# Obstetric Cholestasis (OC)

Intrahepatic Cholestasis of Pregnancy

## Key Points

- The purpose of this guideline is to provide guidance on the management of intrahepatic cholestasis of pregnancy (ICP) and to reduce the associated increased maternal morbidity, perinatal morbidity and mortality.
- Pruritus without skin changes and bile acid levels ≥19 µmol/L are diagnostic of ICP. Treatment is symptomatic, ursodeoxycholic acid has not been shown to be effective and should not routinely be prescribed unless BA ≥40 µmol/L
- Adverse outcomes are more common with bile acids over 100 µmol/L and bile acid levels should be monitored routinely to aid decisions about timing of delivery

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**Abbreviations**

| **ANC** | **Antenatal Clinic** |
|---|---|
| BA | Bile Acids |
| CTG | Cardiotocograph |
| COCP | Combined oral contraceptive pill |
| DAU | Day Assessment Unit |
| HELLP | Haemolysis, elevated liver, low platelets |
| ICP | Intrahepatic Cholestasis of Pregnancy |
| LFT | Liver functions tests |
| MAC | Maternity Assessment Centre |
| OC | Obstetric cholestasis |
| UDCA | Ursodeoxycholic acid |
| USS | Ultrasound scan |

# 1. Introduction

Intrahepatic cholestasis of pregnancy (ICP), also known as obstetric cholestasis (OC) is a liver disorder of pregnancy characterised by pruritus in the absence of a skin rash with abnormal liver function tests (LFT), neither of which has an alternative cause and both of which resolve after birth.[1]

The pathogenesis of ICP is multifactorial, with genetic, hormonal and environmental factors playing important roles.

Prevalence of ICP

- Affects 0.7% of pregnancies in multi-ethnic populations in the UK.[1]
- Affects 1.2 - 1.5% of women of Indian–Asian or Pakistani–Asian ethnicity, 2.4% of South American ethnicity.[1]
- It is more common in multiple pregnancies.[1]
- Reoccurs in 45-90% of affected women.[1]

# 2. Physiology of cholestasis

Although the exact aetiology of ICP remains unknown, there is a relationship between the retention of bile acids and skin irritation. It is thought that the high levels of oestrogen metabolites trigger ICP in genetically susceptible women, leading to cholestasis. An accumulation of bile acids occurs in the liver, spilling into the bloodstream.

# 3. Clinical importance

The importance of diagnosing the condition relates to the associated increase in maternal morbidity, perinatal morbidity and mortality. The severity of maternal symptoms and the degree of abnormality of liver function tests do not directly correlate with obstetric outcome.

However, there is increasing evidence that bile acid levels >100 µmol/L at any time during pregnancy are associated with significantly increased fetal complication rates.[2]

## 3.1 Fetal risks

- **Stillbirth**: recent research shows that stillbirth is only increased in women with peak bile acids >100 µmol/L[1,2] but remains the same as the background population until 38-39 weeks' gestation if peak BA remains <100 µmol/L (0.13% for BA <40 µmol/L, 0.28% for BA 40-99 µmol/L but increases to 3.44% for BA >100 µmol/L)[2,3]. The presence of additional risk factors and comorbidities during pregnancy also increase the stillbirth risk and should be taken into consideration when determining timing of delivery.

- **Premature labour**: spontaneous or iatrogenic, secondary to planned earlier delivery (6.7% in women with BA <40 µmol/L, 8.9 % in those with BA 40-99 µmol/L and 16.5% for women with BA >100 µmol/L)[2]
- **Meconium-stained liquor** (OR 2·60 [95% CI 1·62–4·16])[2]
- **Neonatal unit admission** (OR 1.47 [1.03-2.10])[2]

### 3.2 Maternal risks

- Intense pruritus leading to sleep deprivation[1]
- Higher risk of developing pre-eclampsia or gestational diabetes[1]
- Postpartum haemorrhage due to malabsorption of vitamin K has been reported but is rare
- Increased incidence of gallstones after delivery
- Recurrence in future pregnancy

## 4. Clinical features

### 4.1 History

Good history-taking should explore the presence of risk factors

| Risk factors of Intrahepatic cholestasis of pegnancy[1,4] |
|---|
| Previous intrahepatic cholestasis of pregnancy (ICP) |
| Family history- 1st degree relative affected with ICP |
| Hepatitis C carrier or Gallstones (defined as prior cholecystectomy or ultrasound-verified gallstones) |
| Multiple pregnancy |
| IVF pregnancy |
| Asian, North European and South American ethnicity |

Also ask about history of:

- Pre-existing factors for liver disease
- Presence of risk factors for viral hepatitis, e.g. travel abroad
- Drug and alcohol intake
- Previous problems with combined oral contraceptive pills (COCP), further explained in Section 9.
- Exclusion of allergies, eczema, psoriasis and scabies involving a dermatologist if necessary.

