Prescribing in Pregnancy

Treatment of common minor ailments

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A number of common minor disorders may occur in pregnancy and require drug treatment for control of symptoms. These include headache and musculoskeletal pains as well as a variety of gastrointestinal complaints, including heartburn, nausea, vomiting, dyspepsia, and constipation. This article reviews the drugs used to treat such complaints with respect to efficacy and safety and appraises the available evidence in an attempt to recommend the safest drugs.

Use of analgesics

Simple analgesics are the commonest drugs taken in pregnancy and are often self administered. Aspirin, paracetamol, ibuprofen, and a variety of analgesic combinations are available in Britain without prescription. Many women consume analgesics in the early stages of pregnancy before realising they are pregnant. Collecting and interpreting controlled data on exposure to analgesics and the incidence of congenital defects are therefore difficult.

ASPIRIN

Evidence linking ingestion of aspirin to fetal malformations is suggestive but inconclusive. Massive doses of aspirin given to pregnant rats cause congenital skeletal and eye defects.¹ Many of the studies suggesting a teratogenic effect of aspirin in humans have been retrospective case-control studies. For example, among 833 women who had given birth to malformed babies there was a higher incidence of ingestion of aspirin during early pregnancy than in a control group.² In a large prospective cohort study of more than 50 000 women, however, no increase in congenital abnormalities was found in the babies of mothers who had taken aspirin during pregnancy when compared with control patients who had not taken aspirin.³

Aspirin has been thought to cause a reduction in birth weight and an increase in the stillbirth rate.⁴ In a prospective cohort study of more than 41 000 women, however, the stillbirth rate was 1.4% both in women who consumed large quantities of aspirin and those who took no aspirin during pregnancy.⁵ Similarly, the neonatal death rate was 1.1% in both groups.

Aspirin is freely transferable across the placenta and is excreted by the newborn infant at a slower rate than in adults owing to immaturity of the excretory pathways.⁶ The infant of a woman who ingested regular therapeutic doses of aspirin throughout pregnancy took five days to eliminate the drug.⁶

One potential problem of aspirin in newborn infants is its effect on haemostatic mechanisms. In a case-control study haemostasis

was normal in 33 of 34 pairs of mothers and infants where there was no history of aspirin ingestion.⁷ There were, however, abnormalities of platelet adhesiveness in most of the infants whose mothers had taken aspirin within five days of delivery. There was also a higher incidence of minor bleeding in the babies whose mothers had taken aspirin. Furthermore, intrapartum blood loss from the mothers was greater in those who had recently taken aspirin.

The possible teratogenic effect of aspirin, together with its well documented adverse effects on platelet function and haemostasis when taken in late pregnancy, suggest that aspirin should be avoided in pregnancy, particularly in the treatment of minor disorders. Non-steroidal anti-inflammatory drugs will be discussed in a later article on antirheumatic therapy.

PARACETAMOL

The effects of paracetamol during pregnancy have not been studied as extensively as those of aspirin, but it seems to be generally safe. Studies in animals have shown no adverse effects on fetal or placental growth.⁸ Paracetamol does not have the same effect on clotting as aspirin and for this reason alone is preferable for use in pregnancy. There is nothing to suggest that paracetamol in normal dosage is associated with any specific problems during pregnancy or breast feeding, and it is recommended as the mild analgesic of choice.⁹

Treatment of nausea and vomiting

Although common in early pregnancy, nausea and vomiting are generally of short duration and can often be managed without drugs. Patients should be reassured and advised to take small frequent meals and to avoid large amounts of fluid. Drug treatment is often necessary, however, if symptoms are severe or prolonged.

Antiemetic drugs have been linked to a number of congenital defects. One large prospective series showed an association between vomiting in early pregnancy and certain congenital abnormalities, but no correlation could be established with any specific antiemetic drug.¹⁰ This led to the proposal that it was vomiting rather than antiemetic treatment which was causally associated with birth defects. In a prospective study of more than 16 000 women, however, there was no difference in the incidence of congenital defects between those who had vomited in pregnancy and those who had not.¹¹ The authors concluded that any increased risk in women taking antiemetic drugs was related to the drugs rather than the vomiting and that the risk was low in any case. Specific drugs are considered below.

