sodium cromoglycate. This effect was not due to a difference between the patients, since when we recalculated the results using the same 11 subjects for both placebo and sodium cromoglycate they were the same. Sodium cromoglycate has a slight phosphodiesterase inhibiting effect, which might explain the differences[10]; however, it has no effect on the histamine response of human bronchial smooth muscle.[1] We have also shown that sodium cromoglycate has no effect on tracheal smooth-muscle contraction induced by histamine or methacholine.[11] It does, however, inhibit allergen contraction of the passively sensitised human tracheal smooth muscles.

Our results of the lack of effect of sodium cromoglycate on histamine challenge are consistent with those of Pagelow.[12] He found no difference in the threshold of histamine bronchial reactivity with sodium cromoglycate or phentolamine. In contrast, Kerr *et al*[7] reported complete protection against histamine with both these agents. We have studied the effect of sodium cromoglycate in vitro on the alpha-receptor contraction of isolated human trachea induced by adrenaline in the presence of propranolol. In this system we are unable to show any inhibition by sodium cromoglycate of alpha-receptor contraction.[13]

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Fetal complications of obstetric cholestasis

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Summary

Among 56 pregnancies complicated by obstetric cholestasis five intrauterine deaths and one neonatal death occurred between 33 and 39 weeks, and a further six infants required urgent delivery for intrapartum asphyxia. Eighteen spontaneous premature deliveries occurred. Five mothers required specific treatment for unexplained postpartum haemorrhage. Cholestasis of pregnancy is therefore not a condition benign to the fetus, and it may contribute to increased maternal morbidity.

Introduction

The pattern of recurrent jaundice in late pregnancy has been shown by Svanborg[1] and Thorling[2] to be a clinical entity due to intrahepatic cholestasis. Kater and Mistilis[3] showed that pruritus of pregnancy is a less severe form of the same disorder. Obstetric cholestasis is generally accepted to be entirely benign with no ill effects on mother or child.[4 5] But our data, reported here, suggest that this belief cannot be substantiated.

Patients and methods

We reviewed the obstetric and paediatric records of all women confined in the obstetric section of Royal Prince Alfred Hospital (King George V Memorial Hospital for Mothers and Babies) whose pregnancies were complicated by obstetric cholestasis in the 10 years from 1 January 1965 to 31 December 1974. The criteria for the diagnosis of obstetric cholestasis were described by Kater and Mistilis in a survey at this hospital.[3] Diagnosis based on clinical and biochemical findings was confirmed by liver biopsy in 11 patients.

Prematurity was judged by the clinical features of the newborn[6] in conjunction with the obstetric estimate of gestation.

Results

The perinatal mortality rate in the 56 pregnancies reviewed was 11% and the incidence of premature delivery was 36%. Five fetal deaths occurred among 40 multigravid women, in contrast to a single fetal death among the 16 primigravid patients.

The ethnic composition of the group of mothers who developed intrahepatic cholestasis is shown in table 1. The proportion of patients with a Mediterranean ancestry was much greater than that of the overall population delivered at King George V Hospital.

TABLE I—*Ethnic composition of group of mothers with cholestasis. Percentage of general hospital population that is formed by each ethnic group is shown for comparison*

	Greek	Anglo-Saxon	Italian	Yugoslav	Spanish
No (%) of patients	28 (53)	9 (18)	8 (13)	5 (10)	4 (7)
% of hospital population ..	22	41	6	14	3

For cultural and religious reasons, few of these women had used oral contraceptives, but a history of jaundice in association with these drugs was obtained from three women. Five other patients had previously had a cholecystectomy and another woman had had viral hepatitis five years before her pregnancy. Ten patients had β-thalassaemia minor, one had sickle cell trait, and another suffered from congenital spherocytosis.

Incidence of jaundice and pruritis—Twenty-nine pregnancies were complicated by jaundice and pruritus and 27 by pruritus alone. The gestational period at which symptoms began varied from 13 to 37 weeks (mean 30·5 weeks). The mean interval between the onset of symptoms and delivery was six and a half weeks and was the same

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in the groups of mothers confined before and after 37 weeks. The highest maternal bilirubin level was 145 μmol/l (8·5 mg/100 ml) but it exceeded 103 μmol/l (6 mg/100 ml) in only five pregnancies (normal <17 μmol/l (1 mg/100 ml)). The mean serum alkaline phosphatase level was 344 U/l with a range of 114–1000 U/l (normal 20–80 U/l). Rapid post-partum resolution of clinical and biochemical abnormalities was observed in all cases.

