Optimal treatment of minor ailments in pregnancy requires careful evaluation of the risks and benefits

In this second article of our *Drugs in pregnancy* series Emma Williams tackles how best to manage a range of common minor ailments that many women suffer in pregnancy so that maternal symptoms are relieved while minimising risks to the developing fetus.

Introduction

During pregnancy an expectant mother's body will undergo hormonal changes, which often give rise to a range of relatively minor, yet troublesome ailments such as heartburn, nausea, vomiting and constipation. As the pregnancy progresses, the increasing maternal weight can also cause physical stresses on the body, producing uncomfortable symptoms.

Pregnant women should avoid medication wherever possible, and where appropriate, non-pharmacological treatments can be suggested to ease their symptoms. However, left inadequately treated, chronic conditions, fever, pain or infections can be potentially dangerous. Appropriate treatment is therefore essential to prevent unwanted consequences to the mother and the developing fetus.

Many over-the-counter medicines that are usually appropriate for the treatment of minor ailments are not licensed to be sold for use during pregnancy, although some may be prescribed by a GP or obstetrician if deemed necessary. There are limited data available concerning the fetotoxic effects of drugs during pregnancy, therefore medication should only be considered if it's thought that the maternal benefits will outweigh potential fetal risks.

Concern that conventional medications may be teratogenic has resulted in many women and health care providers looking for alternatives. Although often perceived as 'natural' and 'safer' than conventional medicines, herbal plant preparations are not always harmless, especially in high doses or with excessive use. Additionally, a number of herbal remedies have significant pharmacological activity. To date, there is almost no solid scientific evidence regarding the potential benefits of the various herbal remedies, or the risks they pose to the mother and fetus, and so they should be avoided during pregnancy.

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The following sections provide guidance on the treatment of some minor ailments, which are common during pregnancy. More detailed information about drug exposure in pregnancy is available from the UK Teratology Information Service (contact details below).

Nausea and vomiting

Nausea and vomiting affects up to 80–85% of women during the first trimester of pregnancy. The severity varies greatly, but in about 90% of women symptoms settle by 16–20 weeks of gestation. Although nausea and vomiting does not have harmful effects on the fetus, it can severely impact on a pregnant woman's quality of life. Symptoms can often be managed with non-pharmacological remedies including rest, eating small frequent meals and avoiding large drinks in the morning.

Ginger has been reported as an effective treatment for nausea and vomiting during pregnancy[1–3] although findings are inconsistent and many researchers remain cautious. Three randomised controlled trials have been published regarding P6 (Neiguan point) acupressure for the relief of nausea and vomiting in pregnancy.[4–6] The studies, which had different inclusion and exclusion criteria, have produced conflicting results.

Some studies have suggested that pyridoxine (vitamin B6) is effective at reducing nausea in some cases. However, it may be less effective for reducing vomiting. Other studies have reported the effectiveness of cyanocobalamin (vitamin B12) for nausea and vomiting during pregnancy. However, there are no published data regarding its teratogenicity.

If clinically necessary the antihistamines cyclizine and promethazine may be suitable pharmacological options. One observational

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study including 111 women given cyclizine in the first trimester of pregnancy, found no increase in the congenital malformation rate.[7] A recent case-control study from the Hungarian Congenital Abnormality Registry analysed 3648 cases of *in utero* promethazine exposure and concluded that there was no increased risk of congenital malformations, although the presence of confounders made the study somewhat difficult to interpret.[8]

Other pharmacological options that may be considered, if appropriate, include the anti-emetics prochlorperazine and metoclopramide. Prochlorperazine use during pregnancy has been implicated in reports of congenital malformations, but more recent robust studies have not replicated these findings and no increased risk of adverse outcomes was reported in a recent meta-analysis of 2948 exposed women.[9] Studies have shown no significant increase in the risk of major malformations when metoclopramide was administered during the first trimester of pregnancy.[10] However, metoclopramide may cause maternal dystonic reactions.

Severe nausea and vomiting (hyperemesis gravidarum) presents as severe intractable vomiting occurring before week 20 of pregnancy. Most patients require hospital admission for fluid, electrolyte and vitamin replacement, including thiamine because of the risk of Wernicke's encephalopathy. Investigations to exclude other pathology should be carried out if hyperemesis continues after week 20 of gestation. There is increasing published data to suggest that therapeutic use of ondansetron for hyperemesis gravidarum in pregnancy is not associated with an increased rate of congenital malformations — however, the data are too limited to state that there is no increased risk.

Corticosteroids have been used successfully for intractable nausea and vomiting in hyperemesis gravidarum. A few prospective controlled studies found no increased risk of malformations after first trimester exposure, but a meta-analysis showed that there may be an increased risk of oral clefts.[11]

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Constipation

For most pregnant women with constipation, increasing their dietary fibre, fluids and exercise can be beneficial and should be considered first-line therapy. Symptoms are often caused by raised progesterone levels, which reduces gastrointestinal motility, with medications such as iron therapy being a contributory factor.

Other options for the treatment of constipation comprise stool-bulking agents, such as ispaghula husk, which are not absorbed by the body. If these prove ineffective, lactulose may be considered because it is poorly absorbed and well tolerated. There is no evidence to suggest that lactulose is associated with an increased risk of fetal toxicity.

Senna is minimally absorbed from the digestive tract and there is no evidence to suggest that therapeutic doses of anthraquinone derivatives cause teratogenicity. They do, however, have the potential to stimulate uterine contractions and should be avoided close to term, or in unstable pregnancies.

