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PRESCRIBING IN PREGNANCY (2): FREQUENTLY ASKED QUESTIONS

- **The risks and benefits of pharmacological therapy should be carefully considered before prescribing in pregnancy**
- **Depression in pregnancy: selective serotonin reuptake inhibitors (SSRIs) are generally recommended as first-line pharmacological treatment**
- **Hypertension in pregnancy: labetalol is generally recommended as first-line pharmacological therapy**
- **Nausea and vomiting in pregnancy: oral antihistamines or prochlorperazine are generally recommended as first-line antiemetic therapy**

ANTIDEPRESSANT THERAPY IN PREGNANCY

Background: It is estimated that approximately 12% of women experience depression during pregnancy,[1-3] which is a strong risk factor for the development of post-natal depression.[2,4] **Those with a previous history of depression (especially if severe) are at increased risk of depression during pregnancy.**[1,2] Depression in pregnancy may be associated with pre-term delivery, low birth weight (LBW), and childhood emotional and behavioural difficulties.[2,4] While there is limited evidence that these risks are reduced by treating depression in pregnancy,[4] **the risks of not treating depression include: 1) harm to the mother through poor self-care, lack of obstetric care or self-harm and 2) harm to the fetus or neonate (ranging from neglect to infanticide)**[1] A recent UK report, found that maternal suicide is the third largest cause of direct maternal death during, or within 42 days of the end of pregnancy and remains the leading cause of death within a year after the end of pregnancy;[5] therefore women with depression during and after pregnancy need to be treated appropriately.

In utero exposure to antidepressants has increased in recent decades; a Danish study reported an increase from 0.2% of pregnancies in 1997 to 3.2% in 2010.[1,4] **Most data on the safety of antidepressants in pregnancy has come from observational studies;**[1,4] some studies report increased risks with the use of antidepressants, including pre-term delivery, low Apgar score and autistic spectrum disorder (ASD), but these outcomes may be subject to confounding factors (e.g. maternal depression).[1,4] Some studies also suggest an increased risk of hypertensive disorders in pregnancy with use of antidepressants, however the results are inconsistent and subject to confounding factors.[6-8] Current evidence does not suggest that antidepressants are major teratogens, however some antidepressants have been associated with specific congenital malformations (e.g. cardiac defects),[1,2,9] although causality has not been confirmed.[9] **Use of antidepressants in the third trimester may result in neonatal adaptation syndrome (NAS),**[2] which usually begins within 48 hours of birth. Symptoms include insomnia, agitation, tremors or shivering, irritability, poor feeding, vomiting or diarrhoea, tachypnoea, respiratory distress, nasal congestion, cyanosis (rare) and seizures (rare).[1,2,4,9]

Which antidepressants are suitable for use in pregnancy?

The antidepressant classes used in pregnancy include selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs). The Summary of Product Characteristics (SmPC) should be consulted for full prescribing information (available at **www.hpra.ie** or **www.medicines.ie**).

Selective serotonin reuptake inhibitors (SSRIs) including sertraline, fluoxetine, citalopram, escitalopram and paroxetine are the most commonly prescribed antidepressants in pregnancy.[1,2,4] SSRIs are generally recommended as first-line pharmacological treatment for pregnant women where the benefits outweigh the risks.[1-4,9,10] However, if **the woman is already on another antidepressant or has a history of an effective response to an alternative antidepressant, she should be treated with that antidepressant.**[1-4,9,10] Overall SSRIs do not appear to be major teratogens.[1,9] Some studies report an increased risk of spontaneous abortion, LBW and pre-term delivery with use of SSRIs, however the evidence is conflicting and subject to confounding.[1,9] Some studies have also reported a small increase in absolute risk of cardiac malformations (especially with paroxetine and fluoxetine);[4,9,11-13] however other studies have found no such increased risk and recent meta-analyses failed to confirm the association.[1,2,4,9] There have also been inconsistent reports of an increased risk of postpartum haemorrhage (PPH) with the use of SSRIs.[2,4,14] **An increased risk of persistent pulmonary hypertension of the newborn (PPHN) has been reported following exposure to SSRIs beyond 20 weeks.**[1,2,4,9] It is an uncommon event in terms of absolute risk (0.2 to 1.2% vs 0.1 to 0.2% in the background population), however it represents a potentially serious neonatal complication.[1,2,4,9,15] Third trimester use of SSRIs may result in NAS.[1,4,9] There are also inconsistent reports of associations between use of SSRIs during pregnancy and an increased risk of ASD in childhood; the evidence is conflicting and potentially confounded.[4,9]

