[12] Schapiro, H., *et al.*, *American Journal of Digestive Diseases*, 1968, **13**, 608.
[13] Thomas, J. E., *American Journal of Physiology*, 1964, **206**, 124.
[14] Hong, S. S., and Magee, D. F., *Annals of Surgery*, 1970, **172**, 41.
[15] Malagelada, J. R., Go, V. L. W., and Summerskill, W. H. J., *Gastroenterology*, 1974, **66**, 22.
[16] Moreland, H. J., and Johnson, L. R., *Gastroenterology*, 1971, **60**, 524.
[17] Thambugala, R. L., and Baron, J. H., *British Journal of Surgery*, 1971, **58**, 839.
[18] Konturek, S. J., *et al.*, *Gastroenterology*, 1972, **63**, 273.
[19] Konturek, S. J., Becker, H. D., and Thompson, J. C., *Archives of Surgery*, 1974, **108**, 704.
[20] Isaza, J., *et al.*, *Surgery*, 1971, **70**, 616.
[21] Snape, W. J., *Gastroenterology*, 1948, **10**, 129.
[22] Snape, W. J., Friedman, M. H. F., and Thomas, J. E., *Gastroenterology*, 1948, **10**, 496.
[23] Glanville, J. N., and Ruthie, H. L., *Clinical Radiology*, 1964, **15**, 350.
[24] Rudick, J., and Hutchison, J. S. F., *Lancet*, 1969, **1**, 579.
[25] Parkin, G. J. S., Smith, R. B., and Johnson, D., *Annals of Surgery*, 1973, **178**, 581.
[26] Kelly, K. A., Nyhus, L. M., and Harkins, H. N., *Journal of Surgical Research*, 1964, **4**, 391.
[27] Landor, J. H., *American Journal of Digestive Diseases*, 1964, **9**, 256.
[28] Greenlee, H. B., *et al.*, *American Journal of Physiology*, 1957, **190**, 396.
[29] Feng, T. P., Hou, H. C., and Lim, R. K. S., *Chinese Journal of Physiology*, 1929, **3**, 371.
[30] Brown, J. C., Mutt, V., and Pederson, R. A., *Journal of Physiology*, 1970, **209**, 57.
[31] Bloom, S. R., Vaughan, N. J. A., and Russell, R. C. G., *Lancet*, 1974, **2**, 546.
[32] Russell, R. C. G., Thomson, J. P. S., and Bloom, S. R., *British Journal of Surgery*, 1974, **61**, 821.
[33] Goligher, J. C., *et al.*, *British Medical Journal*, 1968, **2**, 787.
[34] Goligher, J. C., *et al.*, *British Medical Journal*, 1971, **1**, 7.
[35] Dellipiani, A. W., *et al.*, *Gut*, 1969, **10**, 366.
[36] Wheldon, E. J., Venables, C. W., and Johnston, I. D. A., *Lancet*, 1970, **1**, 437.

Use of Oxytocin and Incidence of Neonatal Jaundice

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Summary

A retrospective controlled study using data from the Cardiff Births Survey examined a possible relation between oxytocin administration to induce or accelerate labour and the subsequent development of neonatal jaundice. Among 10 591 infants born in Cardiff between 1970 and 1972 the incidence of neonatal jaundice was higher in infants born after oxytocin administration than among others. Analysis by gestational age at delivery, birth weight, Apgar score, length of labour, sedative and analgesic therapy during labour, and suppression of lactation showed that this association held within all these categories except among small immature infants, who are at high risk of jaundice in any case.