### 4.2 Symptoms

- Pruritus that can be severe. Classically it develops on the soles of the feet and palms of the hands, and spreads to the trunk and limbs.
- Not associated with rash, excoriations may be present. The skin should be inspected to differentiate scratching lesions from other skin disorders such as eczema and pruritic eruption of pregnancy.
- Occurs mostly in the third trimester (80% after 30 weeks) but it can start in the second and, rarely, in the first trimester.
- It may be associated with jaundice, pale stools, dark urine, steatorrhoea and anorexia, but this is very rare.
- Right upper quadrant pain.

## 5. Diagnosis

ICP should be considered as the diagnosis in pregnant women who present with pruritus, no skin changes & peak bile acids ≥ 19 µmol/L[1].

Abnormal liver function tests such as alanine transaminase (ALT) or aspartate transaminase (AST) are not associated with adverse pregnancy outcomes.[2] Therefore, a diagnosis of ICP requires elevated bile acids and a diagnosis should not be made in pregnant patients with pruritus and isolated elevated LFT's but normal bile acid levels.[1]

For those with significantly isolated raised alanine transaminase (ALT) or aspartate transaminase (AST) or complex ICP, management should be individualised.

| Diagnosis | Clinical features |
|---|---|
| Gestational pruritus | Pruritus and peak Bile acids < 19 µmol/L |
| Mild ICP | Pruritus and peak Bile acids 19-39 µmol/L |
| Moderate ICP | Pruritus and peak Bile acids 40-99 µmol/L |
| Severe ICP | Pruritus and peak Bile acids ≥100 µmol/L |

Peak bile acid levels are associated with the stillbirth risk[1], although bile acid concentrations are not associated with the intensity of pruritus.

## 6. Investigations

Initial investigations for a woman who presents with itching without an associated rash should include Liver function tests (LFT's) and non-fasting serum bile acid levels taken as soon as is convenient to do so. A second bile acid measurement should be taken 1 week later and if bile acid levels remain raised this supports the diagnosis[2].

Routine investigations are no longer recommended to rule out other causes of the clinical picture of ICP, especially in cases of mild ICP (BA ≤39 µmol/L).[1] However, further investigations should be considered in pregnant women with an atypical or uncertain picture of ICP. These may include pregnant women with early onset of ICP or markedly elevated liver enzymes e.g. ALT >100 U/L who should be reviewed in WPH MAC/FPH DAU to rule out other causes of abnormal liver enzymes.

- A viral screen for hepatitis A, B, C, Epstein Barr and cytomegalovirus,
- A liver autoimmune screen for chronic active hepatitis and primary biliary cirrhosis (i.e. anti-smooth muscle and anti-mitochondrial antibodies),
- Upper abdominal ultrasound to exclude other causes such as gallstones,
- Serum amylase to rule out pancreatitis,
- FBC, Coagulation screen to help rule out acute fatty liver of pregnancy[5].

**Further investigations when itching persists but blood results are normal i.e. Gestational pruritus:**

- Repeat liver function tests and bile acids levels.
- These investigations should be repeated **every week** until they either become abnormal or the patient delivers due to the possibility of peak BA rising above 100 µmol/L.

Pruritus in pregnancy is common, affecting 23% of pregnancies, of which a small proportion will have obstetric cholestasis. Women who present with classical pruritus on the soles of the feet and palms of the hands may not have biochemical evidence of ICP. They are more likely to develop abnormal liver function and a diagnosis of ICP at a later stage[4].

Pre-eclampsia, HELLP syndrome and acute fatty liver of pregnancy are pregnancy specific causes of abnormal LFTs that might form part of the differential diagnosis in atypical or early cases and should be excluded.

## 7. Management of confirmed ICP

If there is a confirmed diagnosis, the woman should be referred to the ANC for review within 2 weeks of diagnosis.

Peak BA levels should be used to determine management of women with ICP, even if BA levels normalise later during pregnancy.

