MATERNAL DRUGS AFFECTING THE NEWBORN

ESSAY

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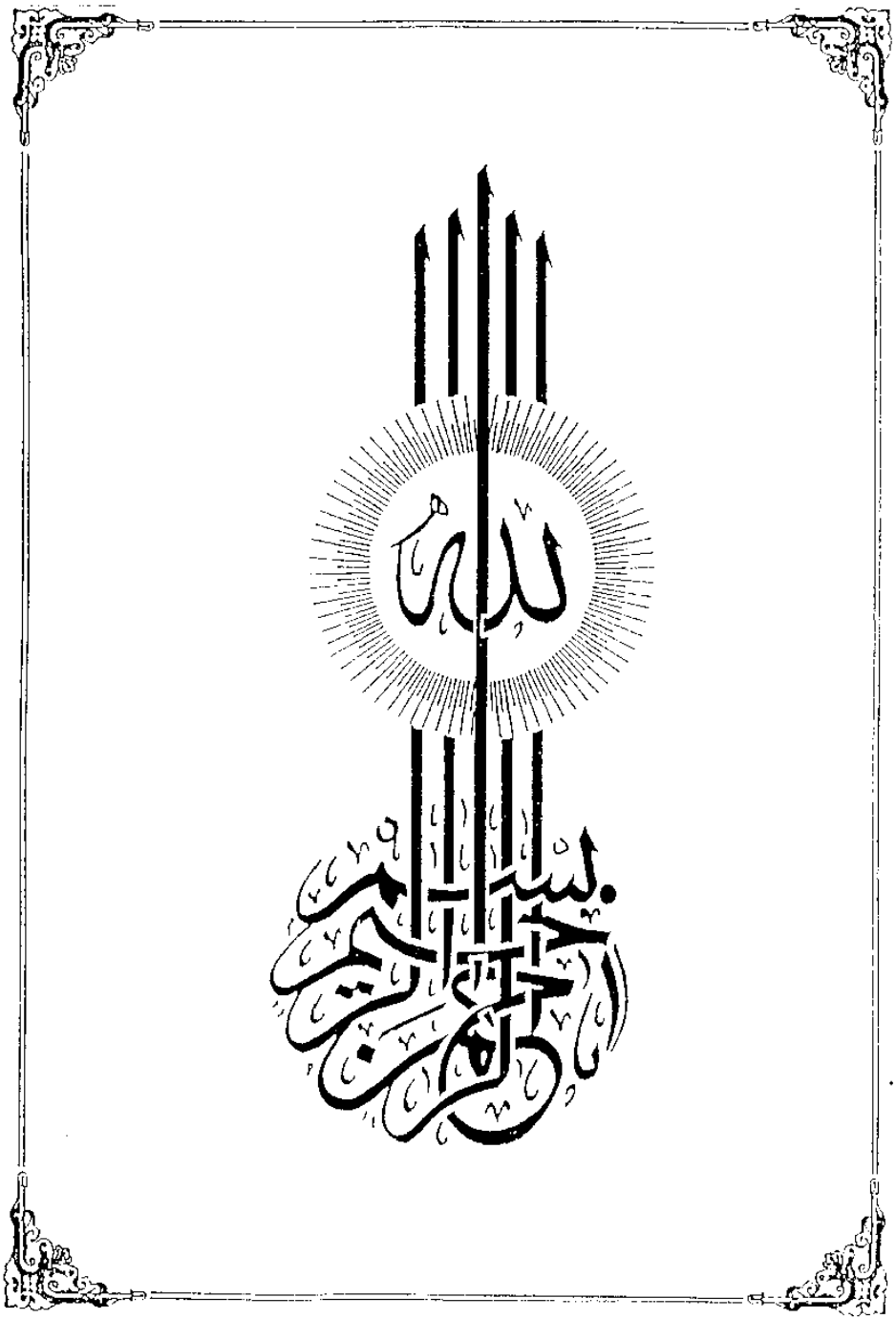
بسم الله الرحمن الرحيم

"قالوا سبحانك لا علم لنا إلا ما علمتنا
إنك أنت العليم الحكيم"

صدق الله العظيم



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Introduction and aim of essay

INTRODUCTION
AND AIM OF THE ESSAY

Mother and fetus are closely linked by a cord via which many beneficial and harmful agents pass. The passage of these agents across the placenta is governed by many factors, some relating to the placenta, whether normal or diseased. Effects of drugs on the yet developing human being vary greatly from tragic congenital anomalies, as caused by thalidomide, to drug addiction, to even mild affections as nasal stuffiness.

