Aust NZ J Obstet Gynaecol
1988; 28: 172

Maternal Features of Obstetric Cholestasis: 20 Years Experience at King George V Hospital

Nicholas M. Fisk[1], FRACOG, MRCOG, DDU, William B. Bye[2], FRACP and G. N. Bruce Storey[3]*, FRACP

Departments of Obstetrics and Gynaecology[1], Gastroenterology[2] and Perinatal Medicine[3], King George V Memorial Hospital, Royal Prince Alfred Hospital, Sydney, New South Wales

Summary: Between 1965 and 1984, 139 pregnancies in 125 women were complicated by obstetric cholestasis (OC). Prevalence increased from 0.1% in the first 10-year period to 0.2% in the second ($p<0.001$), following recognition of the adverse fetal risks of this condition. Perinatal data from both series, 1965-1974 and 1975-1984 have previously been published. Mothers in the latter series were more likely to be of Anglosaxon than Mediterranean origin ($p<0.001$) and did not have underlying haemolytic conditions. Diagnostic criteria changed considerably over the 20 years, such that liver biopsy was no longer needed, gastroenterological consultation was sought less frequently ($p<0.001$) and newer diagnostic criteria of increased bile acids with negative hepatitis serology were increasingly employed. Biochemical data were broadly similar in the 2 groups. An understanding of the clinical and laboratory features of this disease facilitates early diagnosis, which is imperative if intensive fetal surveillance is to reduce the high stillbirth rate in OC.

Obstetric cholestasis (OC) refers to a condition of intrahepatic cholestasis which manifests in the latter half of pregnancy as pruritis with or without jaundice and resolves in the puerperium (1). Abnormal hepatic metabolism of oestrogens has been implicated in the aetiology as has a genetic predisposition (2). OC is characterized by marked geographical variation, occurring commonly in Chile and Scandinavia (3,4), occasionally in Australia and China (1,5) while rarely reported from other countries.

Although essentially benign from a maternal viewpoint, OC is associated with considerable fetal risks. High perinatal mortality rates as well as an increased frequency of meconium-stained liquor and intrapartum fetal distress were identified in a report from this hospital of cholestatic pregnancies between 1965-1974 (6). These adverse perinatal correlates have recently been confirmed in an analysis of OC pregnancies in the 10 years following the former series (7). During the course of such analysis it became apparent that considerable changes had occurred over the 20 years in the diagnosis of OC as well as in certain clinical and laboratory features.

Address for correspondence:
Dr N. Fisk,
Royal Postgraduate Medical School,
Institute of Obstetrics and Gynaecology,
Queen Charlotte's Maternity Hospital,
Goldhawk Road,
London W6 OXG, United Kingdom.

*Current address: The Children's Hospital,
Camperdown, N.S.W. 2050

1. Foreman Fellow.
2. Visiting Medical Officer.
3. Head.

PATIENTS AND METHODS

The medical records of all patients indexed as having OC who confined between January 1, 1975 and December 31, 1984 at King George V Hospital were reviewed. Four pregnancies were excluded as information in the notes suggested primary hepatic or dermatological causes for the pruritus or jaundice. The diagnostic criteria described by Kater and Mistlis at this hospital (1) were used until mid-1982 when the introduction of a total bile acid assay permitted additional criteria of elevated serum bile acids in the presence of negative hepatitis serology. Two pregnancies were excluded due to normal bile acid levels. Eighty-three pregnancies in 71 women were analysed.

Maternal data from the 1975-1984 series were then compared with published data from the earlier series of 56 pregnancies in 54 women, as original data from the 1965-74 series were unavailable for review. Information relating to the frequency of gastroenterological consultation, previous cholecystectomy, and the frequency of hypertensive disease of pregnancy in the earlier series was obtained from a preliminary analysis performed in 1974 of 50 pregnancies in the former series which was retained by one of us (GNBS) who was a co-author of the original fetal series (6).

The total number of confinements by year was obtained from the Labour Ward register. Comparison between the 2 periods was made by chi-square

testing, or Fisher exact where appropriate. Liver function tests were analysed after logarithmic transformation with the aid of a Minitab package (Statistics Dept., Pennsylvania State University).