Serotonin-noradrenaline reuptake inhibitors (SNRIs) such as venlafaxine and duloxetine are also used in pregnancy.[1] There is less safety data available, however **the risks are considered to be similar to SSRIs.**[1,16,17] Recent evidence suggests an increased risk of PPH with SNRIs (in particular venlafaxine).[14,18] Venlafaxine

has been associated with congenital malformations such as cardiac defects and NAS in some studies.[1,16,19] The limited data available on the use of duloxetine does not suggest an increased risk of teratogenic effects; however further studies are required.[17]

Tricyclic antidepressants (TCAs) including amitriptyline, clomipramine, dosulepin, lofepramine, nortriptyline and trimipramine have been used widely in pregnancy and were used as first-line therapy for many years.[1,10] There is now more safety data available on use of SSRIs in pregnancy; therefore TCAs are no longer considered as first-line.[1,10] Possible adverse outcomes associated with the use of TCAs in pregnancy include spontaneous abortion, pre-term delivery, pre-eclampsia and ASD.[1,10] The available data does not provide strong evidence of an association between the use of TCAs as a class and an increased risk of congenital malformation,[10] however **a possible association between the use of clomipramine and cardiac malformation** cannot be excluded.[1,10,20] Use of TCAs in the third trimester may be associated with NAS.[1,10]

Practice points for prescribing antidepressants in pregnancy

- The decision on whether to commence or continue antidepressants in pregnancy needs to be individualised to the woman, who should be informed of the risks and benefits of all treatment options
- Antidepressants should be considered in women with moderate to severe depression who do not respond to psychological therapy, or where such therapy is not available
- Women with a current or past history of severe depression should be referred to secondary mental health services
- The choice of antidepressant depends on 1) the patient's previous response to antidepressants, 2) the stage of pregnancy and 3) the available evidence on the safety of the antidepressant in pregnancy
- Most guidelines recommend SSRIs as first-line pharmacological therapy for depression; paroxetine may be less safe than other SSRIs. Sertraline may be appropriate for a woman with a new episode of depression planning on breast feeding, as there is less exposure to sertraline in breastmilk
- There is an increased risk of relapse in women who discontinue antidepressants in pregnancy, therefore the sudden discontinuation of an antidepressant should be avoided as this does not necessarily remove the risk of congenital anomaly
- Switching antidepressants during pregnancy is not recommended as there is no clear evidence that the safety of one antidepressant is superior to that of another; moreover there is an increased risk of relapse with switching
- Neonates should be monitored for neonatal adaptation syndrome; there is no evidence that reducing the dose of an antidepressant before delivery reduces these symptoms

ANTIHYPERTENSIVE THERAPY IN PREGNANCY

Background: Hypertensive disorders occur in 7 to 9% of all pregnancies and are a major cause of maternal and perinatal mortality and morbidity.[21-25] **Hypertensive disorders in pregnancy remain a leading cause of maternal mortality;**[23,24] other outcomes include intracerebral haemorrhage, stillbirth, pre-term delivery, intra-uterine growth retardation (IUGR) and LBW.[22,23,25] Hypertension (HTN) in pregnancy is defined as a systolic blood pressure (BP) ≥ 140 mmHg and/or a diastolic BP ≥ 90 mmHg; it can be classified as 1) chronic HTN, 2) gestational HTN, or 3) pre-eclampsia or superimposed pre-eclampsia (see below).[22,26] It is estimated that 3% of women are prescribed antihypertensives during pregnancy.[25]

