Drugs Affecting Pregnancy and Lactation with special Reference to their teratogenic Effect

An Essay
Submitted in partial fulfillment
for Master Degree in Gynaecology and Obstetrics

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1992

Acknowledgement

I would like to express my deepest gratitude to our dear **Prof. Dr. Mahmoud Karim**, *Professor of Obstetrics and Gynaecology, Faculty of Medicine, Ain-Shams University. His fatherly care and sincere guidance are beyond the scope of human expression.*

I wish to cordially thank **Dr. Maged MR Abou-Seeda**, *Lecturer of Obstetrics and Gynaecology, Faculty of Medicine, Ain-Shams University, for his generous help and sincere criticism.*

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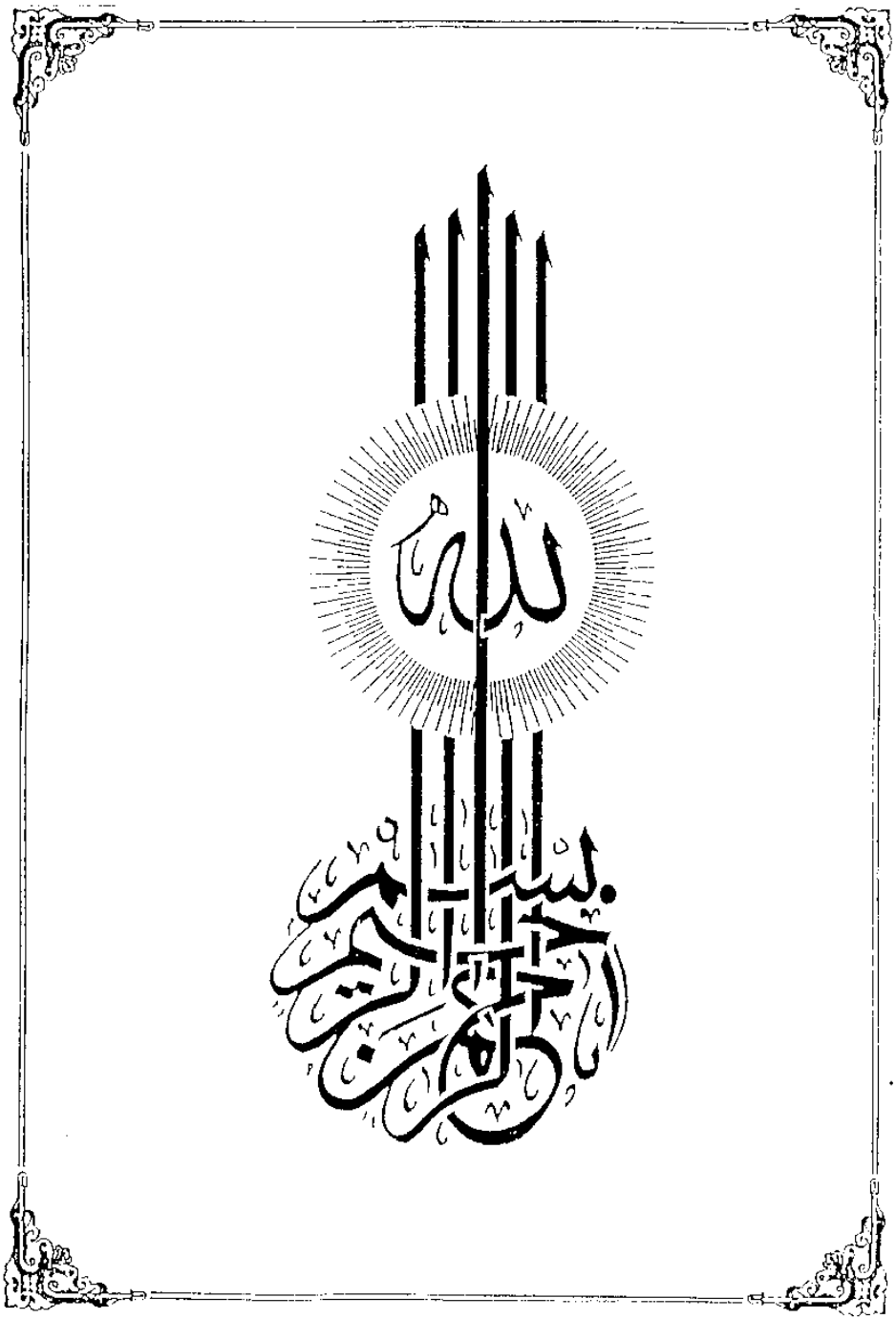

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Teratogenic agents

A teratogen can be defined as any agent that can cause prenatal injury. This agent may be mechanical, chemical, nutritional or infectious. It probably acts within the first 8-12 weeks of gestation **[Warkany and Fraser, 1975]**.