Fetal deaths—In the 56 pregnancies studied five intrauterine deaths occurred before the onset of labour, and a sixth infant died within one hour of birth despite intensive attempts at resuscitation (table II). Notwithstanding the varying degrees of maceration shown by the stillbirths, all of the necropsy specimens showed the pattern of pericardial, pleural, and pulmonary petechiae that characterises severe intrauterine anoxia.[7] There was no evidence of intrauterine malnutrition in these six infants. Four fetal deaths occurred in the 29 women with clinical jaundice in contrast to two deaths among the 27 mothers whose plasma bilirubin levels were less than 34 μmol/l (2 mg/100 ml). No stillbirths and only one case of fetal distress complicated the five pregnancies in which maternal plasma bilirubin exceeded 103 μmol/l. Within the group of icteric mothers, fetal risk did not increase with the severity of the maternal biochemical disturbance.

Premature births—Among the 50 live births 18 infants were delivered after spontaneous labour before 37 weeks' gestation and 13 babies weighed less than 2500 g. Only one of these neonates was small for gestational age, in accordance with the intrauterine percentiles of Kitchen.[8] The mean gestational age of the viable infants was 255 days compared with the hospital mean of 283 days.[9] The mean birth weight of 2880±530 g was also lower than the hospital mean of 3330 g. Among the 25 icteric mothers with living infants 12 were delivered before 37 weeks and 11 babies weighed less than 2500 g. This contrasted with the incidence of six preterm deliveries and two babies of low birth weight in the group of 25 women without jaundice. A significant statistical association existed between maternal plasma bilirubin levels of 34 μmol/l or greater and the occurrence of preterm delivery ($X^2=5·12$; $P<0·05$) or low birthweight ($X^2=14·10$; $P<0·001$).

Complications—Lower segment caesarean section was performed for cephalopelvic disproportion in five cases. The liquor was heavily stained with meconium in 12 (27%) of the remaining 45 live births, an unusual finding in a group whose gestation ranged from 33 to 39 weeks.[10] Severe fetal bradycardia (<100 beats/min) occurred in eight cases, resulting in six urgent forceps extractions for fetal distress and two rapid spontaneous deliveries before forceps could be applied. One of the latter infants died within an hour of birth and a necropsy showed extensive hypoxic damage in an otherwise normal infant. Either fetal death in utero or fetal distress complicated 10 of the 29 pregnancies associated with maternal hyperbilirubinaemia but only three of the 27 pregnancies associated with maternal pruritus alone. This difference was statistically significant ($X^2=6·01$; $P<0·05$). In fact, only seven of the 29 pregnancies in which the maternal plasma bilirubin level exceeded 34 μmol/l were not associated with either preterm delivery or intrauterine stress.

Maternal blood loss—Despite the routine use of ergometrine and controlled cord traction in the management of the third stage of labour, maternal blood loss exceeded 500 ml in 10 of the 50 vaginal deliveries. Haemorrhage was greater than 2000 ml in five women, of whom three received urgent blood transfusions and two required infusion with blood volume expanders. No haemorrhagic complications were detected in the newborn; parenteral vitamin K was administered routinely at birth.

Discussion

The generally accepted view is that obstetric cholestasis is attended by an excellent fetal prognosis.[5 11 12] One of us has, however, reported a 13% perinatal mortality rate in Chilean women.[13] In these 56 pregnancies seen over 10 years at the Royal Prince Alfred Hospital, Sydney, the occurrence of six perinatal deaths, eight cases of fetal distress, and 18 spontaneous premature deliveries constitutes very suggestive evidence that maternal cholestasis is an index of substantially increased fetal risk. In fact, only seven of the 29 pregnancies in which maternal plasma bilirubin exceeded 34 μmol/l were not associated with at least one of these three complications.

The four intrauterine deaths at or before 34 weeks, another stillbirth at 37 weeks, and a neonatal death at 39 weeks from intra-partum asphyxia represent a perinatal mortality rate of 11%.

Although the incidence of hypoxic complications was three

TABLE II—*Analysis of perinatal deaths*

Case No	Maternal factors						Fetal factors			
	Race	Age	Parity	Plasma bilirubin (μmol/l)	Serum alkaline phosphatase (u/l)	Gestation at onset (weeks)	Type of Perinatal death	Maturity (weeks)	Sex	Weight (g)
1	Greek	27	0	39	330	28	Stillbirth before labour	32	F	1290
2	Anglo-Saxon	38	4	62	665	28	Stillbirth before labour	33	F	1890
3	Anglo-Saxon	28	6	5	315	28	Stillbirth before labour	34	F	1500
4	Italian	22	1	62	126	28	Stillbirth before labour	34	M	1990
5	Italian	20	0	91	252	34	Stillbirth before labour	37	F	2800
6	Spanish	28	2	15	114	30	Neonatal death (at 1 hour)	39	M	3650

Conversion: SI to traditional units—Bilirubin: 1 μmol/l ≈ 0·058 mg/100 ml.