Introduction

A relation between oxytocin administration in labour and the subsequent development of neonatal jaundice was first suggested by Mast *et al.* in 1971,[1 2] and later studies have tended to confirm this.[3-7] Summary data presented by Friedman and Sachtleben[8] showed a trend among 12 413 infants which suggested a relation, but the differences in mean bilirubin levels among infants born after spontaneous, accelerated, and induced labour were not statistically significant. Other studies have failed to show an association.[9-12]

Critics of studies which suggest a possible causal relation between oxytocin administration and neonatal jaundice have pointed to the inherent differences between the groups studied: women whose labours were induced or accelerated by oxytocin were necessarily different from those in whom oxytocin was not used.[13 14] Proof of causality in these circumstances could best be inferred from a randomized controlled trial,[15] and this technique has already been used to compare the effects on the fetus of different uterine stimulants.[16] Nevertheless, random allocation of a representative group of women to management schedule which included a group in which uterine stimulation was precluded would be challenged on both ethical and practical grounds, given current obstetric and social indications for induction and acceleration of labour. The earlier discharge of mothers and infants after delivery also militates against collection of complete data on bilirubin levels at a time when these are likely to be maximal.

Thus, further controlled studies with careful matching for all factors thought to be relevant still offer the best means of investigating the hypothesis that there is a causal relation between the induction and acceleration of labour with oxytocin and subsequent development of neonatal jaundice. In our study reported here we used data from the Cardiff Births Survey, which covers all mothers and infants delivered in Cardiff.[17]

Patients and Methods

The study population was drawn from the 17 496 live births in Cardiff during the period 1970-2; 97% of these deliveries were conducted in hospital. Labours were classified in three groups: 1, those in which oxytocin was used either for induction or for acceleration; 2, those of spontaneous onset in which no oxytocin was administered; and 3, those induced by amniotomy alone.

An infant was classed as jaundiced if a plasma bilirubin level of 171 μmol/l (10 mg/100 ml) or more had been found during the neonatal period. The date on which the raised bilirubin was measured was not recorded in the original Cardiff Birth Survey so we could not estimate whether there were differences in the timing of the onset of jaundice. An infant in hospital was more likely to have a bilirubin estimation performed than one who had become mildly jaundiced after discharge home, and analysis of the three groups by day of discharge showed that infants born after oxytocin administration were discharged slightly later than the others. To meet this potential source of bias the study population was restricted to the 11 192 infants discharged from three to eight days after delivery. Bilirubin estimations, indicated by the slightest clinical suspicion of jaundice, had been performed on 23% of all infants. It was unlikely that any significant number of cases of hyperbilirubinaemia remained undetected in those infants in whom no bilirubin estimation had been performed before discharge from hospital.

We further excluded 64 infants delivered by elective caesarian section, 10 delivered by caesarean section after "failed induction," 233 delivered after oxytocin administration without amniotomy, 130 born to rhesus-negative mothers with antibodies, and 164 who developed cephalhaematoma. The 233 infants born after oxytocin

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administration without amniotomy were a mixed group but consisted mainly of infants with congenital malformations—for example, anencephaly—and infants born to mothers who at some stage before delivery had received oxytocin as a "ripening drip."

The final study population consisted of 10 591 infants—61% of the total live births and 95% of those discharged from three to eight days after delivery. Statistical evaluation of the data, based on the methods of Mantel and Haenszel,[18] gave an estimate of the relative risk of jaundice in the oxytocin group compared with the other two groups together, and χ^2 was then calculated for each of the tables.

Results

Of the 10 591 infants 970 (9·2%) had a measured plasma bilirubin of at least 171 μmol/l (10 mg/100 ml). Of 3326 infants born after oxytocin administration (group 1) 412 (12·4%) became jaundiced; of 5896 infants born after spontaneous labour (group 2) 476 (8·1%) were affected; and of 1369 infants born after amniotomy (group 3) 82 (6·0%) developed jaundice. Of the 7265 infants in groups 2 and 3 (no oxytocin) 558 (7·7%) became significantly jaundiced, so the relative risk of jaundice in an infant born after oxytocin administration compared to the risk in other infants was 1·6 (see table). These differences could not have occurred by chance ($P < 0·000001$), but they might have been explicable by the choice of patients to whom oxytocin was given to induce or accelerate labour. Further analysis of the sample population was performed to examine factors which might be relevant in predisposing infants to develop neonatal jaundice.

