Clinical outcome in a series of cases of obstetric cholestasis identified via a patient support group

Catherine Williamson,a,b Laura M. Hems,a Dimitrios G. Goulis,a Ian Walker,c Jennifer Chambers,a Oscar Donaldson,a Michael de Swiet,b Desmond G. Johnstona

Objective To explore the clinical features of obstetric cholestasis pregnancies in UK white Caucasians.

Design A questionnaire survey.

Setting Study coordinated at Queen Charlotte’s Hospital.

Population Clinical features of 352 affected pregnancies in 227 Caucasian women identified via a patient support group.

Methods Evaluation of the gestation at which prematurity and intrauterine death occur, and recording of additional clinical features in pregnancies complicated by obstetric cholestasis.

Main outcome measures The timing of pregnancies complicated by intrauterine death and prematurity.

Results Among the affected pregnancies, 23 (7%) were complicated by intrauterine death (20 singletons and 3 twins) and 133 (38%) were delivered prematurely (56 spontaneous and 77 iatrogenic). Eighteen of the 20 singleton intrauterine deaths occurred after 37 weeks. All three intrauterine deaths in twin pregnancies occurred before 37 weeks. Pruritus started earlier in pregnancies complicated by spontaneous prematurity, but not in those complicated by intrauterine death.

Conclusions Intrauterine death in singleton pregnancies complicated by obstetric cholestasis death mainly occurs after 37 weeks. The gestation at which pruritus is first reported may help to predict spontaneous prematurity.

INTRODUCTION

Obstetric cholestasis is a disease of pregnancy that causes maternal pruritus and liver impairment, and which can be complicated by fetal distress, spontaneous preterm labour and sudden intrauterine death.1–4 It affects 0.6% of pregnancies in UK white Caucasians5 and double this proportion of Indian and Pakistani Asians.5,6 As there are approximately 700,000 deliveries in the UK annually, it can be assumed that there will be 4000 cases of obstetric cholestasis. The diagnosis is confirmed by the demonstration of raised liver transaminase and serum bile acid levels.7,8

Reported perinatal mortality fell from 9.2–11% in older studies1,2 to 2.0–3.5% in more recent series,6–4 perhaps because most women were delivered by 38 weeks of gestation. There were no intrauterine deaths in two recent series, each of approximately 80 women.6,9 However, in most old and recent series, approximately 50% of obstetric cholestasis pregnancies were complicated by fetal distress, defined as fetal heart rate abnormality or meconium-stained amniotic fluid,2–4 and this has not changed despite early delivery. Spontaneous preterm delivery (<37 weeks of gestation) has been quoted as affecting 7% of pregnancies in a recent UK series,6 and 12–44% in studies from Chile and Australia.1,3,4 Placental histology shows non-specific changes consistent with hypoxia, but it cannot be established whether the hypoxia is primary or secondary.11

The aetiology of the fetal complications is poorly understood. The intrauterine deaths are thought to occur suddenly, as there is no evidence of preceding intrauterine growth restriction or uteroplacental insufficiency and the fetal autopsy is normal.3,10 Placental histology shows non-specific changes consistent with hypoxia, but it cannot be established whether the hypoxia is primary or secondary.11

At present, it is not possible to predict which pregnancies are at risk of the fetal complications of obstetric cholestasis. Some studies have demonstrated an abnormal fetal heart rate (≤100 or ≥180 bpm).1,12,13 However, cardiotocograph monitoring is not always helpful and intrauterine deaths have been reported in pregnancies with normal cardiotocographs in the preceding 24 hours.3,5,14,15 It has also not been established whether the absolute levels of maternal total serum bile acids or the severity of maternal symptoms can be used to predict an adverse pregnancy outcome in obstetric cholestasis12,16,17 or whether treatment can reduce the risk of the fetal complications.