Chronic hypertension describes hypertension that **predates the pregnancy or appears at <20 weeks' gestation.**[22,27] Chronic HTN occurs in 0.2 to 5% of pregnancies; this is likely to increase due to the increasing age of mothers and increasing rates of obesity.[21,22] **Women with chronic HTN are at high risk of pregnancy complications;**[22] up to 25% of women with chronic HTN will develop superimposed pre-eclampsia.[27] **It is important to exclude causes of secondary HTN including chronic kidney disease, renal artery stenosis, systemic renal disease and endocrine disorders.**[22]

Gestational hypertension **is characterised by new onset of HTN >20 weeks' gestation**, without significant proteinuria, with return to normal BP within 3 months postpartum it occurs in 6 to 7% of pregnancies.[22,27] Gestational HTN occurring near term is associated with little increased risk of pre-eclampsia, however **the earlier the presentation and the more severe the HTN, the increased likelihood that the woman will develop pre-eclampsia;**[22] this occurs in up to 25% of women with gestational HTN.[27]

Pre-eclampsia is a multisystem disorder, which is diagnosed when HTN occurs at >20 weeks' gestation, accompanied by ≥1 of the following: proteinuria, maternal organ dysfunction (renal insufficiency, haematological involvement, liver involvement, neurological involvement, pulmonary oedema) or fetal growth restriction.[22] Table 1 summarises the risk factors for pre-eclampsia. **Superimposed pre-eclampsia** is diagnosed when a woman with chronic HTN or pre-existing proteinuria develops one or more of the systemic features of pre-eclampsia after 20 weeks' gestation.[22,26] Pre-eclampsia may also first develop in the postpartum period; women at discharge should be advised to contact a HCP if they develop signs of pre-eclampsia (e.g. severe headache, visual disturbance or epigastric pain).[26]

Table 1: Risk factors for pre-eclampsia based on current guidelines[22,23,26,28*]

High risk factors for pre-eclampsia include:	Moderate risk factors for pre-eclampsia include:
Women with: • pre-eclampsia or hypertension in a previous pregnancy • chronic kidney disease • autoimmune disease • diabetes • chronic hypertension	Women with: • first pregnancy • age ≥40 years • pregnancy interval of >10 years • body mass index of ≥35 at first visit • family history of pre-eclampsia • multiple pregnancy

*Irish and UK guidelines on hypertension in pregnancy and pre-eclampsia are currently being updated [28]

Which antihypertensives are suitable to use in pregnancy?

The aim of antihypertensive therapy is to 1) protect the mother from cardiovascular complications and to 2) protect the fetus from the adverse effects of maternal HTN and of treatment.[24] The main antihypertensive classes used in pregnancy include beta blockers, centrally acting alpha agonist therapy (i.e. methyldopa) and calcium channel blockers. The SmPC of each medicine should be consulted for full prescribing information.

Beta blockers, in particular labetalol, have been used extensively in pregnancy. **Labetalol, which also has alpha adrenoreceptor blocking properties, is recommended as first-line treatment.**[22,23] Contraindications for use include maternal asthma.[29] Labetalol decreases BP by lowering peripheral vascular resistance with little or no decrease in cardiac output, maternal heart rate or reduced placental blood flow.[25] Some evidence suggests an increased risk of congenital abnormalities (including cardiac, cleft lip/palate and neural tube defects) and IUGR with beta blockers; however these findings need to be confirmed.[21,25,30] Use of beta blockers near term may be associated with neonatal bradycardia, hypotension and hypoglycaemia.[21,24,25,30]

Calcium channel blockers: Nifedipine (not licensed for this indication in pregnancy) may be used as an alternative to labetalol to treat maternal HTN.[22,23,31] The limited data available do not suggest an increased risk of congenital malformations, spontaneous abortion, stillbirth, IUGR or pre-term delivery; however further studies are required.[31] Severe adverse reactions (hypotension) occur when nifedipine is combined with IV magnesium sulphate (used in the management of pre-eclampsia); careful monitoring is required.[22,25,27] Short-acting nifedipine has been associated with acute maternal hypotension and is not recommended;[22,24] therefore **extended-release nifedipine should be prescribed**.[32]

