It is important to screen the neonate for neonatal thyrotoxicosis. This typically presents soon after delivery and most commonly occurs in the babies of women taking PTU or carbimazole. The infant will continue to have maternal TRAB for approximately three months but will no longer receive the drugs used to control hyperthyroidism via placental transfer.

Normal thyroid levels in pregnancy are not clearly defined and depend on gestation and assay used for the analysis. A summary of suggested ranges produced for TSH levels if the free T4 is normal if your laboratory do not issue a gestation specific normal range.

1st Trimester	0.1 to 2.5 mU/L
2nd Trimester	0.2 to 3.0 mU/L
3rd Trimester	0.3 to 3.0-3.5 mU/L

7.5 Multiple Endocrine Neoplasia (MEN1 and MEN2)

In this condition there is a mutation of the MEN tumour suppressor gene. Affected patients will normally be under a regional MEN clinic or specialist endocrinologist; it is important that they are involved in formulating a care plan. They will usually have received genetic counselling to help assess the risk of carrying an affected fetus (usually 50%) and the variable penetration of this condition. Management plan should be made as advised by the specialist unit.

7.6 Hyperparathyroidism/ hypoparathyroidism

Primary hyperparathyroidism occurs in approximately eight women of child-bearing age in every 100,000. Hypertension or pre-eclampsia occur in up to 25% of affected pregnancies.

Pregnancy can be complicated by maternal morbidity and mortality resulting from pancreatitis, hypercalcaemic crises, confusion or renal stones. There is a significant associated fetal morbidity with mortality rates of up to 40% when the maternal hypercalcaemia is severe (>3.5 mmol/l). The limited evidence available suggests there is little or no mortality/morbidity if Ca <2.85 mmol/l.

There is also an increased risk of miscarriage, intrauterine growth restriction, stillbirth, neonatal tetany and neonatal death.

Hyperparathyroidism is diagnosed by identifying a high plasma-calcium concentration with a corresponding high or inappropriately normal parathyroid hormone concentration and normal/high urinary calcium.

Isotope studies are contraindicated in pregnancy, but ultrasound can be used to identify parathyroid adenomas. Unless surgery is planned no localisation procedures should be undertaken during pregnancy
An observational study reporting on 109 women with PHPT during pregnancy found that parathyroidectomy reduced fetal complications. Some authors favour surgery early in the second trimester of pregnancy if calcium levels reach 2.85 mmol/L to prevent late fetal loss.

The second trimester is the ideal time for surgery but uneventful surgeries in the third trimester have been reported as well.

Hypoparathyroidism:

Hypoparathyroidism in pregnancy is rare, most commonly a complication of thyroid surgery. Patients are treated with the active form of Vitamin D Calcitriol or Alfacalcidol which is metabolised to the active Vitamin D. There is more literature on the use of Calcitriol in pregnancy.

Due to increased calcium demand during pregnancy to mineralize the fetal skeleton and during lactation to ensure adequate calcium in breast milk a variety of physiological adaptations take place, including the production of PTHrP, which makes the management of hypoparathyroidism challenging and unpredictable.

Undertreatment of hypoparathyroidism leads to hypocalcaemia which can be asymptomatic or it can present with a wide range of symptoms including cramps,

tetany, seizures and congestive heart failure. Obstetric complications are abortion, preterm labour and dysfunctional labour. Fetal and neonatal mineralization abnormality, intrauterine fractures, intracranial bleed and neo-natal hyperparathyroidism have been noted with insufficient supplementation.

Over-treatment will cause maternal hypercalcemia and may cause suppression of fetal/neonatal parathyroid glands leading to neonatal hypocalcaemia and the risk of seizures.

There are additional concerns of teratogenicity of the medications needed so minimal doses to maintain low normal to mid-range corrected calcium levels should be used.

These women require careful clinical observation and laboratory monitoring. There should be joint care with their specialist endocrine team to closely monitor calcium levels and dosing of medication. Treatment requirements can be variable in the second half of pregnancy and will invariably decrease during lactation.