(1) Smoking:

The adverse effects of maternal smoking on the fetus are multiple and well documented. They include fetal death, intrauterine growth retardation, and a host of additional problems which may extend beyond infancy (Nieberg et al., 1985).

Hoff et al., [1986] reported that maternal smoking of more than half a pack of cigarettes daily during pregnancy increased the risk of neonatal jaundice.

Tuchmann-Duplessis [1977] reported that the lower birth weight has been attributed to fetal malnutrition which result either from an effect of smoking on uterine circulation or in the mothers ap-

petite, it has been suggested that chronic hypoxia of the fetus carried by mother who smokes heavily may result in lower fetal weight.

It has been suggested that the incidence of spontaneous abortions among smokers is somewhat increased compared with that in nonsmokers **[Murphy and Mulcahy 1978]**. The incidence of both low birth weight infants (less than 2500gm) and preterm deliveries before 37 weeks is higher in mothers who smoke during pregnancy **[Pirani 1978]**.

A contributory factor is the increased incidence of premature rupture of the membranes **[Underwood et al., 1967]**. As pregnancy advances the placenta may develop histopathological changes in heavy smokers **[Asmussen, 1977; and Naeye, 1978]**, including broadening of the basement membrane of the placental villi, intimal damage of the placental vessels, and increase in the collagen content of the villi. These changes are characteristic of under- perfusion from the uterus.

Many authors have found a small decrease in the average size of babies born of mothers who smoke during pregnancy **[Sidle 1982]**. Growth retardation can be assessed with antenatal ultrasonic

biparietal diameter measurements, which show a rather lower than average rate of increase in some women who smoke.

This decrease in growth may be seen from 21 weeks onwards **[Murphy et al., 1980]**. cigarette smoking has been shown to cause a reduction in the incidence of fetal breathing movements in both normal and abnormal pregnancies **[Manning and Feyerabend 1976]**. Many authors have found a decrease in the incidence of pre-eclampsia in smokers **[Pirani 1978, Sidle 1982]**. The reason for this is uncertain; but when pre-eclampsia with proteinuria does develop in a smoker the prognosis is impaired. The incidence of antepartum haemorrhage is slightly increased in women who smoke **[Butler and Alberman 1969]** presumably because of reduced blood flow causing ischaemia.

It is now well established that smoking has adverse effects on the developing fetus and these have recently been reviewed. The main effects are fetal growth retardation, an increase in spontaneous abortion and increased perinatal mortality, the reduction in birth weight correlates directly with the number of cigarettes smoked **[Mac Mahon et al., 1966]**. Excessive smoking has also been incriminated in the aetiology of congenital heart malformations and

retroplacental fibroplasia **[Tuchmann. Duplessis, 1978]**.

Ericson et al., 1979 found a significant increase in the smoking habits of women who had infants with cleft palate and cleft lip. Hinds and Kolonel in 1980 reported a correlation between the percentage of women smokers and the total cancer incidence among their offsprings. This suggests that offsprings exposed transplacentally to carcinogens of smoking may be at increased cancer risk. Nikonava in 1977 found that offspring of mice that had been injected with benzopyrine (one of the polycyclic aromatic hydrocarbons, an important constituent of tobacco smoke) late in pregnancy showed high incidence of neoplasms of lung, liver and mammary gland.

(2) hyperthermia:

In retrospective analysis it was found that febrile illness or sauna bathing during the early weeks or months of pregnancy was associated with prenatal mal-development. Increased frequency of anencephaly, spina bifida, micropthalmia, and unusual faces were reported **[Miller and Smith, 1978]**.