RESULTS:

Among 90,806 confinements over the 20 years, 139 pregnancies were complicated by OC (0.15%). Prevalence increased significantly from 0.1% in 1965-1974 to 0.2% in 1975-1984 ($X^2 = 11.16$ $p<0.001$). Maternal features are compared for the 2 series in table 1. In the first series, 10 mothers had beta thalassaemia trait, one sickle trait and another congenital spherocytosis, whereas no mother in the second series had an underlying mild haemolytic state. Significant differences in racial composition were found between the groups i.e. 84% in the first group were born in a Mediterranean country as compared to 41% in the second. Four mothers in each series had a history of cholelithiasis (i.e. cholecystectomy) and it was noted during review of the second group's notes that a further 3 had undergone cholecystectomy at some stage subsequent to the index pregnancy.

In the second series, 2 of 71 patients had a family history of OC, while 12 had a previous history of OC (32% of multiparas). Four had a previous stillbirth, 1 due to OC, 1 due to chronic villitis and 2 apparently unexplained but from pregnancies in which pruritis was present. Other medical complications of pregnancy in the second series were as follows: diabetes in 6 (4 gestational), immune thrombocytopenic purpura in 1, narcotic addiction in 1 and pulmonary tuberculosis necessitating triple therapy in 2. In 19 of 24 consultations by a gastroenterologist, the diagnosis was felt to be definitely OC or probably OC. In the 4 in which OC was considered a possible diagnosis only, no other diagnosis was made and resolution of symptoms postpartum supported OC as the diagnosis. No skin pathology was found in 2 of 3 consultations by a dermatologist. In the remaining patient, 'pruritic urticarial papules and plaques of pregnancy' was suggested, but OC was preferred as the diagnosis by the obstetric staff in view of the abnormal liver function tests and the occurrences of similar symptoms in the patient's 2 previous pregnancies.

In the latter series, severe pruritis and scratching often became disturbing to the mother (figure 1). Antipruritic treatment was used in 50 pregnancies: cholestyramine (Questran) in 33, phenobarbitone in 28, an antihistamine in 6, 18hydroxyethylrutoside (Paroven) in 1 and aluminium hydroxide in another. Efficacy could not be evaluated from the records.

The distribution of liver function results is shown in figure 2, which also gives the percentage of patients with results above the normal range for each of the 4 tests. Laboratory upper limits of normal (2 standard deviations above the mean) were used except for alkaline phosphatase where a factor of 2 was used to allow for known pregnancy increases. Although any one test was normal in 18-43% of patients, only 1 had all 4 results normal. The frequency of jaundice was similar in the 2 series: 52% in the earlier series had clinical jaundice, while 57% in the subsequent series had biochemical jaundice. From the limited data on liver function tests in the first series, arithmetic mean alkaline phosphatase (344u/l) fell within the range seen in the later series. Bile acids, assayed in 12 pregnancies, had a mean level of 26.9 μmol/l (range 7-125), and by definition were elevated in all OC pregnancies in which measured. Hepatitis serology was negative in all 12 tested. No liver biopsy was performed in the second series in contrast to 11 done in the first series. Prothrombin index (PI) was obtained in 34 pregnancies (median 100% range 57-100%). In 1 of 3 with a low PI (<85%), the value of 65% was attributed to malabsorption of vitamin K secondary to prolonged cholestyramine therapy.

DISCUSSION

The prevalence of OC in a hospital population in Sydney doubled over 2 decades. Several factors may be responsible.

Firstly, increased awareness of the condition may have increased the rate of diagnosis. Both the initial publication from this hospital on fetal complications

Table 1. Comparison of Maternal Characteristics of Obstetric Cholestasis

	1965-1974 (56 pregnancies)	1975-1984 (83 pregnancies)	
Race:			
Anglosaxon	9 (17%)	33 (47%)	
Greek	28 (52%)	7 (10%)	
Other Mediterranean	17 (32%)	22 (31%)	
Other	2 (4%)	9 (13%)	$X^2=9.21$ $p<0.001$
Parity:			
Primipara	16 (29%)	34 (41%)	
Multipara	40 (71%)	49 (59%)	NS
Multiple pregnancy	0	3	
Hypertensive disease of pregnancy	10 (20%)	8 (10%)	NS
Gastroenterology consultation	44 (89%)	24 (29%)	$X^2=43.59$ $p<0.001$
Postpartum haemorrhage	10 (18%)	6 (7%)	NS

NS = not significant.