DEBENDOX

Debendox, a combination of dicyclomine, doxylamine, and pyridoxine, was highly successful in the management of nausea and vomiting during pregnancy. Sporadic case reports linking its use to

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congenital abnormalities caused concern, however, about its safety in pregnancy. This highlights the problems about drawing conclusions from uncontrolled data since both retrospective^{12, 13} and prospective^{14, 15} studies did not confirm any teratogenic effect. In the United States, the Food and Drugs Administration also concluded that there was no firm evidence linking this preparation with birth defects.¹⁶ Nevertheless, the manufacturers withdrew the drug in 1983 because of unsubstantiated claims about teratogenicity.¹³

ANTI-HISTAMINES

Antihistamines are generally recommended for treating nausea and vomiting in pregnancy.¹⁷⁻¹⁹ Meclozine and cyclizine are widely used and appear to be safe. Concern about an association between the use of these drugs and congenital malformations, particularly cleft palate, has not been substantiated in prospective controlled studies.^{20, 21} There may, however, be a weak association between meclizine and congenital eye defects.²¹ Promethazine may be associated with an increased incidence of congenital dislocation of the hips.^{10, 22}

METOCLOPRAMIDE

Data on the effects of metoclopramide on early fetal development are lacking. It has been used in late pregnancy and in the management of hyperemesis gravidarum.²³ Since it increases lower oesophageal sphincter pressure and accelerates gastric emptying metoclopramide has been used in labour and before anaesthesia,²⁴ when it is considered safe and efficacious. Its routine use in early pregnancy cannot be recommended, however, because of the lack of controlled data.

Treatment of heartburn and dyspepsia

Heartburn due to gastro-oesophageal reflux is extremely common during pregnancy, particularly in the second and third trimesters. Lower oesophageal sphincter pressure is reduced throughout pregnancy and is lowest around the 36th week.²⁵

Patients with symptoms of reflux should be reassured and advised to take small, frequent meals rich in carbohydrates and to avoid stooping or lying flat. If drug treatment is necessary teratogenicity is a less important issue because most cases start in late pregnancy. Non-absorbable antacids such as aluminium hydroxide or magnesium trisilicate may be used, although aluminium antacids given alone may cause constipation. Antacids are safe when taken in the second or third trimester, although they have been associated with an increased rate of congenital defects when taken in early pregnancy.¹⁹ Metoclopramide, which raises lower oesophageal sphincter pressure, may be helpful in the management of reflux; its use in late pregnancy seems to be safe.^{23, 24}

Dyspepsia that is not related to oesophageal reflux is unusual in pregnancy. In particular, peptic ulcer rarely presents for the first time during pregnancy. In women with existing peptic ulcer symptoms tend to improve as the pregnancy progresses, but some may still require treatment. Simple measures include cessation of smoking, small regular meals, and antacids for relief of symptoms.

The H₂-receptor antagonists cimetidine and ranitidine are safe and effective for managing peptic ulcer in non-obstetric practice. Routine use in pregnancy cannot, however, be recommended because of the lack of appropriate data on their safety. There is no justification for their use in the treatment of dyspepsia not related to ulceration since they are not even particularly effective.²⁶ H₂-antagonists have been successfully used before general anaesthesia for caesarean section to reduce gastric acidity and prevent aspiration of acid into the lungs (Mendelson's syndrome). Both cimetidine and ranitidine are excreted into breast milk, but there are no data to suggest a harmful effect on the baby.

Sucralfate has not been widely used during pregnancy in the

United Kingdom, but it is an effective treatment for peptic ulcer and has been recommended for use in pregnancy in the United States because it is not absorbed.²⁷ It may, however, cause mild constipation in some patients. Carbenoxolone causes salt and water retention and is therefore contraindicated in pregnancy. Compounds containing bismuth should also be avoided; the effects on fetal development of the absorption of small quantities of bismuth are unknown.

In summary, dyspepsia in pregnancy, whether related to peptic ulceration or not, is probably best managed with reassurance, advice on meals and smoking, and non-systemic antacids.

Treatment of constipation

Patients should be advised to take a diet high in cereal fibre and fresh fruit. Simple constipation is best treated by a bulking agent such as preparations containing bran, ispaghula, or methylcellulose. Stimulant laxatives may be uterotonic and are therefore contraindicated during pregnancy.

Conclusions

It is a counsel of perfection that no drugs should be used in pregnancy, but some minor symptoms of common ailments often require treatment for the comfort of the mother. Paracetamol appears to be the safest minor analgesic; an antihistamine compound can probably be safely prescribed for a short period for treating nausea and vomiting; and heartburn and dyspepsia are best managed along simple lines, with an antacid in early pregnancy and possibly metoclopramide in the later stages.

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