There are no guidelines available but a sensible approach would be to monitor calcium levels every 3-4 weeks during pregnancy, at delivery, 1 week post-partum and every 4-6 weeks while breast feeding to allow safe adjustment of medication. Neonatal calcium levels should be checked during first few weeks of life.

Acute hypocalcaemic crisis has to be anticipated, and multidisciplinary and timely management must be instituted, for successful maternal and fetal outcomes.

7.7 Cushings syndrome

Presentation of Cushing's syndrome in pregnancy is very rare.

Cushing's syndrome refers to the condition caused by excess glucocorticoid production, regardless of the cause. When Cushing's syndrome is caused by a pituitary tumour, it is called Cushing's disease. In pregnancy, most cases of Cushing's syndrome (50%) result from adrenal adenomas (with a small number from adrenal carcinomas) rather than from pituitary adenomas. If suspected urgently liaise with the patient's endocrinologist and tertiary centre.

Previously treated Cushing's syndrome with complete resolution does not alter the course of pregnancy.

The clinical features of excess cortisol, for example weight gain, fatigue, glucose intolerance and hypertension, overlap with those of pregnancy. More specific features that suggest hypercortisolaemia are red or purple striae (compared to pale striae in pregnancy), proximal myopathy, fractures related to underlying thinning of the bone (osteopenia or osteoporosis), and features of high male hormone levels (hyper-androgenism) hirsutism/acne.

Greater incidences of hypertension (68%), pre-eclampsia (9%), preterm delivery (43%) and still birth (6%) are associated with active Cushing's syndrome.
Neonatal adrenal insufficiency can occur because fetal cortisol production is suppressed *in utero* by the high circulating levels of maternal cortisol in women who have Cushing's syndrome, there is an improved live birth rate for those whose treatment was initiated before 20 weeks' gestation.

Treatment in pregnancy is therefore advocated for pregnant women who are diagnosed as having Cushing's syndrome. Management includes identifying the source of hormone production and instituting proper therapy. MRI is warranted especially because of the risk of adrenal carcinoma. Surgery is the mainstay of treatment in 1st and 2nd trimester though it can be delayed in third trimester and delivery expedited.

7.8 Conn's syndrome

Primary hyperaldosteronism is rarely reported in pregnancy. This probably reflects under-diagnosis given the incidence of this condition in the non-pregnant population. The diagnosis is suggested in a patient with hypertension, hypokalaemia and metabolic alkalosis. Adrenal adenoma is the most common aetiology present nearly in 75% of cases

If suspected urgently refer to the endocrinologists. Elevated aldosterone with suppressed renin levels support the diagnosis of primary hyperaldosteronism. Imaging of the adrenals can be performed, but if this does not identify an adenoma and/or biochemical testing is equivocal, further investigation can be postponed until after delivery.

It is associated with high rates of preeclampsia with a corresponding increase in placental abruption and preterm delivery.

Mainstay of management is controlling hypertension with anti-hypertensives and spironolactone. The use of spironolactone is cautioned in pregnancy because of its potent anti-androgen effects, which may affect the masculinisation of a male fetus. Its use could however be considered after a fetus has been confirmed to be female. Amiloride is an alternative potassium-sparing agent that can be used. Laparoscopic adrenalectomy has been used to treat primary hyperaldosteronism in pregnancy.

7.9 Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) is caused by a group of disorders featuring enzymatic defects in adrenal steroid synthesis, the most common types being 21-hydroxylase deficiency (90%) and 11-hydroxylase deficiency. (8-9%). Classical congenital adrenal hyperplasia is rare 1 in 14,000 and is autosomal recessive. If the couple have one affected child the risk of subsequent child having the disorder is 1 in 4.

The "salt wasting" form of CAH is due to 21 hydroxylase deficiency. There is reduced cortisol and aldosterone production and increased androgen synthesis. These individuals have both glucocorticoid and mineralocorticoid deficiency.

