CHAPTER IV

DISCUSSION

Labour or parturition is the process by which the mature products of conception are expelled from the uterus (Taylor, 1976). There are many drugs posses oxytocic activity namely, the ability to stimulate the smooth muscle of the uterus. Oxytocin is the drug par excellence to induce labour at term (Danforth and Hendricks, 1977). It was used for the induction of labour by Watson in 1913. It was used by intravenous drip by Theobald in 1968.

The mechanism of action of oxytocin which increase the intensity and frequency of uterine contractions when infused into pregnant women; however, was poorly understood (Soloff, 1974). It was possible that the increased sensitivity of the uterus of oxytocin, resulted from an increased affinity and/or capacity of uterine receptor for oxytocin (Pauerstein, 1973; Soloff, et al., 1974). The threshold level for an initial response may be as little as 0.5 mU per minute at the very end of pregnancy (Danforth, et al., 1977). Carsten (1974) indicated that oxytocin inhibited ATP-dependent calcium binding which caused calcium released from intracellular storage sites or that it increased the entry of calcium into the cell, those results were consistent with the uterine contractile action of oxytocin.

The increased use of oxytocin for induction and stimulation of labour has been accompanied by a rising incidence of dangerous complications. The dose should probably not exceed 8 mU per minute, and to be administered under close supervision (Pauerstein, 1973). Excessive uterine contractility was almost the result of excessive dose of oxytocin (Danforth, 1977). Intravenous administration of a bolus of 0.5-10 i.u. Oxytocin was associated with a transient fall of blood pressure followed by increased in mother's heart rate (Pauerstein, 1973 ; Tepperman, 1977). Watson (1913) had noted that, in mother, intravenous administration of this agent could caused pallar, cyanosis, trachycardia and sweating. Water intoxication was an uncommon complication of the infusion of oxytocin, it occurred when large doses of oxytocin were administered with large volumes of electrolyte-free fluid over a prolonged period, so that the patients became water logged (Tepperman, 1977). It characterized by confusion, nausea, convulsion and coma. In this study, there were nausea in some mothers, but any other side effect did not occurred.

The only complication that might be due to direct action of oxytocin on the fetal was neonatal hyperbilirubinemia. The relation between oxytocin administration in labour and the subsequent development of neonatal jaundice was first suggested by Mast, et al. in 1971. It was confirmed by Davies (1973); Chalmers (1975); D'Souza (1979) that the incidence of hyperbilirubinemia was increased in neonates of mothers whose labours were induced by oxytocin. It was postulated that this might be due to a toxic effect of synthetic oxytocin.

In this study, the results showed that, there were significant difference in bilirubin levels between infants in control group and subject I group (received less than 4,000 mU of oxytocin) in 24 hours ($P<0.001$) and 48 hours of ages ($P<0.01$), but no significant difference in 72 hours of ages ($P>0.05$).

"Physiologic jaundice" is the most common form of unconjugated, non-hemolytic hyperbilirubinemia in the neonatal period. Maximum serum bilirubin concentration occurs at three to four days of ages (mean 6 to 8 mg. per 100 ml.) and rapidly diminishes thereafter. Certain Asian group, some American Indian and some population groups in Greece have higher peaks of "physiologic" hyperbilirubinemia (Johnson, 1975). It is believed to result from delayed development of hepatic gluculonide conjugating system (Lathe, et al., 1957; Brown, et al., 1958; Gartner, et al., 1963), particularly glucuronyl transferase (Lucey, et al., 1962).

Since maximum bilirubin concentration of physiologic jaundice occurred at three to four days of ages, so it may interfere the result of this study especially on the third day of minimal dose of oxytocin induction (table 8). The further study may be needed about this phenomenon.

From the comparison of bilirubin level between infants in control group and subject II group (received more over 4,000 mU. of oxytocin), there were significant difference in ages 24 hours ($P<0.001$), 48 hours ($P<0.001$) and 72 hours ($P<0.01$).

This study similar to the earlier studies of Ghosh and Hudson (1972); Davies, et al. (1973); Calder, et al. (1974); Robert and Weaver (1974); Chalmers, et al. (1975); Sims and Neligan (1975); Conways, et al. (1976); Chew (1977); Smith and Wilson (1978) and D'Souza (1979), that oxytocin infusion using in labour induction was associated with raised level of plasma bilirubin in neonatal blood.

