Top Ten

things to know about intrahepatic cholestasis of pregnancy (ICP)

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In the UK around 5,000 women per year will be diagnosed with a condition called intrahepatic cholestasis of pregnancy (ICP). ICP was first described in 1883 by Ahlfeld, who wrote about a pregnant woman with jaundice that resolved after the birth of her baby (Thorling 1955). Since 1883, the emphasis has changed from jaundice to that of pruritus (itching) due to the work of Thorling (1955) and Svanborg (1954) in the 1950s; however researchers are still challenged to fully understand this complex condition. Although studies have identified genetic variants that make some women susceptible to ICP, and suggest that bile acids play a key role in the risk to the fetus, there are still no clear guidelines on how to treat and manage the condition. This is because of a lack of agreement on the precise nature of the risk to the fetus, which is partly due to a lack of consensus on the biochemical tests used to diagnose ICP. There is also limited evidence to prove the mechanisms by which complications occur. It is of little surprise that many health professionals are often left debating how best to recognise, investigate and support women whose pregnancies are affected by ICP. However, what we do know is that the increased risk of stillbirth in pregnancies affected by ICP, referred to in the literature, means that it is a condition that should be taken very seriously.

1 Definition

ICP is also known as obstetric cholestasis (OC). It is a pregnancy-specific liver condition which is characterised by raised levels of bile acids in the mother's blood and pruritus (itching). Cholestasis means sluggish or interrupted bile flow.

2 Symptoms

Pruritus, defined as an unpleasant sensation that evokes the desire to scratch, (Geenes & Williamson 2009) is the most common presenting symptom of ICP. It can vary in intensity, from one woman's description '*like a tingle under the skin*' to another's '*like an army of ants underneath my skin*'. It tends to affect the palms of the hands and the soles of the feet, but it can present anywhere on the body. It is often more intense at night, and may disturb the woman's sleep. Other symptoms may include dark urine, steatorrhea (pale stools) and, in less than 20% of women, jaundice (Lunzer 1989). Some women also tend to feel generally unwell with a loss of appetite.

3 Investigating

Approximately 80% of affected women will be diagnosed after 30 weeks of gestation (Reyes 1992, Kenyon *et al* 2002), but there are reports of diagnosis as early as eight weeks (Berg *et al* 1986). The diagnosis of ICP is made by excluding and investigating other causes of liver impairment or pruritus. Blood tests should therefore include liver function, bile acids, anti-mitochondrial and anti-smooth muscle antibodies, hepatitis B and C serology. It is not uncommon for bile acid levels to rise before liver function results become abnormal (Geenes & Williamson 2009) and recent research has focused on bile acids being the contributing factor to the risk to the fetus. Glantz *et al* (2004) report that the risk of adverse fetal outcomes is increased with maternal bile acid levels greater than 40µmol/l (fasting sample). A recent UK study that included >700 pregnant women with severe ICP (bile acids >40µmol/L) confirmed this risk, which in this study also included stillbirths (seven of 10 stillbirths in ICP cases were associated with co-existing pregnancy complications) (Geenes *et al* 2013). Although researchers are yet to fully understand how bile acids put the unborn baby at risk, there is some research from laboratory experiments using human and rodent heart cells that suggests that they may cause fetal heart cells to develop cardiac arrhythmia (Williamson *et al* 2001, Abdul Kadir *et al* 2013, Miragoli *et al* 2011). Miragoli also showed that the drug ursodeoxycholic acid (UDCA) protects against bile acid-induced arrhythmia in rats (Miragoli *et al* 2011).

4 Causes

The aetiology of the condition is yet to be fully understood but researchers speculate that genetics, hormones and the environment all play a part. ICP has been identified in several female family members, which suggests a genetic link and to date several genetic variants have been identified (Dixon & Williamson 2008, Dixon *et al* 2009). ICP only manifests in pregnancy and it is more common in multiple than singleton pregnancies (Gonzalez *et al* 1989), which suggests that hormones may be a contributory factor. Some studies have suggested that the environment plays a role; some women with ICP have lower levels of selenium (Reyes *et al* 2000), higher rates of hepatitis C infection (Marschall *et al* 2013) and drug sensitivities (Johnston & Baskett 1979). Furthermore, there is marked seasonal variation, with more cases reported cases in winter months in Scandinavia and Chile (Geenes & Williamson 2009).

5 Risks

There is little morbidity for the woman although there may be an increased risk of postpartum haemorrhage (PPH) (Kenyon *et al* 2002) in women with steatorrhoea, due to malabsoprtion of fat soluble vitamin K. However, there are no studies to date that can quantify either the incidence or risk of haemorrhage, but anecdotally the risk is thought to be low (less than 20%). Some clinicians may prescribe oral vitamin K in an attempt to further reduce the risk of PPH (Geenes & Williamson 2009).