Consider earlier review in WPH MAC/FPH DAU if the woman is ≥ 34 weeks' pregnant with peak BA ≥100 µmol/L and/or ALT >100 U/L to discuss birth planning.

If peak BA ≥40 µmol/L at the time of diagnosis (i.e. moderate to severe ICP), refer these women to WPH MAC/FPH DAU for discussion with an obstetrician to offer Ursodeoxycholic acid.

Any woman with BA ≥40 µmol/L or who is more complex should be referred to the maternal medicine MDT for review.

Additional follow-up in the Day Assessment Unit (DAU) should be arranged as detailed below.

**Information to women**

- Explain the diagnosis carefully
- **Advise the woman to monitor the fetal movements and to contact the hospital with any concerns or changes in the pattern of the movements immediately.**
- Offer information leaflet (RCOG/British Liver Trust patient information leaflets)[11]

https://www.rcog.org.uk/for-the-public/browse-our-patient-information/intrahepatic-cholestasis-of-pregnancy/

www.britishlivertrust.org.uk

https://www.icpsupport.org

## 7.1 Fetal Surveillance

No specific antenatal fetal monitoring modality for the prediction of fetal death can be recommended (RCOG). However, the protocol for fetal surveillance should include:

- CTGs in MAC/DAU as required for women with reduced fetal movements or anxiety.
- Symphysis fundal height measurement (USS should be used for the usual obstetric indications or if there are concerns about reduced fetal movements).
- As above, reiterate to the woman the importance of contacting the hospital immediately if she has any concerns regarding fetal movements.
- Fetal death is usually sudden. There is no evidence of placental insufficiency. Fetal growth restriction and oligohydramnios are not features of ICP.
- CTG's and USS are not reliable methods for preventing fetal death in ICP,[1] (unless there are other risk factors present and ultrasound scanning will be of benefit).

## 7.2 Maternal Surveillance

Weekly monitoring has previously been recommended for surveillance of ICP. New guideline suggests monitoring based on severity of ICP:

- **Mild ICP**- Weekly testing until 38 weeks' gestation to inform timing of delivery
- **Moderate ICP**- Weekly testing should be considered especially if approaching 35 weeks' gestation as timing of birth may be affected if BA levels rise ≥ 100 µmol/L
- **Severe ICP**- Routine testing/retesting of bile acids may not be required as it may not impact timing of delivery

| Maternal ICP surveillance |
| --- |

| Maternal ICP surveillance |
| --- |
| Blood tests: LFT, Bile acids |
| Blood pressure monitoring & urinalysis to screen for pre-eclampsia |
| Gestational diabetes screening should be as per national recommendations |

## 7.3 Treatment options for ICP

- **Topical emollients**

  Options include menthol in aqueous cream 1%, Calamine lotion, Diprobase, Balneum® and Aloe vera gel. All of these products are available to purchase over the counter (OTC). These can be kept cool in the fridge to increase relief from itch. (Please note that Aloe vera gel is not a prescribable item and Menthol in aqueous cream 1% is non formulary and should not be prescribed on an FP10)

- **Antihistamines**

Chorphenamine - 4mg (Max QDS Daily) or Promethazine - 25mg at night. Other antihistamine agents such as Loratidine & Cetirizine have been used safely in pregnancy for other indications and don't have sedative effects

- **Ursodeoxycholic Acid (UDCA):**

The PITCHES trial randomised UDCA vs placebo and results showed that UDCA does not reduce serious adverse outcomes for babies. There is a small reduction in ALT in women using UDCA which is of uncertain clinical significance but no reduction in bile acids and no clinically meaningful reduction in maternal itching.[4]

However, more recent evidence does show a reduction in late preterm birth in women with BA above 40 µmol/L.[3] It is therefore suggested that UDCA should be considered for these women with disease onset before 37 weeks' gestation, following discussion with the woman about the limitations of the evidence currently available[3].

- **Vitamin K**

Routine Vitamin K use is not indicated for the majority of women with ICP. If there is evidence of reduced fat absorption e.g. steatorrhoea or prolonged prothrombin time then treatment with water soluble vitamin K (Menadiol sodium phosphate 10mg daily) is indicated. This should only be prescribed after careful counselling about the likely benefits but small theoretical risk of neonatal haemolytic anaemia, hyperbilirubinaemia and kernicterus.[1] Clotting studies should be repeated if the BA are above 100 µmol/L with worsening LFT.

**General advice**

- Provide emotional and psychological support.