Methyldopa (a centrally acting alpha agonist) has been one of the most frequently used antihypertensives in pregnancy;[21,24] it is recommended as an alternative to labetalol.[15,16] Contraindications for use include maternal depression.[33] Limited data does not suggest increased risks of pre-term delivery, LBW, small for gestational age, intrauterine death, neonatal complications or adverse neurodevelopmental outcomes with use of methyldopa compared to other antihypertensives or untreated hypertension.[27,34] Maternal adverse effects include dizziness and sedation, which may occur on initiation of therapy or with dose increases;[24,33] hepatotoxic effects have also been reported.[24,27] There is no licensed preparation currently available in Ireland.[35]

Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are contraindicated in pregnancy in the second and third trimesters;[22,23,27,36-39] they are associated with fetotoxicity (e.g. decreased renal function and oligohydramnios) and neonatal toxicity (renal failure, hypotension). They are not recommended in the first trimester; treatment should be stopped as soon as pregnancy is confirmed.[22,23,27,36-39]

Practice points for prescribing antihypertensives in pregnancy

- Women with hypertension (HTN) in pregnancy should be referred to hospital for investigation and monitored closely for the development of pre-eclampsia
- Women with chronic HTN and gestational HTN should be cared for by an obstetrician
- It is not uncommon for women with chronic HTN to have lowered BP in early pregnancy, requiring discontinuation of oral antihypertensives for a period of time; however the BP may rise again in the second trimester, therefore regular monitoring is required
- Guidelines recommend that for women with uncomplicated HTN and no underlying co-morbidities, antihypertensive therapy should be used to keep systolic BP <150 mmHg and diastolic at 80-99 mmHg
- Oral labetalol should be considered as first-line antihypertensive treatment
- The use of low dose aspirin (75mg) [not licensed for this indication] should be considered for women at high risk of pre-eclampsia or with >1 moderate risk factor (see table 1); aspirin should be taken from 12 weeks' gestation typically up to 36 weeks[40,41]
- The National Clinical Programme for obstetrics and gynaecology has published guidelines on the management of HTN in pregnancy and pre-eclampsia which are available on **www.hse.ie** in the National Clinical Programme section (Obstetrics and Gynaecology)

ANTIEMETIC THERAPY IN PREGNANCY

Background: Nausea and vomiting in pregnancy (NVP) is a common condition affecting up to 80% of women during pregnancy.[42-46] The cause of NVP is unknown, however it is thought to be associated primarily with rising levels of human chorionic gonadotrophin hormone.[42-46] The symptoms of NVP usually appear at between 4 and 7 weeks' gestation; the peak severity is at approximately 11 weeks and 90% of cases resolve by 20 weeks' gestation.[43,44] Studies have reported lower rates of miscarriage in women who experience NVP.[46] NVP is a diagnosis of exclusion; **other causes of NVP should be excluded, particularly in women who experience nausea and vomiting for the first time after 10 weeks' gestation;**[44-46] these include urinary tract infection, multiple pregnancy, molar pregnancy, gastrointestinal and metabolic causes.[44-46]

Most cases of NVP are self-limiting; however NVP can have a significant impact on a woman's quality of life.[42,43] NVP may range from mild discomfort to a severe form of NVP known as hyperemesis gravidarum, which occurs in 1% of all pregnancies.[44,46] **Hyperemesis gravidarum is the most common indication for admission to hospital in the first trimester;**[46] it is a diagnosis made when there is severe persistent NVP (not related to other causes) associated with weight loss of >5% pre-pregnancy weight, ketonuria, dehydration and electrolyte imbalances.[45,46] Hyperemesis gravidarum is associated with other maternal complications including vitamin and mineral deficiencies and accompanying conditions (e.g. Wernicke's encephalopathy), thyroid, renal and hepatic dysfunction, and fetal complications including IUGR as a result of maternal vitamin deficiencies.[42,44]

Most mild forms of NVP can be managed with supportive therapy in the form of lifestyle and dietary changes (e.g. frequent small meals) and antiemetics.[43-46] **Early treatment of NVP may be beneficial to prevent progression to hyperemesis gravidarum.**[46] A validated assessment tool, the Pregnancy Unique Quantification of Emesis and Nausea (PUQE) scoring index can be used to assess the severity of NVP and to track progress with treatment.[44-46]

Which antiemetics are suitable to use in pregnancy?