There have been no large studies of the clinical features of obstetric cholestasis pregnancies complicated by, for example, intrauterine death or spontaneous prematurity. The women with obstetric cholestasis in the present study were recruited through a patient organisation, and it is therefore likely that the series was ‘enriched’ with pregnancies where such complications occurred. However, this was the only practical way to obtain such a large series of obstetric cholestasis pregnancies complicated by intrauterine death and prematurity and it has allowed the features of these clinically important complications to be studied in a large number of cases. Previous studies have been of mixed, or of non-Caucasian, ethnic groups and this is the first study of solely Caucasian women with obstetric cholestasis.

METHODS

Women with obstetric cholestasis were identified via the UK Obstetric Cholestasis Patient Organisation (OCPO) and were invited to participate in a study of the genetic aetiology of obstetric cholestasis. Index cases were mailed a questionnaire to ascertain details of their symptoms, their pedigree and whether they were willing to participate. Returned questionnaires were reviewed to confirm the diagnosis, using the criteria of pruritus and raised serum bile acids and/or raised serum transaminases in at least one pregnancy. As hospitals have different normal ranges for liver transaminase levels, the upper end of the normal range in pregnancy was assumed to be 80% of the level quoted outside pregnancy at the local hospital for each case, consistent with published studies, and any values above this were considered to be abnormal. For some women who fulfilled the diagnostic criteria in a later pregnancy, some previous pregnancies had been complicated by pruritus, but biochemical confirmation had not been obtained. These prior pregnancies were included as affected pregnancies providing the diagnosis had been confirmed in the subsequent pregnancy. Further details were obtained by telephone. Women were asked at what gestational week the different features of the condition occurred. In most cases, this was given as total weeks. If a woman also quoted the number of days (e.g. 35 weeks and 4 days gestation), the figure was rounded down to the number of completed weeks. Women were also asked whether they had experienced pruritus with exogenous oestrogens and whether they had cyclical pruritus or a history of gallstones.

As almost all of the women who had contacted the OCPO were white Caucasians, it was decided to limit the study to this ethnic group.

The gestation at delivery was recorded for all pregnancies that progressed past 24 weeks of gestation. Deliveries less than or equal to 36 weeks and 6 days gestation were divided into spontaneous and iatrogenic premature deliveries. The latter included those that were induced and those delivered by elective caesarean section. The gestational week at which any intrauterine deaths occurred, the sex of the fetus and any treatment given were recorded. Meconium-stained amniotic fluid or cardiotocograph abnormalities were not recorded because accurate information could not be obtained without access to the hospital notes, but information on infant admission to the neonatal intensive care unit (ICU) was collected as an indicator of the condition of the child at birth.

The number of twin pregnancies and the frequency of clinically apparent gallstones were also determined.

Local research ethics committee approval had been granted for this study, and all subjects who participated in the study did so voluntarily having given their informed consent.

The Mann–Whitney U test was used to identify differences in the values between two groups, whereas the Kruskal–Wallis H test was used for more than two groups. The χ² test 2 × 2 was used to compare proportions and replaced by Fischer’s exact test when there were small sample sizes. Statistical analysis of the data was performed using SPPS for Windows, release 10.0, SPSS, Chicago, Illinois.

RESULTS

Details of the 227 women with obstetric cholestasis are given in Fig. 1.

Twenty-three (7%) obstetric cholestasis pregnancies were complicated by an intrauterine death; 20 were in singleton and 3 were in twin pregnancies. The median gestation at which intrauterine death occurred was 38 weeks (IQR 2.5) (Fig. 2). Of the intrauterine deaths in this group, 13 of the fetuses were...
female and 7 were male. There was an additional female intrauterine death delivered at 26 weeks of gestation, but this pregnancy was not complicated by pruritus (i.e. not defined as being affected by obstetric cholestasis).

This gender difference in singleton pregnancies complicated by intrauterine death (female preponderance) compared with the gender in other obstetric cholestasis pregnancies ($\chi^2, P = 0.16$) was not statistically significant. The median gestational week at which intrauterine death occurred in singleton pregnancies was 38 for females and 39 for males.