- Advise women to keep cool whenever possible.
- Advise frequent cool baths/showers
- Advise wearing loose cotton clothing
- Advise women to have short nails to avoid scratching the skin.
- Use a baby's hairbrush to alleviate itchiness as bristles are gentler.

## 8. Timing of birth

Stillbirths in women with ICP have been reported at all gestations.

The risks of prematurity must be balanced against the fetal risk of continuing the pregnancy. Therefore, timing of delivery should be decided with the woman after careful consideration of risks and benefits.

The peak bile acid levels as well as the presence of additional risk factors and comorbidities should determine timing of delivery.

| Severity of ICP | Timing of delivery |
|---|---|
| Mild ICP: peak BA ≤ 39 µmol/L | 40 weeks' gestation |
| Moderate ICP: peak BA ≤99 µmol/L | 38-39 weeks' gestation |
| Severe ICP: peak BA ≥100 µmol/L | 35-36 weeks' gestation |

Mode of delivery should be based on usual obstetric indications and a caesarean section should only be considered if there are other indications.

Consider antenatal steroids for fetal lung maturity for women undergoing a planned caesarean section before 35 weeks' gestation. There should be an informed discussion with the woman about the potential risks and benefits such as the risk of neonatal hypoglycaemia against the short-term respiratory benefits.[3,6,7]

### Intrapartum care

- Offer continuous EFM on the labour ward for women with severe ICP or in the presence of additional risk factors for women with mild or moderate ICP.
- IV access- take blood for FBC, LFT and clotting studies, group and save serum
- Active management of 3rd stage of labour is advised
- Vitamin K 1 mg (IM) (or calculated appropriate dose if preterm/low birth weight) to neonates immediately after birth for prevention of haemorrhagic disease of the newborn.

## 9. Postnatal Care

- Stop all treatment (Vitamin K, antihistamines etc.). Cessation of symptoms confirms the diagnosis of ICP and is usually immediate but may take up to two weeks or longer in some cases.
- For uncomplicated ICP, LFTs should not be measured until at least 4 weeks after delivery to allow levels to return to normal limits[1]. This information including the diagnosis should be included on the postnatal discharge summary to the GP.
- Physician review at six weeks postpartum if any biochemical abnormalities persist. To be organised by the GP.
- The combined oral contraceptive pill (COCP) can be used by women with a history of ICP according to UKMEC guidance, provided there is no history of contraception related cholestasis[1].
- There is emerging evidence of increased risk of liver disease and maternal diabetes following a diagnosis of ICP.[4]

## Auditable standards

1. The diagnosis is informed by appropriate investigations.
2. Consultant led care once the diagnosis is made.
3. Continuous EFM in labour.

