FETAL AND NEONATAL COMPLICATIONS OF MATERNAL DRUG THERAPY IN PREGNANCY AND LABOUR

THESIS

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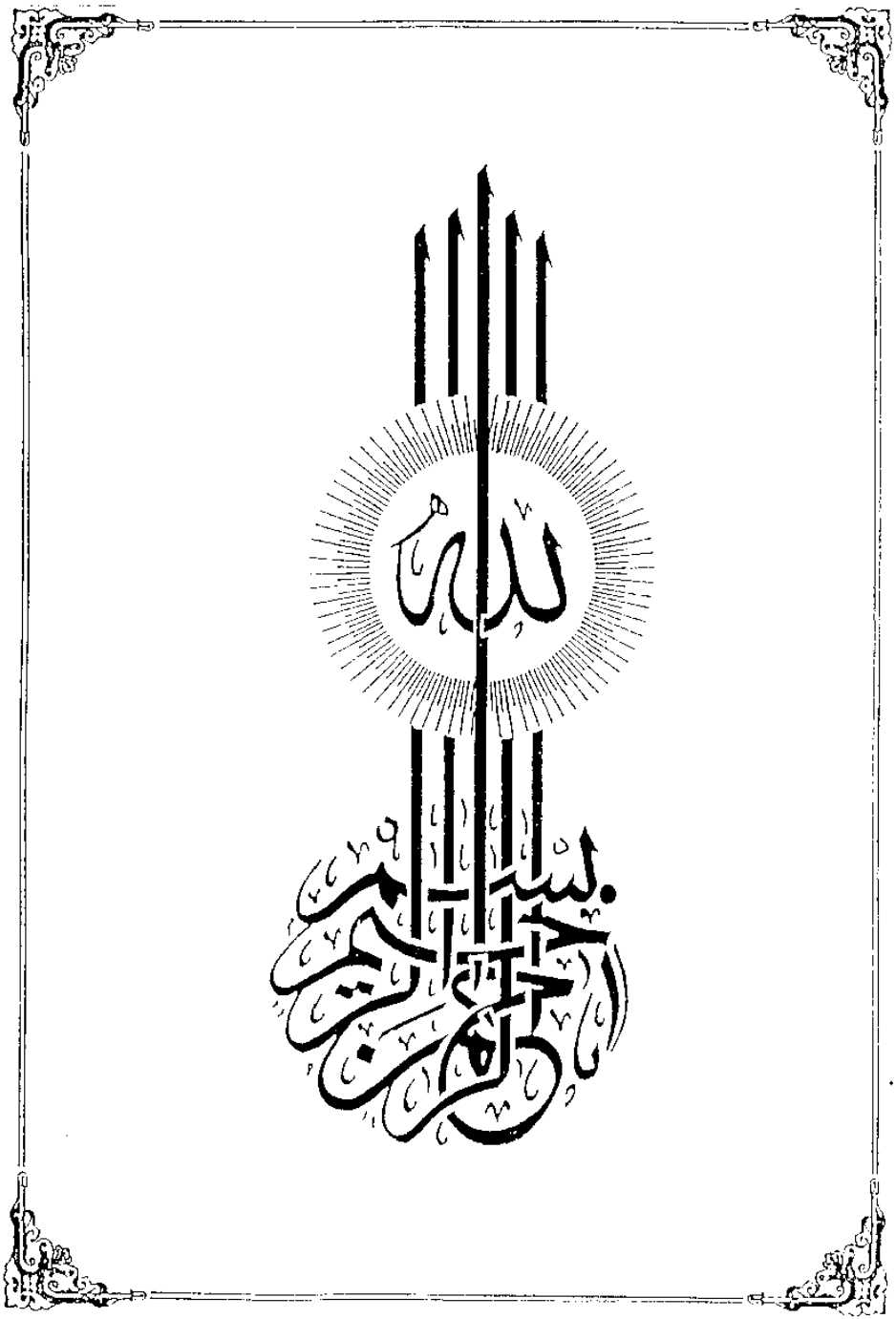

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Clinicians have become increasingly aware of the risks to which the fetus and newborn baby are exposed due to drugs ingested by the mother during pregnancy and labour.

Many drugs could be avoided if we learn its hazards and complications.