D'Souza (1979) suggested that in induced labour, there was an increased loss of fetal red blood cells. Increased level of plasma bilirubin may therefore reflect an increased rate of red cell breakdown and an enhancement of hemoglobin catabolism. This implied that induced labour was in some way damaging to fetal red cells. One cause for such damage may be trauma due to the contracting uterus under the influence of oxytocin acting directly on the fetus from the onset of labour. Singhi and Singh (1977), and Buchan (1979) indicated that the vasopressin-like action of oxytocin caused activation of electrolyte and water transport across the erythrocyte membrane with consequent osmotic swelling, which is a well recognized cause of reduced erythrocyte deformability and leads to more rapid erythrocyte destruction, hence more rapid destruction with resultant hyperbilirubinemia in the neonate. They suggested that time and dose related reduction in erythrocyte deformability in response to oxytocin.

Buchan's study was shown that the hyperbilirubinemia after induction of labour was related to the dose and the duration of

the oxytocin administration. Beazley and Aldermann (1975) showed that there was a relation between the total dose of oxytocin adminised to mother and the level of plasma bilirubin in blood. Ghosh and Hudson (1973) virtually eliminated neonatal hyperbilirubinemia of unknown etiology in their hospital by lowering the dose of oxytocin used for induction. Friedman (1974), Chalmers (1975), and Sims (1975) supported this suggest that there was a dose relationship. Jeffares (1977) suggested that a dose of about 20 mU. per min. was required before the effect was appearance.

In this study, in age 24 hours, the difference of bilirubin levels between subject I group (received oxytocin less than 4,000 mU.) and subject II group (received oxytocin more over 4,000 mU.) showed no significant ($P>0.05$) but showed significantly in age 48 hours ($P<0.01$) and in age 72 hours ($P<0.02$). This result was confirmed by clinical observation in neonate in subject II group, that three of them (18.75%) had bilirubin level more over 14.75 mg. % (Table 6), and had to be treated by phototherapy. This results were similar to to D'Souza study that, the higher doses of oxytocin administered were reflected by higher level of plasma bilirubin.

Beazley and Alderman (1975) had suggested that the higher dosage level of oxytocin should be used with caution, disadvantages of neonatal jaundice may occur.

There are many other factors which may cause the elevation of bilirubin level in neonatal blood or hyperbilirubinemia. Among them

are genetic factors such as blood group incompatibility, glucose 6-phosphate dehydrogenase deficiency, caloric intake, decrease gut motility and stool frequency, increased red blood cell mass at birth, drugs and hormones that alter hepatic microsomal metabolism, infection, poor illumination in nursery, birth trauma, and reduced in liver perfusion. This study have carefully eliminated a large number of environmental factors which can be resulted the difference in bilirubin levels.

Claireaux, et al. (1953) had commented on the significant of the fact that neonate, haemolytic disease (ABO incompatibility, Rh factor incompatibility) these occur much greater concentrations of plasma bilirubin than are found in the adult. In this study, all ABO and Rh factor incompatibility between mothers and infants were excluded.

Arias, et al. (1964) showed that breast feeding is well recognized causal factor in the production of neonatal jaundice because some mothers secrete pregnane 3-alpha,20-beta, diol; a hormone which interfere with bilirubin conjugation, in their breast milk and infant become severely jaundices (Davies, 1964). Newman and Gross (1963) found that prolonged jaundice was more common in breast-fed than in artificially fed newborns. In this study, all infants were fed with cow's milk, breast-fed were excluded. Smallpiece and Davies (1964) suggested that infants who are fed late or inadequately in the first few days had higher serum bilirubin levels than those fed early and adequately. Possibly different types of feeding might lead to different degrees of jaundice in newborn infants. In this study, all

infants were started with water-fed in 6 hours of ages, milk-fed in 12 hours of ages. All of them received milk-fed every 4 hours, of the same amount and the same times.

Sims (1975) showed that lower gestational age (less than 37 weeks) cause neonatal jaundice, in this study, mean gestational age of all groups were similar and all of them were at term, that were 38-42 weeks (see table 7).

The mean packed cell volume varies with the age of the infant. Fetal blood is relatively rich in erythrocytes which number between five and seven million per cubic millimeter. There may be a transient in increase during the first few hours after birth due to redistribution of plasma water and electrolytes, but there is a rapid fall to lower level during the first week due to breakdown of fetal red blood cell, and more gradual fall in the next three months (Vaughan, V.C., et al., 1975).