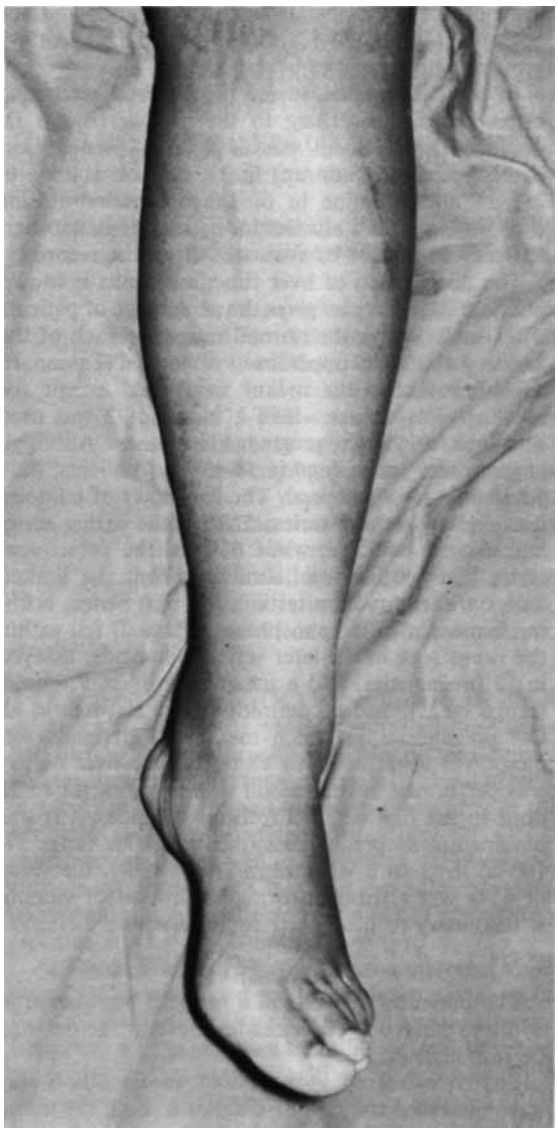

Figure 1. Pronounced scratch marks in a woman presenting with pruritus and fetal death in utero.

of OC (6) plus the unusual and unexplained nature of still birth and meconium-stained amniotic fluid in this disease have resulted in OC being considered earlier than previously as a diagnostic possibility in women presenting with pruritus in advanced pregnancy. Prior to 1975, it was possible that patients with third trimester itching and puerperal resolution may have gone undiagnosed.

Secondly, milder forms of OC may have been diagnosed more frequently in the second series, especially following the demonstration that anicteric 'pruritus of pregnancy' was a form of OC (1). Biochemical data however were broadly comparable in the 2 groups. The absence of need to perform a liver biopsy and the significant fall in frequency of gastroenterological consultation suggest that diagnosis of OC is now well within the ambit of the obstetrician. Overdiagnosis may have been a possibility prior to the introduction of the bile acid assay. However, the high frequency of perinatal complications in the second series, especially management independent complications such as meconium-stained liquor and fetal distress, suggests that any effect of an altered pattern of diagnosis has not influenced fetal risk (7) and therefore has been minor.

Thirdly, changes in disease epidemiology may have accounted for the rise in prevalence. Nevertheless at King George V the prevalence of OC is still much lower than reported from Melbourne (8). Steel and Parker attributed their 1.5% incidence to a high frequency of women of Mediterranean origin and a strong association with thalassaemia, both features also noted in the 1965-1974 Sydney series (6). In the second series however, no patient had any underlying haemolytic state and the racial composition had altered significantly to a distribution similar to the general hospital population. The known genetic predisposition to OC was supported by data in the second series, showing a previous history in 32% and a family history in 3%. The frequency of temporally unrelated cholelithiasis appeared similar to that in the population at large (8).

The distribution of liver function results in the second series (figure 2) is in agreement with previous studies suggesting that alanine aminotransferase is the most sensitive of the conventional tests (9,10). OC produces a milder elevation in transaminases than seen in viral hepatitis, with a rise in alanine aminotransferase occurring before a rise in asparate aminotransferase (9). Heikkinen et al, who had previously considered an alanine aminotransferase >40 IU/l a prerequisite for diagnosis, recently suggested that mild forms of OC were possible in the presence of normal transaminases (11), and this has since been substantiated (4). In our series only 25% of patients had an alanine aminotransferase within the normal range and 13 of 64 had values $\leqslant 40$ IU/l.