Women with CAH are at increased risk of miscarriage, pregnancy- induced hypertension, gestational diabetes mellitus and intra uterine growth restriction

Management includes glucocorticoid and mineralocorticoid replacement, sick day rules for intercurrent stress such as infection and increased steroids to cover delivery. Increased surveillance for pre-eclampsia is advised. Delivery can be complicated by cephalopelvic disproportion, which can result from the android pelvis and can be affected by previous genital surgery.

When the fetus is at risk of CAH, the couple should be referred for preconceptual counselling and management plan:

If the couple have one affected child or if the partner of an affected woman is a carrier for the same mutation.

One option is termination of pregnancy if the investigations suggest an affected female fetus.

Alternatively high dose dexamethasone (1-1.5mg/day) can be given which will cross over the placenta, suppress fetal adrenal production and prevent masculinisation of a female fetus. Treatment should be started preconception or <5 weeks to optimise the chances of normalisation before differentiation of the genitalia. Genetic diagnosis via chorionic villi biopsy is possible around 10-11 weeks but should only be performed if the couple have a previously affected child and each of their genetic mutation is known. Only one in 8 fetuses (1 in 4 chance of being homozygous and 1 in 2 chance of being female) may benefit from high dose steroids and 7 out of 8 will be treated unnecessarily for about 6 weeks.

Care of such woman should be in close conjunction with the neonatal team. All female neonates should receive corticosteroids both to treat CAH and also because the neonatal adrenals will be suppressed following long-term dexamethasone treatment of mother.

If it is thought that if the female fetus is affected treatment of the mother should continue till term to prevent late masculinisation and neuroendocrine effects of exposure to high dose androgens.

Male fetuses don’t require treatment in utero.

Unfortunately prevention of virilisation with the above mentioned regimen is not always possible and parents should be fully counselled.

8. High Risk lesions

8.1 Pheochromocytoma

Pheochromocytoma is a rare catecholamine producing tumour uncommon in pregnancy. Unrecognised phaeochromocytomas have a mortality of up to 50% at the time of labour or during induction of general anaesthesia. The catecholamines produced can cause uteroplacental vasoconstriction and placental insufficiency or abruption. The fetal mortality is about 26% in undiagnosed cases and 11% in diagnosed cases.

In pregnancy pheochromocytoma can cause a hypertensive crisis or congestive heart failure. The signs and symptoms may mimic those of severe gestational hypertension although paroxysmal hypertension, orthostasis and absence of significant proteinuria and oedema may help in diagnosis. Patients may also complain of palpitations and headaches.

Diagnosis depends on the measurement of catecholamines and their metabolites on a fasted blood sample or in a 24 hour urine collection. Elevated metanephrine excretion is the most sensitive and specific finding although isolated elevated levels of vanillylmandelic acid excretion may be present. MRI is the investigation of choice to localise the tumour.

Once suspected patients should be referred to the tertiary centre and further investigation and management of patients should be done there. Pharmacological blockade and surgery is the mainstay of treatment.

Caesarean delivery is preferred to minimize potential catecholamine surge associated with labour and vaginal delivery.

9. Intrapartum care

Senior input and multidisciplinary care are imperative with a clear plan for delivery and after care.

Aim for a vaginal delivery unless obstetric indications for caesarean section.

Women with endocrine disease who are on long term steroids should see the *obstetric anaesthetist* on admission to labour ward as they will need stress dose steroids at the onset of labour or if they need a caesarean section and repeated every 6-8 hours until able to take oral corticosteroids.

For some endocrine conditions, (pheochromocytoma) *hypertensive surges* may be poorly tolerated. Syntocinon is preferred to syntometrine. This should be specified in the care plan.

10. Postnatal care

Postnatal care will depend on the endocrine condition. Management should be individualised and a plan of care should be made in the antenatal period by the multidisciplinary team.

Women with endocrine disease should be supported with breastfeeding, given appropriate contraception advice and offered lifestyle advice (diet, smoking, exercise).

Medication should be reviewed and appropriate endocrine follow-up arranged prior to discharge from maternity care. A comprehensive discharge summary should be prepared by the woman's obstetrician or medical physician.