Three of the intrauterine deaths occurred in twin pregnancies (i.e. 3 of the 17 [18%] twin pregnancies in women with obstetric cholestasis). Two female intrauterine deaths occurred in a male plus female twin and a female plus female twin at 35 weeks and 31 weeks of gestation, respectively. One male intrauterine death occurred in a male plus male twin pregnancy at 36 weeks of gestation.

If all intrauterine deaths are considered, 22% occurred before 37 weeks of gestation. However, only 10% (2/20) of singleton intrauterine deaths occurred before 37 weeks of gestation, and the fetus in both cases was female.

There were no significant differences in gestational week for the onset of pruritus in obstetric cholestasis pregnancies complicated by an intrauterine death when compared with other obstetric cholestasis pregnancies.

A clinical diagnosis of obstetric cholestasis had been made in two of the pregnancies before they were complicated by intrauterine death. One woman was told that the condition is not associated with intrauterine death and that treatment is not necessary. The other was treated with cholestyramine for cholestasis and the pregnancy was otherwise managed expectantly. In the other 21 cases, the diagnosis of obstetric cholestasis was confirmed by retrospective review of blood specimens taken in the affected pregnancy and/or was made in subsequent pregnancies. Overall, in 14 of the obstetric cholestasis pregnancies complicated by intrauterine death reported in this manuscript, the diagnosis was confirmed by retrospective study of liver function tests from the affected pregnancy and in another case the bile acids were measured using a stored TORCH specimen from the time of the intrauterine death. In the remaining eight cases, the diagnosis of obstetric cholestasis was not confirmed from laboratory tests in the pregnancy that was complicated by intrauterine death, but the diagnosis was made in a subsequent pregnancy.

One hundred and thirty-three (38%) obstetric cholestasis pregnancies were delivered prematurely. There were 56 (16%) spontaneous premature deliveries, and the gestation at which spontaneous prematurity occurred is shown in

<table>
<thead>
<tr>
<th>Gestation pruritus started</th>
<th>Total no. cases</th>
<th>Spontaneous prematurity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25 weeks</td>
<td>91</td>
<td>20 (22%)</td>
</tr>
<tr>
<td>25.1–29 weeks</td>
<td>79</td>
<td>15 (19%)</td>
</tr>
<tr>
<td>29.1–33 weeks</td>
<td>111</td>
<td>18 (16%)</td>
</tr>
<tr>
<td>33.1–37 weeks</td>
<td>63</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>&gt;37.1 weeks</td>
<td>8</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td>352</td>
<td>56</td>
</tr>
</tbody>
</table>

Fig. 2. Gestational week at which intrauterine death occurred in singleton pregnancies complicated by obstetric cholestasis.

Fig. 3. Gestational week at which spontaneous prematurity occurred in pregnancies complicated by obstetric cholestasis.

Fig. 4. Gestational week at which pruritus started in obstetric cholestasis pregnancies complicated by spontaneous prematurity and in those in which there was no prematurity.
Fig. 3. The median gestation of the spontaneous premature deliveries in the obstetric cholestasis group was 34 weeks (IQR 3.6). There were 33 (55%) female and 27 (45%) male fetuses in the obstetric cholestasis spontaneous prematurity group. The pruritus started earlier in pregnancies complicated by spontaneous prematurity (median 28.0 weeks [IQR 6.8]) when compared with other obstetric cholestasis pregnancies (30.0 [IQR 7.0] weeks) (P < 0.001) (Fig. 4). Also, when all obstetric cholestasis pregnancies were considered, those in which pruritus started earlier were more likely to be complicated by spontaneous prematurity (χ², P = 0.04) (Table 1).

There were 77 (22%) iatrogenic premature deliveries in obstetric cholestasis women (i.e. 46 induced, 25 elective caesarean sections and 6 pre-labour emergency caesarean sections).

