What guidance is there available on the use of vitamin K for the management of obstetric cholestasis?

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Background
Obstetric cholestasis (OC) or intrahepatic cholestasis of pregnancy has been described as a multifactorial condition of pregnancy characterised by intense pruritus with the absence of a skin rash, with abnormal liver function tests, neither of which have an alternative cause and both of which resolve after birth(1). It is associated with a significantly increased risk of adverse perinatal outcomes, including stillbirth (2). The use of vitamin K as part of the management of OC is common practice. Obstetric cholestasis can result in reduced absorption of dietary fats, due to failure of the excretion of bile salts into the gastrointestinal tract and reduced micelle formation (1). As vitamin K is fat-soluble patients with fat malabsorption may become deficient (3). Vitamin K is required for the production of blood clotting factors and proteins required for the normal calcification of bone (3). Whether to use a water soluble or fat soluble preparation of vitamin K for the management of OC is a commonly asked question. In addition, there have been reports of neonatal toxicity following menadiol sodium diphosphate administration in late pregnancy or during delivery (4).

Answer
Menadiol sodium phosphate is a water-soluble synthetic vitamin K derivative that can be given orally for the prevention or treatment of vitamin K deficiency due to malabsorption, as it is absorbed without dependence on the presence of bile salts (3,4). Phytomenadione however, is the fat-soluble synthetic vitamin K derivative and requires the presence of bile for its absorption from the gastrointestinal tract when administered orally (3,4); a parenteral preparation may be required in patients with fat malabsorption to ensure clinical effectiveness (4).

There are two authoritative guidance documents providing advice on the use and choice of vitamin K preparation for the management of obstetric cholestasis and there are also a number of general review articles.

Websites
• Royal College of Obstetricians and Gynaecologists: Green-top Guideline No. 43. Obstetric Cholestasis. April 2011(1)
  https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg43/

• UK Teratology Information Service (UKTIS): Treatment of obstetric cholestasis in pregnancy. March 2015 (4)
  *Registration with Toxbase is required (free for UK health care professionals)*
  o UKTIS also operate a telephone information service for UK health care professionals.

• A corresponding bumps patient information leaflet on treatment of obstetric cholestasis in pregnancy is available at www.medicinesinpregnancy.org.

In April 2011, the Royal College of Obstetricians and Gynaecology (RCOG) (1) updated the obstetric cholestasis guidelines regarding treatment with vitamin K due to BNF recommendations of avoiding water soluble vitamin K (menadion sodium phosphate) therapy late in pregnancy and labour because of a risk of neonatal toxicity. New evidence and guidance in this field were reviewed in 2014 and it was decided that revision of this guideline would be deferred to a later date. The version available on the website and app remain valid (1). The UK Teratology Information Service (4) advises that there
are no randomised controlled clinical trials that support or refute the use of vitamin K supplementation in the management of OC. Although there are very limited published data to assess the impact of antenatal use of vitamin K in patients with OC, there are good physiological reasons why this may be beneficial. Current RCOG guidelines recommend that women with OC should be counselled about vitamin K supplementation and where the prothrombin time is prolonged, the use of menadiol in doses of 5–10mg daily is indicated. Women should be advised that when prothrombin time is normal, menadiol in low doses should be used, however, women should be counselled about the small theoretical risk of neonatal haemolytic anaemia, hyperbilirubinemia and kernicterus associated with use of water soluble vitamin K analogues in late pregnancy (1,4). It should be noted that the evidence for these risks following in utero exposure to menadiol is limited, but there are several reports of similar effects following menadiol administration to newborn infants. However the RCOG guidelines also state that postnatal vitamin K must be offered to neonates in the usual way (1).

Publications and other resources

General Review Articles


Ovadia C and Williamson C. Intrahepatic cholestasis of pregnancy: Recent advances. Clinics in Dermatology 2016; 34: 327-334


Related Correspondence :


International Guidelines

European Association for the Study of the Liver* EASL Clinical Practice Guidelines:

Available through Specialist Pharmacy Service at www.sps.nhs.uk
Summary

There are currently two published authoritative guidance documents on the management of obstetric cholestasis (1, 4).

Both give recommendations on the use of vitamin K in the management of obstetric cholestasis (1, 4).

The Royal College of Obstetricians and Gynaecologists recommend that a discussion should take place with the woman regarding the use of vitamin K. Women should be advised that when prothrombin time is prolonged, the use of water-soluble vitamin K (menadiol sodium phosphate) in doses of 5-10mg daily is indicated. When prothrombin time is normal, water soluble vitamin K (menadiol sodium phosphate) in low doses should be used only after careful counselling about the likely benefits and theoretical risks.

The UK Teratology Information Service (UKTIS) document (4) cites the Royal College of Obstetricians and Gynaecologists (RCOG) recommendations (1)

Limitations

A discussion of the neonatal toxicity associated with the use of vitamin K during pregnancy is beyond the scope of this review.

References


Quality Assurance

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Search strategy
1. Embase: (OBSTETRIC CHOLESTASIS) OR [exp *PREGNANCY COMPLICATION and exp *CHOLESTASIS. Limit to: Publication Year 2014-2016


3. In-house database/ resources
4. NHS Evidence: (cholestasis and pregnancy) (Vitamin K and pregnancy) (obstetric cholestasis)
5. Google Scholar: (obstetric cholestasis and vitamin K)
6. Toxbase: Obstetric Cholestasis Treatment In Pregnancy