Antiemetics used in pregnancy include antihistamines, dopamine antagonists and serotonin antagonists (primarily ondansetron). Each SmPC should be consulted for full prescribing information.

Antihistamines are the oldest class of drugs used in the management of NVP and are recommended as first-line pharmacological therapy for NVP;[45-47] these include **promethazine and cyclizine.**[47] The large amount of safety data available on their use for NVP do not indicate an increased risk of congenital malformations.[47-50] A combination of the antihistamine **doxylamine** and pyridoxine (vitamin B6) is widely used in the US, Canada and Spain (as Cariban®); it is currently not licensed in Ireland, however is recommended as a first-line option for NVP in the Irish Clinical Practice Guideline for NVP.[44] **Adverse effects of antihistamines include sedation, dry mouth and constipation.**[43,46]

Dopamine antagonists such as **prochlorperazine** and metoclopramide are also used for the management of NVP.[45,47] The available data does not indicate an increased risk of teratogenicity.[46,47,51,52] **Drug-induced extrapyramidal effects and oculogyric crisis can occur** with the use of prochlorperazine and especially with metoclopramide.[44-46,53] Some guidelines recommend prochlorperazine as a first-line option, however metoclopramide should not be used as first-line in view of the risks of these extrapyramidal effects.[45]

Serotonin antagonists: There is limited efficacy and safety data on the use of serotonin antagonists (including ondansetron) for NVP; however their use for this indication seems to be increasing.[42,46] The data suggest that ondansetron has similar efficacy to metoclopramide and is more effective than doxylamine/pyridoxine in NVP.[42,46] The limited safety data available suggest a possible association with cleft palate and an increased risk of cardiac defects when ondansetron is used in the first trimester; the evidence is conflicting and further studies are required.[46,47,54-56] **Ondansetron should not be used as first-line therapy**, however it may be an option when other antiemetics are unsuccessful.[45] **Adverse effects include headache, drowsiness, fatigue and constipation.**[46] There are insufficient data to support the use of the other serotonin antagonists (e.g. granisetron) in the treatment of NVP.[47]

Practice points for prescribing antiemetics in pregnancy

- Most women with nausea and vomiting of pregnancy (NVP) can be managed in primary care with supportive care and oral antiemetics
- Clinicians should use antiemetics that they are familiar with to treat NVP
- Most guidelines recommend oral antihistamines or prochlorperazine as first-line therapy
- Women who do not respond to oral antiemetics or oral fluids require hospital assessment for consideration of parenteral fluids, vitamins and antiemetics
- The HSE NCP for Obstetrics and Gynaecology has produced a guideline on the management of NVP and hyperemesis gravidarum, which includes the PUQE scoring system; it is available on **www.hse.ie** in the National Clinical Programme section (Obstetrics and Gynaecology)

USEFUL RESOURCES

- The British Association for Psychopharmacology has consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum (2017) available at **www.bap.org.uk/pdfs/BAP_Guidelines-Perinatal.pdf**
- The National Clinical Programme for Obstetrics and Gynaecology has produced guidelines at: [available at **www.rcpi.ie** and **www.hse.ie**]
  - Management of hypertension in pregnancy
  - Diagnosis and management of pre-eclampsia and eclampsia
  - Hyperemesis and nausea/vomiting in pregnancy
- Hyperemesis Ireland contains information for healthcare professionals and patients available at: **www.hyperemesis.ie**
- Best Use of Medicines in Pregnancy (BUMPs) information leaflets for patients and healthcare professionals available at **www.medicinesinpregnancy.org/**
- UK Teratology information service (subscription required for full monographs) available at **www.uktis.org/**
- MotherToBaby is a US teratology information website which provides information for patients and healthcare professionals **https://mothertobaby.org/**
- The Motherisk Program at The Hospital for Sick Children (based in Canada) has information on their website **www.motherisk.org/**
- The Summary of Product Characteristics (SmPC) for individual medicines is available at **www.hpra.ie** and **www.medicines.ie**
- The NMIC clinical enquiry answering service is available to deal with specific enquiries on use of medicines in pregnancy: e-mail **nmic@stjames.ie** or telephone **01 4730589**

List of references available on request. Date of preparation: August 2018

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