The mean packed cell volume is also related to the volume of intravascular fluid. The inadequate intake or excessive fluid lost will reduce intravascular fluid, so apparently packed cells volume may be relatively higher.

In this study, all the infants in both control and subject groups were almost in same condition (all in same room and fed almost the same amount). So mean packed cells volume in the study should related to the destruction of red blood cell only and should vary reversely with bilirubin level.

Drugs which displace bilirubin from binding sites on plasma albumin may also produce kernicterus in neonate, such drugs include sulphonamides, aspirin and other acidic anti-inflammatory drugs, and vitamin K analogues. These drugs can cross the placenta and should be avoided in pregnant women near term and used with caution in neonates (Bowman and Rand, 1980). There can be no doubt that synthetic and other diphosphate derivatives of menaphthone raise the serum bilirubin levels in premature infants when given intramuscularly in doses of 10 mg. or more (Bound and Telfer, 1956; Meyer and Angus, 1956). Their action is probably haemolytic. In this study, all infants received vitamin K1 intramuscularly in the first day of life, which Hutchison (1975) demonstrated that, it did not raise the serum bilirubin level and is now available in using in nurseries.

The aspect of this study was to considered the effects of drugs, which mothers had received 3 months before delivery (near term), on serum bilirubin concentration in the newborn infant. Such drugs were listed by trade name in table 11, 12 and 13. The pharmacologically active ingredient were shown in appendix part. From the 3 months retrospective studied about drugs which all mothers had received, none of them had ingested all drugs in table 3. Mothers who received chronic drugs were excluded from this study, so that the most frequently ingested drugs in this study were prenatal supplement such as Satibon® (40.59%), Fero-B-Cal® (33.66%) etc.

Abdul-karim (1977) were observed that no adverse effect in the

neonates of the patients who consumed acetaminophen compound during pregnancy.

The antibiotic, Penicillin, Ampicillin and Tetracycline were prescribed for respiratory tract infection rather than urinary traction infection. The administration of Penicillin and Ampicillin resulted in no observable alterations in infant serum bilirubin concentration (Drew and Kitchen, 1976). Tetracycline cross the placenta and found in fetal tissue and can have toxic effect on the developing fetus (often related to retardation of skeletal development) (PDR.,1980), no reported about its effect on neonatal bilirubin levels.

About Mycostatin® vaginal tablet, no adverse effect or complication had been attributed to nystatin in infants born to women treated with this drug (PDR., 1980).

Pethidine is one of the most commonly used narcotics for maternal analgesia. The fetus acquired high concentrations of pethidine within the first hour after maternal administration (Cooper, et al., 1977), and neonatal depression may result if delivery occurred more than an hour after its administration (Morrison, et al., 1976). Beyond neonatal depression, less obvious effects on feeding and ventilation up to 48 hours after delivery had also been attributed to pethidine (Wiener, et al., 1977). Brackbill, et al. (1974) found that the inhibitory ability of the infant was most sensitive to maternal pethidine dosage. In this study some mothers had received pethidine during labour, but there were no reported about its effect on

bilirubin level in infants. The further study is needed.

Phenergan was injected combined with pethidine for sedative effect, and it used for antiemetic effect in obstetric used. The safe use of phenergan has not been established with respect to the possible adverse effects upon fetal development. The suggestion that phenergan altered serum bilirubin concentration may not be correct as significant changed were not achieved as test by regression analysis (Drew and Kitchen, 1976). An isolated study of the influence of this drug on bilirubin concentration is required. Therefore the need for the use of this drug during pregnancy should be weighed against the possible but unknown hazards to the developing fetus.

A major problem of this study on drug effect is the effects that could be due to other factors such as an interaction of many drugs. The drugs which mothers had received in first and second trimester must be considered, the influence of those drugs that increased serum bilirubin level in neonatal needs discussion in more detail. The amounts of drug consumed in this study could have been under estimated because some mothers failed to remember that they had taken more any-other drug excepted in prescription. Schenkel and Vorherr (1974) suggested that pregnant women should never use drugs without a doctor's advice whenever drug treatment appears to be necessary the risks of drug-intake have to be weighed against the benefits. For the therapeutic purposes for relief from discomfort, the least harmful drug, dosage and route of administration with consideration of the gestation phase,

will keep embryonic and fetal damage to minimum. Self-medication should be avoided.