Gestational Age at Delivery.—The proportion of cases selected for oxytocin administration remained fairly constant after 36 weeks' gestation (fig. 1). At 36 weeks gestation or earlier there were proportionately more deliveries after spontaneous labour and the overall incidence of jaundice was high. At every other gestational age over 36 weeks there was an increased risk of jaundice to those infants born after oxytocin administration (see table).

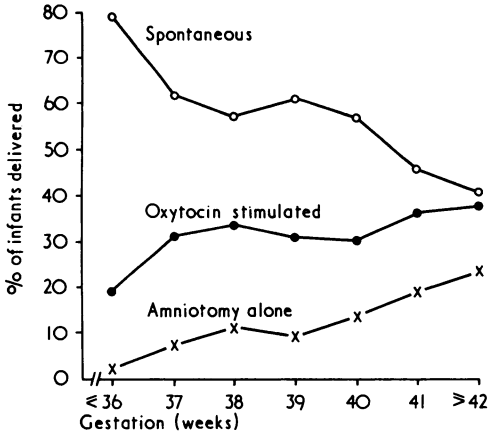

FIG. 1—Proportions of 10 591 infants delivered after spontaneous labour, oxytocin stimulation, and amniotomy alone according to gestation.

Incidence and Relative Risk of Neonatal Jaundice and Use of Oxytocin in 10 591 Infants according to Gestation

Gestation (Weeks)		Group 1	Group 2	Group 3	Overall Incidence of Jaundice (%)	Relative Risk of Jaundice 1/(2+3)
≤36	No. of cases	110	454	12	33·2	0·75
	% Jaundiced	28·2	35·2	0·0		
37	No. of cases	126	248	30	22·0	2·78
	% Jaundiced	34·9	14·5	0·0		
38	No. of cases	362	618	110	13·7	2·38
	% Jaundiced	21·0	9·5	12·7		
39	No. of cases	594	1180	174	8·2	2·16
	% Jaundiced	12·6	6·8	2·9		
40	No. of cases	1272	2347	572	5·7	1·94
	% Jaundiced	8·4	4·4	5·1		
41	No. of cases	629	795	327	5·8	1·89
	% Jaundiced	8·1	3·5	6·7		
≥42	No. of cases	233	254	144	6·5	4·05
	% Jaundiced	12·0	3·9	2·1		
Total*	No. of cases	3326	5896	1369	9·2	1·61
	% Jaundiced	12·4	8·1	6·0		

*$\chi^2 = 90·418$; D.F. = 1; $P < 0·001$.

Birth Weight.—The infants were divided into three groups by birth weight (fig. 2). For premature infants of less than 2500 g the incidence of jaundice was 24·8% and the relative risk for the oxytocin patients compared with the other two groups was 1·0; for infants weighing 2500 g-3490 g the incidence of jaundice was 8·9% and the relative risk 2·1; for infants weighing 3500 g and over the incidence of jaundice was 5·7% and the relative risk 1·8. Again, the association between oxytocin administration and jaundice was shown in all but the smallest infants (< 2500 g), among whom the overall incidence of jaundice was high ($\chi^2 = 71·8$; $P < 0·001$).

Apgar Score.—The infants were further analysed to take into account the degree of hypoxia at birth as estimated by the Apgar score. As Apgar score increased both the proportion receiving oxytocin and the proportion jaundiced decreased, but the relative risk of jaundice associated with oxytocin increased (fig. 2). Infants with an Apgar score of 7 or less had an incidence of jaundice of 13·6% and a relative risk for the oxytocin patients of 1·3, whereas for those with Apgar scores of 8 or over the incidence was 8·0 and the relative risk 1·8 ($\chi^2 = 45·8$; $P < 0·001$).