There is considerable debate about the risk to the unborn baby. ICP has been linked to an increased risk of fetal distress, premature labour (spontaneous and iatrogenic), meconium staining and, in severe cases, stillbirth (Geenes *et al* 2013). It is interesting to note that there is no consistency of data on fetal risk and Wikström Shemer *et al* (2013) attribute this in part to the unclear diagnostic criteria for ICP. Wikström Shemer *et al* (2013) suspect that this may also be attributed to common, albeit unproven, changes in the management of ICP in the last 20 years, which Geenes and Williamson (2009) refer to as 'active management'.

6 Management

The most effective treatment has yet to be established, but a number of strategies are used, those that Geenes and Williamson (2009) refer to as 'active management'. Active management may include regular blood tests (liver function and bile acids), the use of UDCA (Glantz *et al* 2005), the use of cardiotocograph (CTG) monitoring (although it should be noted that there is no evidence to suggest that it can identify an 'at risk' baby but it may offer reassurance) and induction of labour at 37-38 weeks' gestation (although this may be earlier depending on the mother's blood results and/or any concerns for the baby). One of the most recent cohort studies concluded that there is an increased concern of moderate prematurity, but no increased risk of stillbirth in ICP pregnancies, when active management is followed (Wikström Shemer *et al* 2013).

7 Physical impact

Recent findings from the Pregnancy Intervention Trial in Cholestasis (PITCH) showed that UDCA does reduce the sensation of the itch for some women (32% or 14 out of 44) (Chappell *et al* 2012). Some will also find relief with the use of aqueous cream with menthol and/or antihistamines. The use of antihistamines has never been fully evaluated and they are often prescribed as they may help the woman to sleep. There is no evidence to suggest that they can help with the itch. It is also important to acknowledge that is not uncommon for a woman to describe feeling very unwell in an ICP pregnancy.

8 Emotional impact

The psychological impact of being affected by this complex condition should never be underestimated and the woman (and her partner too) may need some additional support. There are a number of contributing factors to the emotional strain of suffering with ICP: heightened anxiety because of the increased risk of stillbirth, together with additional monitoring of the pregnancy, and/or, the intensity of the pruritus on top of sleep deprivation caused by the itch being even more intense at night. The constant scratching and lack of sleep can lead to a woman with ICP feeling completely exhausted and anecdotal evidence shows a link to antenatal depression.

How can the midwife offer emotional support? Perhaps just taking a little more time to listen to the woman and her partner is all that is needed. It may also be helpful for the professional to be aware of ICP Support as a charity to signpost women to. The charity provides research and evidence-based information, in addition to support via online forums and a phone service (www.icpsupport.org).

9 After ICP for the mother

It is important for liver function and bile acids to be checked around 6-12 weeks after the baby's birth. Women are generally advised to avoid hormonal contraception as the theory is that it may cause them to become cholestatic again or to itch. There have been no trials to investigate this theory but women developing pruritus on the oral contraceptive pill has been reported (Williamson *et al* 2004). For future pregnancies, recurrence has been quoted as being more than 60% (Mays 2010), although it is thought to be less than this following a multiple pregnancy (Geenes & Williamson 2009).

10 After ICP for the baby

There are limited data available regarding the long-term effects of ICP for the baby, but recent research (a mouse study and analysis of a human cohort) has suggested that offspring born to ICP mothers may have an increased risk of obesity, abnormal lipid profiles and type 2 diabetes (Papacleovoulou *et al* 2013).

Conclusion

We have attempted to select the 'top ten things you need to know about ICP', but we recognise that there are many other aspects of this complex condition that warrant further exploration. For example, a whole article could have been dedicated to just the symptom of 'itch' because of how variable it can be whilst not being a true indicator of the severity of the condition (or indeed a reflection of how high the woman's bile acids are).

We also hope this article has emphasised how important further research will be in helping health professionals support and provide choices for women with ICP. Research has identified some of the genetic variants that are linked to susceptibility to ICP but more work is needed in this area to identify further variants. New treatments need to be identified to help both with itch and improving biochemical results as it is clear that the current choice, UDCA does not work for all women.

So this leaves clinicians with a condition that is both challenging and frustrating to provide support for, with no easy way to reassure women that all is well in their pregnancy. As a charity our 'take home message' based on expert opinion would therefore be that all women experiencing ICP should be offered active management (Geenes & Williamson 2009) until researchers can identify the exact mechanisms for fetal death and further, identify how to prevent stillbirth.

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