## References


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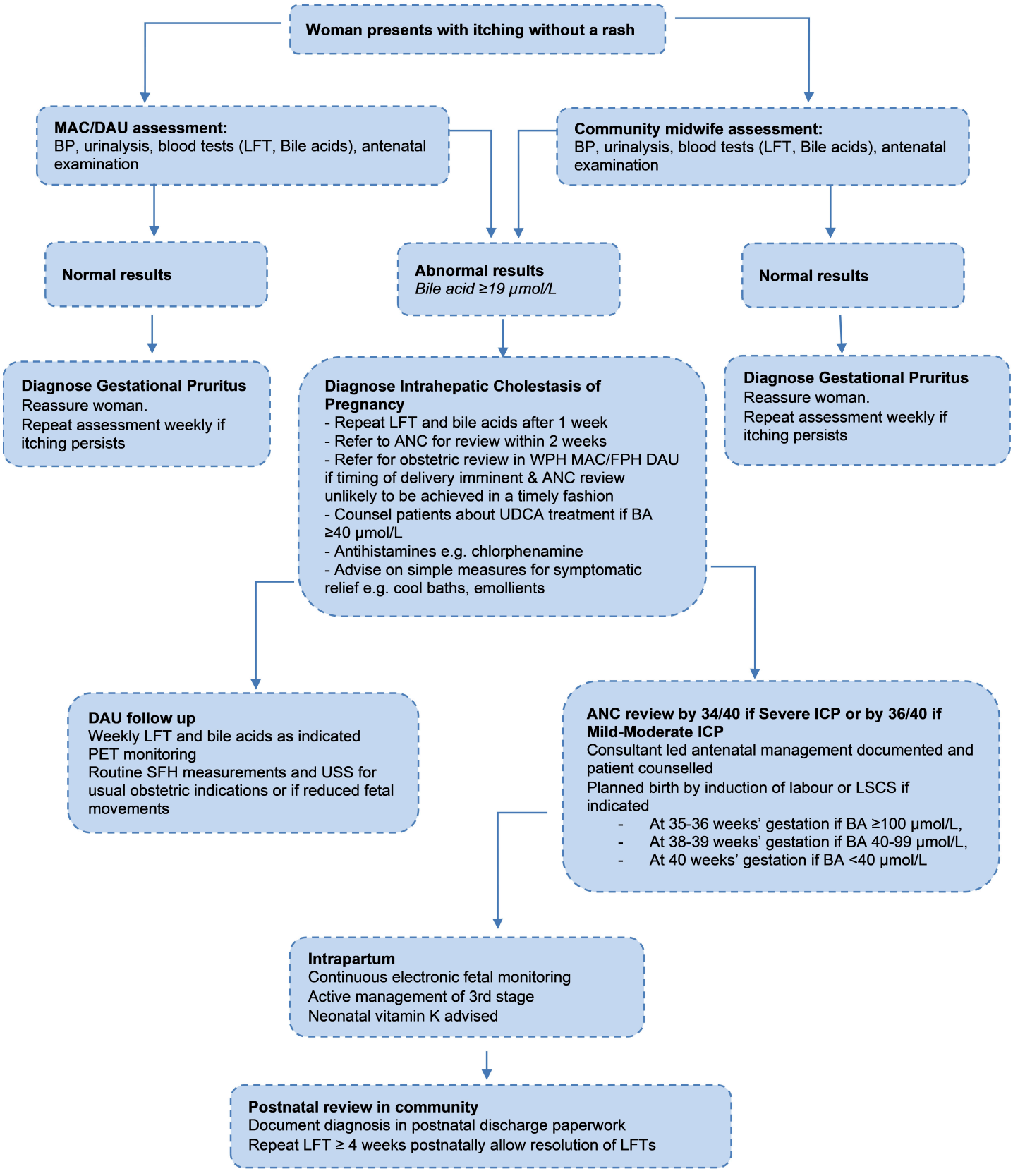
# Appendix 1. Intrahepatic Cholestasis of Pregnancy – Antenatal, Intrapartum and Postnatal Management Care




# Appendix 2

Epic smart text message to patients

*Date: ****

*Dear ***,*

*I am writing to inform you that we have had the results from your blood tests taken on ***. The result shows raised bile acids which are ****

*This can indicate a condition called intrahepatic cholestasis of pregnancy. Please click this link for a patient information leaflet from RCOG. Intrahepatic cholestasis of pregnancy | RCOG*

*These results will mean that we will continue to monitor your bloods for the rest of the pregnancy every week. You will be referred to antenatal clinic for a review by a consultant unless you have been told otherwise (sometimes it may be necessary to*

*review you in the Maternity Assessment Centre (Wexham Park) or Day Assessment Unit (Frimley Park)*

*We would like to take some more blood tests. An appointment has been arranged for *** in our day assessment unit, where we will listen to the baby's heartbeat, check your blood pressure and vital signs, check your urine sample and take more blood tests to identify any changes.*

*As always, if you have any concerns with your baby's movements, please call MAMAS line as soon as you are concerned, on 0300 013 2004.*

*If you wish to discuss this further, please contact us - we are open 24hours a day 7 days a week.*

*If you are booked at Frimley Park Hospital it will be Day Assessment Unit– telephone 0300 613 4527*

*or*

*If you are booked at Wexham Park Hospital it will be at the Maternity Assessment Centre. Telephone 0300 615 452*

*Please do not reply to this message through your app as there may be delays in receiving any reply. If you have any questions or concerns, please do not hesitate to contact the MAMAs line on 0300 013 2004.*

*Yours sincerely*

*Midwife*

*Maternity in Frimley Health NHS Trust*

## Full version control record

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| Guidelines Lead(s): | O. Eniola (Consultant Obstetrician WPH), A. Adekunle (Specialty Registrar WPH) |
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This guideline is for use in Frimley Health Trust hospitals only. Any use outside this location will not be supported by the Trust and will be at the risk of the individual using it.

**Version History**

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|---|---|---|---|---|
| 1.0 | September 2016 | S. Islam (Locum Consultant Obstetrician WPH), O. Eniola (Consultant Obstetrician WPH). | Final | First cross site version |
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