More patients had an elevated alkaline phosphatase than alanine aminotransferase (82% versus 75%). However, there is dispute concerning the upper limit of normal in pregnancy with reported increases ranging in magnitude from factors of 1.5 to 4 (4,10,12). Placental production of thermostable alkaline phosphatase masks the liver isoenzyme, rendering it an unreliable index of liver function in pregnancy.

The role of the bile acid estimation is exclusion of patients with normal levels and is especially useful in pruritic patients without jaundice or abnormal liver function tests in which it is the sole diagnostic test. In the second series, 2 such patients were excluded

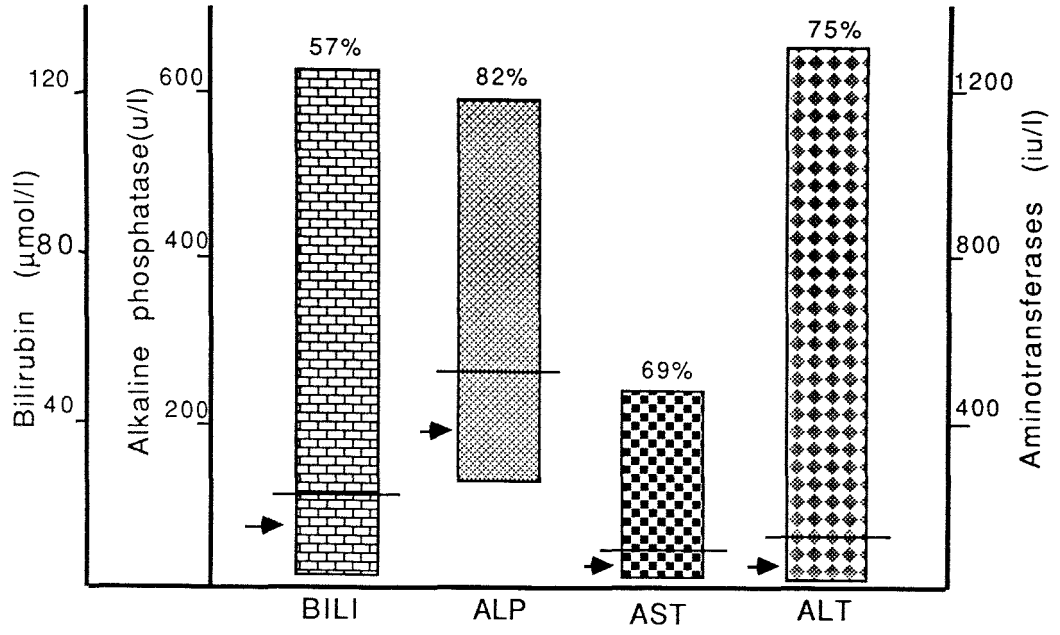

Figure 2. Geometric means and 95% data intervals (mean ± 1.96xSD) for liver function tests in OC pregnancies 1975-1984. Upper limit of normal range (arrow) and % of those with result above the normal range. BILI = bilirubin; ALP = alkaline phosphatase; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

due to normal levels, while one with normal liver function tests had the diagnosis confirmed by elevated total bile acids. Serum bile acids are the most sensitive diagnostic test for OC (10,11,13). In about 50%, elevation of bile acids actually precedes the onset of symptoms or other laboratory evidence of OC (11). Previous studies have noted increases in total bile acids by factors of 3-100 (9,13), whereas in this study geometric mean bile acids were only just above 4 times the upper limit of normal, consistent with speculation that milder forms of the disease are diagnosed more frequently with bile acids. Assays of individual bile acids greatly increase this sensitivity, but may lead to diagnosis in asymptomatic patients without increased fetal risk. Lunzer et al recently described postprandial elevations in cholylglycine in 10% of a Sydney antenatal population (14).