(3) Alcohol:

It has been known for centuries that alcohol taken in excess in pregnancy may damage the fetus. An increase in perinatal mortality and morbidity was noticed during the English gin epidemic of 1720 to 1750 **[Warner and Rosett 1975]**. During the past few decades more reports have appeared of the adverse effect on fetal growth and development and in the 1973 the term "fetal alcohol syndrome" was coined by Smith and his colleagues in the united states of America **[Jones and Smith 1973]**.

Heavy drinking (more than 40gms alcohol daily) during pregnancy is associated with a characteristic pattern of fetal abnormalities known as the "fetal alcohol syndrome". In its complete form this consists of fetal and postnatal growth retardation, craniofacial abnormalities, microcephaly, behavioural abnormalities and mental retardation. The facial abnormalities include short palpebral fissures, short nose with sunken nasal bridge, epicanthic folds and micrognathia, producing a distinctive picture when all abnormalities are present. Other congenital abnormalities such as cleft lip and palate, skeletal deformities and congenital heart lesions may also be present. Moderate drinking in pregnancy may carry a risk, and epidemiological evidence suggests a dose, response relationship.

Thus the risk of having a child with the fetal alcohol syndrome has been estimated at approximately 10% for women drinking 30-50gm daily, increasing to 40% in chronic alcoholic women consuming more than 50gm daily **[Hanson et al., 1978]**. Incomplete forms of the syndrome are probably more common. There is no good evidence that an average intake of less than 20gm daily can be teratogenic or produce the fetal alcohol syndrome. But growth retardation alone has been reported with regular consumption of as little as 10gm (1drink) daily **[Mills et al., 1984]**. There may also be increased incidence of midtrimester spontaneous abortion in women who drink regularly during pregnancy **[Harlap and Shiono, 1980]**. The incidence of fetal alcohol syndrome has been estimated to be approximately 1-2 per 1000 births in U.S.A. and Sweden. Accurate figures for the UK are not available but an incidence greater than I in 2500 births has been suggested **[Poskitt, 1984]**.

Mechanism: The effects of alcohol appear to be independent of associated factors such as social class, smoking and malnutrition but whether alcohol acts as a direct fetal toxin or in some other way is unknown.

One suggestion is that the toxic agent may be acetaldehyde de-

rived from alcohol breakdown. Drinking might be particularly dangerous and it would be important to avoid the use during pregnancy of drugs which inhibit aldehyde dehydrogenase. These include not only disulfiram but also metronidazole, procarbazine, cephamandole, latamoxef and chlorpropamide even small amounts of alcohol could produce toxic levels of acetaldehyde in the presence of an inhibitor of its breakdown **[Dunn et al., 1979]**. It is of interest that the incidence of fetal alcohol syndrome is particularly high in American Indians many of whom have a genetically determined deficiency of aldehyde dehydrogenase activity **[Aase, 1981]**. The effect of alcohol on intrauterine growth is thought to occur throughout pregnancy and is reduced if a women stops drinking before the end of pregnancy [**Larsson et al., 1985**]. The teratogenic effects must occur in the first trimester but the developing brain remains vulnerable beyond the first trimester and may be especially at risk when neuroblasts are most actively dividing between the 12th and 18th weeks.

The reported pattern of anomalies in offspring from alcoholic pregnancies is consistent in three particular parameters. These three parameters make up the primary presentation of the fetal alcohol syndrome (FAS): (a) prenatal growth deficiency in length and

weight,(b) microcephaly, and (c) short palpebral fissures. Mild to moderate mental retardation is reported frequently, with average intelligence quotient (10) scores being around 68, although the range is quite wide. Delayed motor and language development is recognized in early infancy in most cases, and there is no improvement in developmental abilities as the child matures.

Hyperactivity, hyperacusis, hypotonia, and tremulousness are commonly described in young FAS infants, and symptoms of withdrawal similar to those of narcotic abstinence in neonates have also been noted. Evaluation of infants born to alcoholic mothers has revealed that they have lower levels of arousal, poor habituation, and are more restless and irritable than drug-free infants **[Schneider and Chasnoff, 1987]**.

(4) Cocaine:

The cocaine abuse during pregnancy may be associated with adverse perinatal outcome. The perinatal morbidity that has been reported with cocaine abuse includes lower mean gestational age at delivery and increased incidence of preterm delivery. In addition, increased frequencies of abruptio placenta, congenital anomalies, and neonatal withdrawal symptoms have been observed. Neonatal