When analysing the number of pregnancies in which the infant was admitted to the neonatal ICU for more than three days, the 23 pregnancies complicated by intrauterine death were not considered. Therefore, of 329 affected obstetric cholestasis pregnancies, 64 (20%) infants were admitted to the neonatal ICU. When only premature deliveries (spontaneous and iatrogenic) were considered, 41% (53/128) of infants were admitted to the ICU. The proportion for spontaneous prematurity was 27/54 (50%) and for iatrogenic prematurity was 26/74 (35%).

Of the 131 women, 80 (61%) had obstetric cholestasis in all pregnancies and 51 (39%) did not. If a woman had obstetric cholestasis the previous pregnancy, her risk of having it in a subsequent pregnancy was 90%. The pruritus started at an earlier gestation in subsequent pregnancies (Kruskal–Wallis, P = 0.006) (Table 2).

Cyclical pruritus was present in 46 (20%) of women with obstetric cholestasis. Some women experienced pruritus at the time of ovulation (day 14), others just prior to or during the menses, supporting the role of oestrogen and progesterone in the pathogenesis of obstetric cholestasis.

Pruritus was experienced following the oral contraceptive pill in 30 (14%) of women with obstetric cholestasis. Cyclical pruritus occurred in combination with oral contraceptive-induced pruritus in 15 women. Therefore, 61 (27%) women with a history of obstetric cholestasis had either cyclical or oral contraceptive-induced pruritus.

In addition, 30 (13%) women with obstetric cholestasis had a history of gallstones; 21 had symptomatic gallstones and 9 had asymptomatic gallstones documented following ultrasound examination in pregnancy.

### DISCUSSION AND CONCLUSION

The data in this paper represent the largest collection of affected obstetric cholestasis pregnancies in the world literature. Specific features were demonstrated that will be of use to clinicians managing the condition; in particular, the findings that in singleton pregnancies intrauterine death mainly occurs from 37 weeks (although the intrauterine deaths in multiple pregnancies occur earlier); also the finding that the earlier in gestation at which pruritus is first reported, the higher the incidence of spontaneous prematurity.

The high prevalence of complications in the obstetric cholestasis group in this study probably results from ascertainment bias, as the women had self-referred to the OCPO. Therefore, this study does not claim to predict the frequency of intrauterine death or prematurity in the total obstetric cholestasis population. It does however allow features of the pregnancy complications of the condition to be studied.

The demonstration that the majority of the intrauterine deaths occur from 37 weeks of gestation is consistent with the largest previous series and should be of clinical value. Elective delivery at 37 weeks of gestation may prevent intrauterine death in affected singleton obstetric cholestasis pregnancies, particularly given that there have been no reliable methods reported for the prediction of fetuses at risk to date.

However, there are fetal risks from early delivery. A study of neonatal respiratory morbidity following elective caesarean section reported a higher incidence of respiratory distress syndrome and transient tachypnoea of the newborn in those that were delivered during the week 37–38 compared with 38–39 and a similar difference was seen when this was compared with the following week. Another study demonstrated that a markedly higher proportion of babies required ventilation for respiratory distress syndrome when delivered at an earlier gestation; that is, 1:37 (1.4%) at 35 weeks, compared with 1:557 (0.2%) at 37 weeks (and 1:1692 at 38 weeks). These risks are lower than the published rates of intrauterine death in obstetric cholestasis pregnancies that are not delivered by 38 weeks (i.e. 9–11%).

A diagnosis of obstetric cholestasis had only been made in two of the pregnancies complicated by intrauterine death in this study. If a diagnosis had been made in more cases, it is possible that treatment with ursodeoxycholic acid (UDCA) or dexamethasone, both of which improve symptoms and liver function tests including serum bile acid levels, could have reduced the risk of intrauterine death in these pregnancies. Animal studies have implicated bile acids in the pathophysiology of intrauterine death and spontaneous prematurity. If future prospective studies...
support the suggestion that bile acids cause the intraterine death in obstetric cholestasis, it may be justifiable to defer delivery to a later gestation than 37 weeks in women who have responded to treatment.