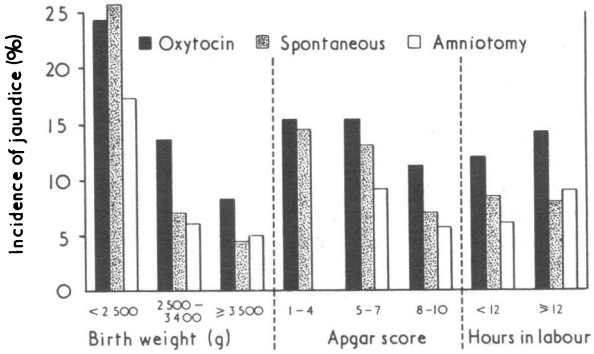

FIG. 2—Incidence of neonatal jaundice in 10 591 infants according to birth weight, Apgar score, length of labour, and oxytocin use.

Length of Labour.—There was no significant difference in the incidence of jaundice by length of labour, but the relative risk for the oxytocin patients rose from 1·6 for patients in labour for under 12 hours to 2·0 for patients in labour 12-24 hours and to 2·6 for patients in labour over 24 hours (fig. 2) ($\chi^2 = 56·5$; $P < 0·001$).

Pain Relief and Sedation during Labour.—The study population was divided into five groups by the method of pain relief and sedation used during labour. An increased relative risk to the oxytocin group was shown in all the subgroups (fig. 3). Of the 87 patients who received an epidural anaesthetic with oxytocin 17 (19·6%) delivered infants who became significantly jaundiced. There were no jaundiced infants born to 20 mothers who received epidural anaesthetic but no oxytocin ($\chi^2 = 56·6$; $P < 0·001$).

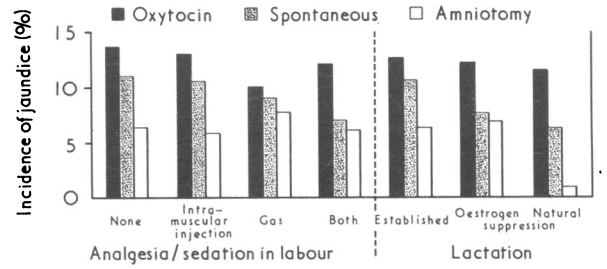

FIG. 3—Incidence of neonatal jaundice in 10 591 infants according to use of analgesia or sedation in labour, establishment or suppression of lactation, and oxytocin use.

Method of Infant Feeding.—In view of the known icterogenic effect of lactation and an apparent association between steroid hormone administration and neonatal jaundice the infants were classified by whether or not they were breast fed, and if not what method had been used to suppress lactation. The increased relative risk of jaundiced infants in the oxytocin group was present in all the subgroups (fig. 3). In mothers normally lactating the relative risk of a

jaundiced infant after oxytocin was 1·4, in mothers in whom lactation was suppressed by oestrogens the relative risk was 1·8, and in those in whom lactation was suppressed by classical measures the relative risk was 2·4 ($\chi^2 = 57·2$; $P < 0·001$).

Discussion

Mast *et al.*[1 2] are the only other workers to examine in detail and confirm a possible association between oxytocin administration and neonatal jaundice in a large number of neonates. The degree of jaundice was found to increase with increasing doses of oxytocin, and the association was stronger in mature infants than in premature infants. The possible influence of hypoxia was examined, but no correlation was found between bilirubin levels and scalp pH levels or the Apgar score.

Our data largely support these findings. The only subgroup in which the incidence of jaundice was higher in either group 2 or 3 (no oxytocin) than in group 1 (oxytocin) was immature infants weighing less than 2500 g who experienced a very high incidence of jaundice.

In view of the possible role of hypoxia in the aetiology of neonatal jaundice our study population was examined by gestation, infant weight, the condition of the infant at birth, and the length of labour. With the exceptions noted above an excess of jaundiced infants born after oxytocin administration was shown in all the subgroups. This excess was statistically significant except among infants who were in poor condition at birth. Unlike Quackernack and Mast[2] we found that the overall incidence of jaundice in the group of infants with low Apgar scores was high (13·5%).