During labour, the mother is offered many drugs, some to facilitate delivery some to relieve pain, and some to treat conditions as epilepsy or eclampsia. The effect of such a wide range of drugs, on the newborn, is evident in the first few hours of its life.

Lactation offers the baby nutrition and love, together with these it carries any lipid soluble drug which the mother takes.

With the same love and pain the mother carries, delivers,and feeds her baby, she must keep a vigilant eye on what, through her, reaches this baby,

The aim of this essay is to discuss the following :

1- Effect of drugs taken by the female before conception on her offspring.

2- Effect of drugs taken during pregnancy on the fetus; and factors affecting the passage of drugs through the placenta.

3- Effect of drugs used during delivery on the newborn.

4- Drug excretion in milk and factors affecting it.

Effect of drugs taken before conception

EFFECT OF DRUGS TAKEN BEFORE CONCEPTION

1- Drugs causing chromosomal damage in offspring :

Toxic effects on chromosomes are reported to occur with the use of perphenazine and, to a lesser degree, chlorpromazine. Chromosome abnormalities have also been reported in patients treated with lysergide (LSD) **(Gill and Davis , 1974)**.

Infants born to mothers exposed to LSD during pregnancy have shown an increase in chromosomal fragmentation **(Egozcue et al, 1968)**.

No increase in risk for chromosomal abnormalities was found among women who had used oral contraceptives prior to becoming pregnant **(Harlap et al, 1985)**.

2- Drugs used to induce ovulation :

The rate of dizygous twinning is variable and is influenced by drugs which induce ovulation. The average twin weight at term is approximately 2600 gm. There is increased incidence of complications especially pre-eclampsia, polyhydramnios, and premature delivery **(Stark, 1985)**.

Congenital anomalies occur about twice as frequently in twins compared to singletons **(Stark, 1985)**.

Perinatal mortality is increased 4-11 times among twins compared to singletons **(Marviste, 1982)**.

3- Drugs used to prevent conception :

These drugs may act by interfering with ovulation or implantation, and it is suggested that they may have long term effects on maternal metabolism, and previous use of the "pill" may affect the fetus **(Gill and Davis, 1974)**.

In susceptible women vitamin A levels are high for some months after cessation of treatment with oral contraceptives , and such high levels may possibly be teratogenic **(Gal et al, 1971)**.

There are probably genetic differences in the way vitamin A is metabolized, both in mother and fetus, and these may influence the outcome. Very small malformed, or absent ears ; atretic ear canals, cleft palate, cortical blindness, severe congenital heart-defect, particularly involving anomalies of the great vessels and interrupted aortic arch were reported. Also central nervous system malformation, including hydrocephaly, decreased cerebral tissue, and posterior fossa cysts, have been seen singly and in combination **(Stern et al, 1985)**.

The frequency and severity of respiratory distress syndrome in the newborn seem to be reduced after pre-pregnancy use of oral contraceptives, and there is a possibility of an increased chance of subsequently delivered infants being female. **(Gill and Davis, 1974)**.

It is also reported that neonatal jaundice in breast fed babies is associated with the taking of oral contraceptive prior to conception. **(Wong and Wood, 1971)**.

Drugs affecting the fetus during pregnancy and transplacental passage of drugs

DRUGS AFFECTING THE FETUS DURING PREGNANCY AND TRANSPLACENTAL PASSAGE OF DRUGS

A- Physiologic Considerations :

1- The utero placental circulation :

This is responsible for bringing nutritive materials and oxygen to the fetus, and taking away carbon dioxide and other fetal waste products. The dynamics of the maternal side of the circulation are such to produce vis-a-tergo effect that favours unimpeded flow from maternal arteries to the intervillous space and then to the maternal veins **(Ramsey, 1962)**.

Perfusion pressure is often increased in disease such as toxemia, and placental damage may increase the size of placental pores **(Gill and Davis, 1974)**.