Liquid paraffin interferes with the intestinal absorption of fat-soluble substances, including fat-soluble vitamins, and this may affect fetal development. Fluid and electrolyte disturbances can occur with use of saline laxatives, macrogols and sodium and phosphate enemas, and for this reason these laxatives are not recommended for use during pregnancy.

Gastro-oesophageal reflux

Gastro-oesophageal reflux is prevalent during the later months of pregnancy. Symptoms are caused by the reflux of gastric juice into the lower oesophagus, triggered by the upward pressure on the stomach from the enlarging uterus, as well as a relaxed muscle tone in the lower oesophageal sphincter from raised progesterone levels.

Non-pharmacological treatments for heartburn include eating small, frequent meals to avoid distending the stomach, not eating for around three hours before sleep, propping up the head of the bed during sleep and avoiding unnecessary stooping.

Over-the-counter antacids may be used to treat mild symptoms. The available data does not suggest teratogenic effects with therapeutic use during pregnancy. Preparations containing calcium carbonate have the greatest neutralising capacity, but preparations containing aluminium and magnesium salts are also long-lasting and effective. Because aluminium salts tend to cause constipation and magnesium salts tend to cause diarrhoea, products combining the two can balance out these effects.

Caution should be taken with the long-

term or unrestricted use of antacids, because chronic consumption of high doses can cause alterations in mineral metabolism. Compounds containing high sodium content can increase blood pressure, which is obviously undesirable. Compounds containing bismuth salts are also not recommended during pregnancy because absorbed bismuth may be neurotoxic.

Histamine H_2-receptor antagonists may be considered if antacids are unsuccessful. The best studied agent is ranitidine, with documented experience from more than 1500 pregnancies suggesting no increased teratogenic risk.

The proton pump inhibitor (PPI) omeprazole (Losec®) is licensed for use during pregnancy, and there is documented experience from over 1300 pregnancies. Data from a large meta-analysis showed that exposure to omeprazole does not pose a significant teratogenic risk.[12,13] Although there is no evidence of teratogenicity, experience with the use of other PPIs, such as lansoprazole, rabeprazole and pantoprazole is very limited.

Pain

Headache, backache and other types of musculoskeletal pain are commonly experienced during pregnancy. Pain can often be relieved with rest, relaxation and direct application of heat or cold.

Severe or chronic pain can be very debilitating, and if inadequately treated, can interfere with the maternal cardiovascular system, which may cause secondary effects on the fetus. Some patients may require medication, but this should be assessed on an individual-case basis.

More than 40 years of use has provided substantial information on the safety of paracetamol in pregnancy. In the absence of maternal toxicity, there is no clear evidence that therapeutic doses are associated with an increased risk of malformations. Results from one study have suggested an association between frequent use of paracetamol during late pregnancy and an increased risk of asthma and wheezing in the children at seven years of age.[14,15] However, this study should be interpreted with caution, because no clear causal link was established and further data are needed to clarify the clinical significance of the results. Paracetamol remains the analgesic of choice during all stages of pregnancy.

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Although recent data have suggested there may be an increased risk of cardiac malformations associated with non-steroidal anti-inflammatory drug (NSAID) use in early pregnancy, this finding has not been confirmed. However, NSAIDs are relatively contraindicated after week 28 of gestation, because their use has been associated with premature closure of the ductus arteriosus and oligohydramnios. These effects are related to the inhibitory action of NSAIDs on prostaglandin activity.

Data regarding the use of codeine during pregnancy provides inconsistent evidence of an association with congenital malformations. Codeine may cause constipation and should not be used in patients at risk of dependency. Long-term maternal codeine use may be associated with neonatal withdrawal symptoms, so where clinically appropriate, maternal codeine therapy should be reduced near to term. This will also minimise the risk of respiratory depression in the fetus and neonate.

Candidiasis

During pregnancy, the vagina is rich in glycogen, which promotes candidal growth and vaginal candidiasis (thrush) occurs much more frequently in pregnant women. If treatment is required during pregnancy the topical anti-mycotic agents clotrimazole or miconazole can be considered. Data from the Hungarian case-control surveillance of congenital abnormalities, showed that neither topical clotrimazole or miconazole were clearly associated with an increased risk of congenital abnormalities.[16,17]

Experience with systemic anti-mycotic therapy is limited, although data from the Danish medical birth registry did not detect an overall increased risk of congenital malformations after 1079 cases of maternal exposure to low dose fluconazole were examined.[18] However, there have been a small number of cases reported of Antley-Bixler syndrome (a multiple congenital malformation syndrome with complex aetiology) and although cause and effect has not been demonstrated, an increased risk of malformations cannot be discounted with high dose chronic fluconazole therapy (>400 mg/day).[19,20]

Summary

Minor ailments are common during pregnancy and non-pharmacological therapies should be considered as the first-line treatment, if appropriate. However, medication may be required to ensure the well-being of the mother and prevent secondary adverse effects to the fetus. If a clinician deems that drug treatment will provide maternal benefits that outweigh

potential risks to the fetus, then medication choice should be evaluated carefully and prescribed at the lowest effective dose, for the shortest period of time. Drug choice should be considered on an individual-case basis and will depend on the available published and anecdotal evidence.

For more information regarding drug and chemical exposures in pregnancy, access pregnancy information via TOXBASE (http://toxbase.org). This is available by free registration for health care professionals in the UK and Ireland. Alternatively, contact the UK Teratology Information Service on 0844 892 0909 to speak with a teratology specialist.

Declarations of interest

The author has no interests to declare.

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