Three of the five intraterine deaths that occurred before 37 weeks of gestation were in twin pregnancies, suggesting that twin pregnancies may be at risk of intraterine death at an earlier gestation than singleton pregnancies. There was a non-significant tendency towards female fetuses in pregnancies complicated by intraterine death. The data on intraterine deaths in twin pregnancies and in female fetuses also did not reach statistical significance, and a much larger series would be required to assess a possible gender difference. A recent initiative is the establishment of a Web-based international registry of all obstetric cholestasis-related intraterine deaths (http://escuela.med.puc.cl/iris/welcome.html). This is called IRIS (International Registry of Intrahepatic Cholestasis of Pregnancy-related Stillbirth) and should permit prospective information from pregnancies complicated by intraterine death to be collected.

The rate of spontaneous prematurity in women with obstetric cholestasis (16%) was lower than in most other studies (36–44%), with the exception of one recent UK study. This may be because 22% (77/352) of obstetric cholestasis pregnancies in this present study had received treatment with either UDCA alone or in addition to dexamethasone. While it has not been proved that treatment reduces the rate of spontaneous prematurity, studies in animals and using myometrium from women with obstetric cholestasis have implicated raised serum bile acids in the aetiology of prematurity.

This study has demonstrated that the onset of pruritus occurs at a significantly earlier gestation in obstetric cholestasis pregnancies complicated by spontaneous preterm delivery when compared with unaffected obstetric cholestasis pregnancies. A Chilean study has also found a positive correlation between prematurity and earlier gestation at the onset of pruritus during pregnancy. If bile acids are the cause of the spontaneous prematurity, it is possible that the duration of exposure to bile acids may influence myometrial contractility or other processes that can initiate labour.

It was not possible to obtain accurate data about the rates of fetal distress in this study as most women did not know whether they had cardiotocograph abnormalities or fetal distress in their pregnancies. However, admission to the neonatal ICU was used as a surrogate marker of fetal distress, and the rates were high in obstetric cholestasis pregnancies. When the results were analysed further, the risk appears to be related more to preterm delivery than to obstetric cholestasis. It was beyond the scope of this study to assess the subsequent morbidity of the infants that were admitted to the neonatal ICU. However, given that elective delivery at 37 weeks is currently advocated as the best strategy for the prevention of intraterine death, a large prospective study of the outcome of such obstetric cholestasis pregnancies would allow the consequences of both iatrogenic and spontaneous preterm delivery to be evaluated.

The prevalence of oral contraceptive pill-induced pruritus was higher than in a smaller French study of 24 women diagnosed with obstetric cholestasis during their pregnancies in which only one (4%) suffered pruritus and abnormal liver function tests after taking the oral contraceptive pill. This may be because obstetric cholestasis in French women has a different aetiology, or because of the small number of cases in the study. These symptoms disappear once women stop taking the oral contraceptive pill. At present, there is no evidence that prolonged use of oral contraceptives in women with obstetric cholestasis can cause permanent liver damage. Given that 34% of women with cyclical pruritus also developed pruritus if they took oral contraceptives, these women may have a stronger genetic predisposition to obstetric cholestasis.

In summary, we have demonstrated that the majority of intraterine deaths occur from 37 weeks of gestation in singleton pregnancies. Intraterine deaths complicating twin pregnancies occur at an earlier date. The gestation at which the pruritus started did not allow prediction of pregnancies complicated by intraterine death, but did occur at an earlier gestation in pregnancies complicated by spontaneous prematurity.

Acknowledgements

This work was supported by a grant from the Wellcome Trust.

References


Accepted 27 February 2004