It will be easier to manage a newborn without such hazards by knowing a more detailed pharmacology of different drugs that could be used by mothers during pregnancy and labour.

In this way we can help the paediatrician as well as the obstetrician to choose the safer, to avoid the hazardous drugs and weighing the maternal need against the risk of fetal damage.

So the aim of this work will be a trial to show the effects on the fetus and the newborn of different drugs that could possibly be taken by mothers during pregnancy and labour.

The adverse drug effects will be categorized in such a way so as to avoid those with teratogenic effects, as well as those which have an effect on early pregnancy different from those of late pregnancy and labour.

We shall as well consider the indications and possible substitution by other safer drugs.

EFFECTS OF DRUGS ON THE EMBRYO AND FETUS

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Drugs may affect a fetus either directly after passage across the placenta, or indirectly through altering maternal physiology.

These drug effects may be a direct insult to the fetus if given to the mother at a crucial stage of embryological development leading to teratogenecity (Reynolds, 1970), or through pharmacological actions acting on many sites as on the placenta, uterus or uterus or on the mother's hormones and biochemistry.

Certain drugs are predictably teratogenic especially if they have an effect on cell division, enzymes, protein and DNA synthesis. So cytotoxic drugs, as alkylating agents, antimetabolites and antibiotics are all potentially teratogenic (Scott, 1977).

The teratogenic potential of a drug depends upon:

1- the actual passage of this drug into the fetus.

2- the ability of the fetus to carry out the appropriate metabolic processes; which depends upon the necessary enzyme systems that are present to a small extent in human fetal liver (Reynolds, 1970).

The placenta is not simply a passive "barrier" between mother and fetus. Essential substances as amino acids are transferred actively against a concentration gradient. However drugs administered to the mother pass chiefly through passive diffusion down a concentration gradient. The principal factor affecting transfer solubility in lipids. Consequently lipid soluble drugs pass rapidly into the fetus, but drugs that are insoluble in lipids still can cross placenta if present in high concentration. Also the accurate prediction of entry into the fetus depends on knowing the rate of transfer from fetal to maternal circulation, and the dose and duration of the administration(Laurence and Bennet,1980).

Placental transfer means the rate of movement of the drug across the placental membrane. So this rate depends upon placental area and thickness of the membrane as well as the blood flow on either sides. It is presumed that the placental membrane is thicker in early pregnancy and this is supposed to reduce placental drug transfer (Kennedy et al.,1979).

Drug factors such as the diffusibility and lipid solubility are much more important in determining placental transfer, than the placental thickness. Pethidine is a

good example for drugs which are highly lipid soluble so easily diffuses the placenta from mother to fetus (Crawford and Rudofsky, 1965).

A drug which is neither ionized nor bound to plasma protein is freely diffusible across a lipid membrane (Ehrnebo et al., 1971). Thus for weak acids and bases a higher degree of ionization and high protein binding in maternal plasma both reduce the effective diffusion concentration.

Drug concentration on either side of the placental membrane is another factor which affects the rate of diffusion. If a full dose of a lipid soluble drug is given rapidly intravenously to a mother; it will pass more rapidly across the placental membrane than if given intramuscularly or slowly intravenously (Reynolds, 1983).

Since lipid soluble drugs cross the placenta very rapidly, they are taken and concentrated in fetal tissues. Therefore the longer the persistance of the drug in maternal plasma, the more it can accumulate in fetal tissues. Tissue uptake of drugs by the fetus has been studied in animals and is related to the site of embryo toxicity. Tetracyclines have been shown to be concentrated in the skeleton in the mouse fetus (Ullberg, 1973).
Chloroquine and chlorpromazine are highly concentrated in the fetal eye and may be associated with retinal damage (Ullberg, 1973; Dencker, 1978). Also the drug pharmaco-

kinetics in the fetus are different from that of the mother because of undeveloped metabolic and excretory processes leading to persistance of a drug and its metabolites. A clear example is, when CNS depressants are given to the mother it may persist in the baby for days after birth. However some drugs as the enzyme inducers e.g. phenobarbitone are effective to enhance the ability of the newborn to conjugate free bilirubin by inducing the enzyme glucuronyl transferase if given to the mother prior to labour. This prevents the occurrence of kernicterus (Laurence and Bennet, 1980).