11. References

1) Endocrine disease in pregnancy Charlotte J Frise and Catherine Williamson *Clinical Medicine* 2013, Vol 13, No 2: 176–81

2) High risk Pregnancy James Steer Weiner 5th edition

3) Handbook of Obstetric medicine 4th edition by Catherine Nelson Piercy

4) 2014 European Thyroid Association Guidelines for the Management of Subclinical Hypothyroidism in Pregnancy and in Children. Eur Thyroid J 2014;3:76–94

5) Prolactinoma and pregnancy: From the wish of conception to lactation Maiter D[1] Ann Endocrinol (Paris). 2016 Jun;77(2):128-34. doi: 10.1016/j.ando.2016.04.001. Epub 2016 Apr 26

6) J Endocr Soc. 2018 May 3;2(6):533-546. doi: 10.1210/js.2018-00090. eCollection 2018 Jun 1**Subclinical Hypothyroidism in Women Planning Conception and During Pregnancy: Who Should Be Treated and How?** Maraka S[1,2], Singh Ospina NM[2,3], Mastorakos G[4], O'Keeffe DT[5].

7) Turk J Med Sci. 2016 Nov 17;46(5):1374-1378. doi: 10.3906/sag-1507-33.**Relationship between gestational transient thyrotoxicosis and vitamin D** Küçükler FK[1], Şimşek Y[2], Görkem Ü[3], Ayçiçek Doğan B[4], Güler S[1]

8) Thyroid-Stimulating Hormone Receptor Antibodies in Pregnancy: Clinical Relevance Ines Bucci,[1,*] Cesidio Giuliani,[1] and Giorgio Napolitano[1] Published online 2017 Jun 30. doi: 10.3389/fendo.2017.00137 Front Endocrino (Lausanne) v8 2017

9) Norman J., Politz D., and Politz L.. 2009. Hyperparathyroidism during pregnancy and the effect of rising calcium on pregnancy loss: a call for earlier intervention. Clin. Endocrinol. 71:104–109. [PubMed]

10) Kelly T. R. 1991. Primary hyperparathyroidism during pregnancy. Surgery 110:1028–1033.

11) Prolonged hypoparathyroidism presenting eventually as second trimester abortion. Eastell R, Edmonds CJ, de Chayal RC, McFadyen IR Br Med J (Clin Res Ed). 1985 Oct 5; 291(6500):955-6.

12) The relationship between vitamin D and the craniofacial and dental anomalies of the supravalvular aortic stenosis syndrome.Friedman WF, Mills LF Pediatrics. 1969 Jan; 43(1):12-8.

13) Al-Azem H, Khan AA. Hypoparathyroidism. Best Pract Res Clin Endocrinol Metab 2012;26:517–22. doi:10.1016/j.beem.2012.01.004

14) Ananthakrishnan S Endocr Pract. 2009 May-Jun;15(4):377-82. doi: 10.4158/EP09090.RA.Diabetes insipidus in pregnancy: etiology, evaluation, and management

15) Hatswell BL et al Management of hypoparathyroidism in pregnancy and lactation - A report of 10 cases Bone Rep. 2015 Jun 30;3:15-19. doi: 10.1016/j.bonr.2015.05.005. eCollection 2015 Dec

16) Pregnancy in Acromegaly Bashir A Laway Ther Adv Endocrinol Metab. 2015 Dec; 6(6): 267–272. doi: 10.1177/2042018815603927

17) Surgical Interventions and Medical Treatments in Treatment-Naïve Patients With Acromegaly: Systematic Review and Meta-Analysis Katznelson et al J Clin Endocrinol Metab. 2014 Nov; 99(11): 4003–4014. Published online 2014 Oct 30. doi: 10.1210/jc.2014-2900 PMCID: PMC5393500 PMID: 25356809

18) Maternal Thyroid Function During Pregnancy and the Child's Linguistic and Sensory Development in the Northern Finland Birth Cohort 1986 Pakkila et al Front Endocrinol (Lausanne). 2018; 9: 127. Published online 2018 Mar 26. doi: 10.3389/fendo.2018.00127