TABLE III—*Analysis of eight infants with fetal distress*

Case No	Age	Parity	Maternal bilirubin (μmol/l)	Maternal serum alkaline phosphatase (u/l)	Gestational age (weeks)	Birth weight (g)	Liquor characteristics	Lowest fetal heart rate/min	Delivery method	Apgar score at 1 and 5 min	Fetal outcome
6	28	2	15	114	39	3650	Meconium stained	60	Spontaneous vertex	0, 0	Neonatal death (at 1 hour)
7	26	1	45	250	32	1780	Meconium stained	96	Low forceps	5, 8	Survived
8	19	0	41	564	36	2200	Meconium stained	80	Low forceps	7, 10	Survived
9	32	1	51	450	36	2680	Meconium stained	90	Kielland's forceps rotation	6, 9	Survived
10	22	0	58	335	38	2500	Meconium stained	80	Spontaneous vertex	6, 8	Survived
11	31	1	46	640	38	3400	Meconium stained	70	Low forceps	9, 10	Survived
12	25	0	115	275	38	3090	Meconium stained	60	Low forceps	6, 9	Survived
13	30	0	12	198	40	3650	Clear	70	Manual rotation and forceps	8, 8	Survived

times more common in the group of icteric mothers, it must be emphasised that two perinatal deaths occurred in pregnancies associated with only maternal pruritus. Within the jaundiced group fetal outcome was not affected by the severity of the maternal biochemical disturbance or the gestational age at which symptoms began. In short, the individual fetus at risk is not identified by the indices currently used to gauge the severity of the maternal cholestasis.

The cause of these sudden intrauterine deaths is not known. The birthweights of both the surviving and stillborn infants were normally distributed for their various maturities.[8] Hence probably, unlike the chronic nutritional deficiency seen in intrauterine growth retardation, impaired placental perfusion or transfer is not a feature of this disorder. The consistent neocropsy evidence of intrauterine fetal hypoxia and the high associated incidence of intrapartum asphyxia do, however, suggest that some form of metabolic disturbance may occur.

The reason for the increased rate of premature births is also unexplained. In pregnancies complicated by maternal cholestasis Laatikainen *et al*[14] showed a change in fetal steroid synthesis. In particular, the fetus's liver has a reduced capacity to change 16-α-hydroxylate dehydroepiandosterone (DHAS) into the major precursor of the inert metabolite, oestriol. As a result, increased amounts of DHAS may reach the placenta and thus be metabolised through an alternative steroid pathway to the active hormone, oestradiol. In view of the recent implication of rising maternal plasma oestradiol 17-β levels in the initiation of premature labour[15], it is tempting to postulate that the impairment of 16-α-hydroxylase activity in pregnancies affected by cholestasis produces an "oestradiol surge" and consequent premature delivery.

The increased incidence of postpartum haemorrhage in these women is more easily explained. The hepatic synthesis of coagulation factors II, VII, IX, and X requires adequate tissue levels of vitamin K. As this is a fat soluble vitamin adequate absorption depends on the secretion of enough bile salts to promote mixed-micelle formation in the gut. Vitamin K deficiency may thus occur if maternal cholestasis is severe or prolonged. One of our patients was admitted from the antenatal clinic with generalised bruising together with greatly prolonged prothrombin and partial thromboplastin times. These values had been normal two weeks earlier and became so again within two days of parenteral vitamin K administration.

In view of the present inability to identify the individual fetus at risk of intrauterine death, we believe that pregnant women with cholestasis should be managed with watchful expectancy until 37 weeks' gestation. Then induction of labour should be considered. It seems desirable to conduct the pregnancy at a hospital fully equipped for intrapartum fetal monitoring and the intensive care of infants of low birth weight. In view of the possibility of a secondary disturbance in maternal coagulation we recommend the prophylactic administration of parenteral vitamin K.

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Therapeutic experience with fludrocortisone in diabetic postural hypotension

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Summary

Fourteen patients with diabetic postural hypotension were treated with fludrocortisone for a mean of 12 months (range 6-30 months). The mean daily dose of fludrocortisone was 0·2 mg (range 0·1 mg-0·4 mg). Standing systolic and diastolic blood pressures increased significantly (P <0·001) after treatment with fludrocortisone and the postural hypotension decreased significantly (P <0·001). Thirteen patients noted considerable symptomatic improvement. Fludrocortisone should be used cautiously in patients with congestive cardiac failure or the nephrotic syndrome.

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Introduction

Postural hypotension is a prominent and disabling symptom of diabetic autonomic neuropathy.[1] Although the use of fludrocortisone (9-α-fluorohydrocortisone) is well known in the treatment of idiopathic postural hypotension,[2 3] its use has been only briefly mentioned in the management of diabetic postural hypotension.[4-6] We have recently reported the acute changes produced by fludrocortisone in diabetics with postural hypotension[7] and now report our clinical experience with this drug in the long-term treatment of this condition.