Bodendorfer et al. (1979) have proved that pregnant women, despite the thalidomide tragedy and extensive amount of research and literature on teratology, are still exposed to a variety of potential teratogens. They showed that there is a relatively high rate of fetal exposure to salicylates and cigarette smoking. The incidence was 5 1/2% with Bodendorfer while it had been 2% by Nelson and Forfar (1971) and 13% by Hill (1973).

Next to this is the outstanding usage, routinely, of iron supplements, caffeine-containing beverages, alcoholic beberages and vitamin therapy which are commonly used in early pregnancy (Bodendorfer et al., 1979).

After these in frequency comes in order of common use: The antiemetics, barbiturates, diazepam, hallucinogens and

VITAMINS AND MINERALS

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Many physicians recommend routine prophylactic administration of iron and folic acid during pregnancy (Kitay and Harbort, 1975) while some are doubting about the benefit of such a routine (Hall et al., 1976). The prophylactic use of other vitamins is less often recommended (Hemminki and Starfield, 1978). Most pregnant women have iron and vitamin levels which are lower than in the nonpregnant state (Hytten and Leitch, 1971). Some consider declining hemoglobin levels during pregnancy to be physiological (Hytten and Leitch, 1971). This may be considered to be pathological due to increased requirements not met by the diet or iron reserves (Haynes, 1969). Women with low hemoglobin values have a higher incidence of low birth weight infants. Kalterider and Johnson (1976) found that mothers who had not taken any iron or vitamin supplements had more pre-term infants.

Some surveys have shown an association between low folic acid levels and pregnancy wastage but others have not (Davies, 1981). It has become a policy in recent years to withhold prophylactic oral iron from patients during the first 12 or 14 weeks of pregnancy. This probably arose partly from Nelson and Forfar's (1971) survey which suggested that there might be an association between iron given in the first few weeks and congenital malformations. Although

Nelson and Forfar's (1971) retrospective study suggested a possible association between oral iron given in the first few weeks of pregnancy and a low incidence of fetal abnormality. This was not confirmed in the Royal College of General Practitioners' prospective study (1975). However other workers have resolted to a wisdom of not giving iron supplements unless it is indicated (Hemminki and Starfield, 1978). Nonetheless, obstetricians do not object to the avoidance of oral iron administration during the first trimester, while morning sickness may be a problem.

Iron preparations have been said to be the commonest cause of vomiting in pregnancy and may give rise to constipation or diarrhea (Hawkins, 1983).

It has been proved through clinical trials that vitamin B_6 supplementation produced fewer dental caries. And when accompanied by supplementation with different minerals and vitamins, it has produced fewer deliveries before the 40th week and less pre-eclampsia (Hemminki and Starfield, 1978).

Vitamin A:

Animal experiments, demonstrated that vitamin A was teratogenic, both as a deficiency and as an excess in the diet (Hale, 1933; Warkany and Roth, 1948; Cohlan, 1953; Kalter, 1968). A wide variety of malformations have been produced experimentally, including neural-tube defects.

Human studies have been few, but isolated cases have been cited which could attribute a teratogenic effect to dietary vitamin A, if present in insufficient amounts (Houet and Ramioul Lecomte, 1950; Sarma, 1959; Lamba and Sood, 1968) or when consumed in excess (Pilotti and Scorta, 1965). Smithells et al. (1980) found that vitamin supplementation including vitamin A, during pregnancy in a dose of 4000 I.U. daily reduced the incidence of neural tube defects, and Parkinson and Tan (1982) suggested that vitamin A should not be included in supplements until there is definite evidence that it is harmless and animal studies have shown the contrary.

Gal et al. (1972) estimated serum vitamin A levels, during the post partum period, in 106 women who had given birth to a baby with neural tube defect. The vitamin A levels were significantly higher compared with those in a group of control women whose babies were normal. They also found that fetuses with neural tube defects tended to have higher liver concentrations of vitamin A compared with those in normal fetuses.

Parkinson and Tan in 1982 have found that the vitamin A content of amniotic fluid is significantly greater in the presence of a fetal neural tube defect and that the vitamin A levels show a positive correlation with amniotic fluid zinc, alpha fetoprotein and copper concentrations. Their