From the intervillous space the oxygen and nutrients are transferred across placental membrane to the fetal circulation which consists of a capillary network contained in the chorionic villi. The dynamics of the fetal circulation are also such as to produce a vis-a-tergo effect **(Ramsey, 1962)**.

2- Placental Transfer :

Placental transfer is achieved by a simple and facilitated diffusion, active transport which includes active enzymatic transfer and enzymatic destruction, and through special processes, including pinocytosis and breaks in the placental villi **(Moya and Thorndike, 1962)**.

The rate of diffusion of drugs is governed mainly by Fick's Diffusion Equation:

$$\frac{Q}{t} = Ka \frac{(Cm - Cf)}{D}$$

Where

$\frac{Q}{t}$ = quantity of drug diffusion in unit time

a = the surface area over which diffusion is occuring.

(Cm-Cf) = concentration gradient between the maternal (Cm) and fetal (Cf) circulation.

D = thickness of the membrane.

K = diffusion coefficient or constant, **(Corke, 1984)**.

Compounds with a molecular weight below 600 readily cross the placenta, whereas the placenta is relatively impermeable to those above 1000. **(Corke, 1984)**.

Non ionized drugs with high solubility are transferred rapidly, whereas lipid insoluble drugs penetrate poorly despite a low degree of ionization **(Bonica, 1969)**.

The degree of ionization of a drug is an important determinent of placental transfer because only nonionized drugs readily cross the placenta. The degree of ionization of a substance depends on the nature of the substance (acid or base), its dissociation constant (pka), and the pH of the medium in which it is present. The pka of a drug is the pH at which it is 50 percent ionized and 50 percent unionized **(Corke, 1984)**.

The degree of plasma binding of a drug has an important effect on placental transfer in the pregnant female because it is only the free or unbound drug

At the third month of gestation, human fetal liver microsomes have significant cytochrome P-450 levels and NADPH cytochrome C reductase **(Ralston, 1981)**.

The human fetal adrenal gland possesses the ability to catalyze certain important oxidation reduction reactions **(Corke, 1984)**.

Drugs taken by the female after conception, but before implantation, have been shown in animal experiments to reach the pre-implantation blastocyst **(Sieber and Fabro, 1971)**. It is thus conceivable that drugs, particularly those which may accumulate in the uterine secretions, could harm the conceptus before implantation, and this is relevant to the introduction of a morning after contraceptive pill **(Gill and Davis, 1974)**.

Drugs taken by the mother during pregnancy can affect the fetus in either or both of two ways ; either directly after passage of the drug or its metabolites across the placenta, or indirectly by interfering with maternal or placental metabolism **(Gill and Davis, 1974)**.

5- Mechanisms of Teratogenicity :

One of the most obvious mechanisms of teratogenicity is damage to genetic material. A number of anticancer drugs have the ability to damage desoxyribonucleic acid (DNA) or messenger ribonucleic acid (m RNA). The antibiotic actinomycin D forms a stable complex with DNA, thereby preventing the formation of m RNA and ultimately leading to a complete breakdown of protein synthesis within the cell. Diethyl ether may inhibit transport of m RNA **(Smith, 1968)**.

Anesthetics even in low concentrations have antimitotic effects, and nitrous oxide is known to be a metaphase blocker in cell culture **(Rao, 1968)**.

Another mechanism by which drugs cause malformation is metabolic alteration. Anesthetics have profound effects on normal energy metabolism and in particular depress oxidation in the electron transfer chain and oxidative phosphorylation **(Cohen and Marshall, 1968)**.

B- Beneficial Effect of Drugs Used During Pregnancy :

Management of Maternal Diabetes Mellitus :

Miller et al (1981) reported that women with poor diabetic control in the first trimester had more infants with anomalies than did those with euglycemic control diabetes.

With rigorous diabetic control before and throughout pregnancy , no offspring were born with congenital anomalies (risk lower than for a normal population). **(Schaffer, 1984)**.

Types of anomalies seen in infants of diabetic mothers are central nervous system malformations, anencephaly, meningocele syndrome, cardiac defects, vertebral dysplasia, other bony anomalies , renal anomalies , and the caudal regression syndrome (sacral agenesis) **(Cloherty and Epstein, 1980)**, and micro-colon **(Schaffer, 1984)**.

Women needing treatment beyond dietary control should receive insulin rather than oral agents **(Zucker, 1968)**.