Maternal management of OC is essentially symptomatic. Phenobarbitone aims to induce hepatic excretion of bile acids but fails to alter bile acid concentrations in prospective trials (15,16). Cholestyramine, an anion exchange resin which binds bile acids in the intestinal lumen, lowers bile acids and produces better symptomatic relief, but usually works only in those with moderate elevations of bile acids (15). Furthermore cholestyramine may lead to depletion of fat soluble vitamins as evidenced by the low PI in one patient. Pruritus correlates better with skin than serum bile acid concentrations, and thus hydroxyethylrutosides, which relieve itching in primary biliary cirrhosis by reducing bile leakage from dermal capillaries (17) were tried in one patient who had not responded to cholestyramine. Subjective improvement occurred but was transient. We have noted a similar response in 2 further patients since the completion of this study. Vitamin K is widely advocated in OC to prevent depletion of dependant clotting factors. This may have been instrumental in the fall in incidence of postpartum haemorrhage over the 2 studies (18% to 7% $p = 0.06$).

Fetal management has been reviewed elsewhere (7). Perinatal mortality fell from 107/1,000 in the first series to 35/1,000 in the second series due to intensive fetal monitoring, including amniocentesis for meconium and a policy of induction at fetal maturity (7). An understanding of the maternal features of OC and changes in its diagnosis are essential if early diagnosis is to allow timely fetal surveillance and intervention.

References

1. Kater RMH, Mistilis SP. Obstetric cholestasis and pruritis of pregnancy. Med J Aust 1967; 1: 638-640.
2. Reyes H, Ribalta J, Gonzalez MC, Segovia N, Oberhauser E. Sulfobromophthalein clearance tests before and after ethinyl estradiol administration in women and men with family history of intrahepatic cholestasis of pregnancy. Gastroenterology 1981; 81: 226-231.
3. Rencoret R, Aste H. Jaundice during pregnancy. Med J Aust 1973; 1: 167-169.
4. Berg B, Helm G, Petersohn L, Tryding N. Cholestasis of pregnancy: clinical and laboratory studies. Acta Obstet Gynecol Scand 1986; 65: 107-113.

5. Zhong-Da Q, Qi-Nan W, Yue-Han L, He-Zhang M. Intrahepatic cholestasis of pregnancy: clinical analysis and follow up study of 22 cases. Chin Med J 1983; 96: 902-906.
6. Reid R, Ivey KJ, Rencoret RH, Storey B. Fetal complications of obstetric cholestasis. Br Med J 1976; 1: 870-872.
7. Fisk NM, Storey GNB. Fetal outcome in obstetric cholestasis. Br J Obstet Gynaecol 1988; in press.
8. Steel R, Parker ML. Jaundice in pregnancy. Med J Aust 1973; 1: 461.
9. Heikkinen J. Serum bile acids in the early diagnosis of intrahepatic cholestasis of pregnancy. Obstet Gynecol 1983; 61: 581-587.
10. Laatikainen T, Ikonen E. Serum bile acids in cholestasis of pregnancy. Obstet Gynecol 1977; 50: 313-318.
11. Heikkinen J, Maentausta O, Ylostalo P, Janne O. Changes in serum bile acid concentrations during normal pregnancy in patients with intrahepatic cholestasis of pregnancy and in pregnant women with itching. Br J Obstet Gynaecol 1981; 88: 240-245.
12. Fagan E, Chadwick V. Disorders of gastrointestinal tract, pancreas and hepato-biliary system. Chapt pp 270-346 in De Swiet M (ed) Medical Disorders in Obstetric Practice. Blackwell, Oxford 1984.
13. Shaw D, Frohlich J, Wittman BAK, Willms M. A prospective study of 18 patients with cholestasis of pregnancy. Am J Obstet Gynecol 1982; 142: 621-625.
14. Lunzer M, Barnes P, Byth K, O'Halloran M. Serum bile acid concentrations during pregnancy and their relationship to obstetric cholestasis. Gastroenterology 1986; 91: 825-829.
15. Laatikainen T. Effect of cholestyramine and phenobarbitol on pruritus and serum bile acid levels in cholestasis of pregnancy. Am J Obstet Gynecol 1978; 132: 501-506.
16. Heikkinen J, Maentausta O, Ylostalo P, Janne O. Serum bile acid levels in intrahepatic cholestasis of pregnancy during treatment with phenobarbitol or cholestyramine. Europ J Obstet Gynecol reprod Biol 1982; 14: 153-162.
17. Hishun S, Rose JD, Hunter JO. The relief of pruritus in primary biliary cirrhosis by hydroxyethylrutosides. Br J Dermatol 1981; 105: 457-460.