A possible influence of drugs given during labour was examined. Again the incidence of jaundice was uniformly highest among those infants born after oxytocin administration though the differences failed to reach statistical significance among infants born to those women who either had no sedative or analgesic drugs in labour or had inhalational agents alone.

Because of the icterogenic effect of lactation and a suggested relation between steroid hormone intake and neonatal jaundice[1 9] the three groups of infants were compared within those breast fed, those whose mothers had received oestrogens to suppress lactation, and those in whose mothers lactation had been suppressed "naturally." The association between increased neonatal jaundice and oxytocin persisted. The data were also examined serially for each of the three years covered by the study. The overall incidence of jaundice varied slightly, but the relatively increased risk to those infants born after oxytocin administration was shown in each of the three years.

Our results might suggest that the incidence of jaundice after amniotomy alone was genuinely lower than after spontaneous labour, but the apparent protection against jaundice conferred by amniotomy reflected the low incidence of amniotomy at those early gestational ages (36 and 37 weeks) which showed a high overall incidence of jaundice. Thereafter groups 2 and 3 were comparable with respect to the incidence of jaundice.

This study was originally prompted by an increasing clinical awareness of otherwise normal infants developing jaundice at about five days of age and consequent delay in the mothers' discharge from hospital. Without more complete data on trends in the overall incidence of neonatal jaundice this impression, which is shared by others, is difficult to substantiate. Nevertheless, this impression together with our results and those of others tend to support the hypothesis that increasing resort to induction and acceleration of labour has been associated with a higher incidence of neonatal jaundice. Further studies are planned to examine separately the incidence of neonatal jaundice in infants born after labour induced with oxytocin and the incidence after labour accelerated with oxytocin.

Though physiological neonatal jaundice is a well-known phenomenon which may not be important in the future development of the child an increase in the incidence of jaundice raises the possibility that other enzyme systems, not associated with the metabolism of bilirubin, may also be compromised. The exact aetiology and therefore the significance of these apparent changes remain matters for speculation.

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Full details of all the tables for each variable examined are available on request from I.C.

References

1 Mast, H., *et al.*, *Geburtshilfe und Frauenheilkunde*, 1971, **31**, 443.
2 Quackernack, K., and Mast, H., *Archiv für Gynaekologie*, 1971, **211**, 144.
3 Ghosh, A., and Hudson, F. P., *Lancet*, 1972, **2**, 823.
4 Davies, D. P., *et al.*, *British Medical Journal*, 1973, **3**, 476.
5 Roberts, G., and Weaver, A., *Lancet*, 1974, **1**, 935.
6 Alderman, B., and Beazley, J. M., *British Medical Journal*, 1974, **3**, 624.
7 Calder, A. A., *et al.*, *Lancet*, 1974, **2**, 1339.
8 Friedman, E. A., and Sachtleben, M. R., *Lancet*, 1974, **2**, 600.
9 Davidson, D. C., Ford, J. A., and McIntosh, W., *British Medical Journal*, 1973, **4**, 106.
10 Gould, S. R., *et al.*, *British Medical Journal*, 1974, **3**, 228.
11 Gray, H. G., and Mitchell, R., *Lancet*, 1974, **2**, 1144.
12 Thiery, M., *et al.*, *Lancet*, 1975, **1**, 161.
13 Mills, W. G., *British Medical Journal*, 1973, **3**, 637.
14 Fisher, M. C. R., *British Medical Journal*, 1973, **3**, 637.
15 Chamberlain, G., *British Medical Journal*, 1974, **3**, 684.
16 Blackburn, M. G., *et al.*, *American Journal of Obstetrics and Gynecology*, 1973, **116**, 847.
17 Andrews, J., M.D. Thesis, University of London, 1973.
18 Mantel, N., and Haenszel, W., *Journal of the National Cancer Institute*, 1959, **22**, 719.
19 McConnell, J. B., Glasgow, J. F. T., and McNair, R., *British Medical Journal*, 1973, **3**, 605.