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PRESCRIBING IN PREGNANCY

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ABSTRACT

While prescribing in pregnancy, the physician is confronted with the problem of alleviating the mothers symptoms and ensuring that no or minimal harm is produced in the unborn. Unfortunately, the rising trend of drug consumption during this period appears often to be in near-disregard to the unintended recipient "the unborn baby". This article examines various aspects that have to be considered before deciding on the appropriate therapy in a pregnant (possibly pregnant) woman as well as in lactating mothers.

Keywords: Drug Prescription, Pregnancy, Humans, Foetal Effects, Neonatal Effects

Number of Tables : 6 Number of References : 44

INTRODUCTION

While prescribing in pregnancy , the clinician is confronted with the problem of causing minimal side effect to the fetus or neonate, the unintended recipient and to ensure the maximum benefit to the pregnant woman. Despite the thalidomide tragedy of the sixties, drugs continue to be used with relative carelessness and surprisingly many for minor indications. Surveys of drug use in select obstetrics populations of United States, (Hill, 1973; Doering and Steward, 1978) and Northern Ireland (Harron et al., 1980) have revealed this trend. It is estimated that 4-5% of congenital defects in humans are related to the use of drugs or other chemical agents in pregnancy (Iams and Rayburn, 1982). However greater media awareness and medical education seems to have sensitized the treating physicians to prescribe drugs with greater caution (Rubin, 1986) The possible noxious effect of drugs used by lactating mothers on newborn and later life also needs to be taken into account by the clinicians. The drug distribution in pregnant women is also likely to be altered due to factors such as increased blood volume, decreased albumin concentration, and altered state of liver metabolism of xenobiotics , increased renal plasma, raised glomerular filtration,etc and therapeutic monitoring of drugs(Rubin,1986)

DISTURBANCES IN PRENATAL DEVELOPMENT – ROLE OF DRUGS

Drug use in pregnant (or possible pregnant) woman may be associated with four major types of disturbances in the development of the offspring (Saxen and Rapola, 1969).

Gametopathies- defects in gametes induced before conception. Few drugs are known or suspected to be causing gametopathies.

Blastopathies-corresponding to the early embryonic period of about 0-15 days postfertilization. Drugs are generally believed not to penetrate the blastocyst. However, cyclophosphamide and the cholesterol lowering drug, triparanol are thought to be embryotoxic at this stage (Brook and Von Kreybig, 1964; Roux, 1964).

Embryopathies- defects produced during the period of about 16-72days postfertilization. This phase corresponds to the period of organogenesis when foundation is laid for most, if not all our organ systems. This period is believed to be the classical period for drug induced teratogenicity.

Fetopathies- disturbances arising during the period of about 72 days postfertilization and the time of delivery. Generally termed as foetal period, this corresponds to the period of foetal growth and maturation. The characteristic drug effect at this stage is intrauterine growth retardation. Drugs can also induce functional deficits or compromise the ability of the newborn to adapt to extrauterine existence. The above mentioned four periods of prenatal development are not clearly defines and may overlap.

PLACENTAL TRANSFER - SOME CONCEPTS

Drugs cross over from maternal to foetal circulation almost exclusively by the process of diffusion, obeying the Fick's equation

(Seeds, 1968).

$$\frac{Q}{t} = KA \frac{Cm - Cf}{T}$$

Q/T = quantity transferred per unit time, K= diffusion constant, Cm & Cf = concentrations in maternal and foetal blood respectively and T = thickness of placental membrane A = placental surface area.It follows from the equation that the rate of placental transfer of a drug is directly proportional to the concentration gradient and the placental surface area and is inversely proportional to the placental membrane thickness. The thinning of the placental membrane and the increased availability of free drug in late gestation seem to explain for the greater drug transfer towards the foetus than in the early gestation. Factors of low molecular weight , high lipid solubility, low degree of ionization and low protein binding facilitate transfer while the reverse reduces it. Exhaustive reviews on placental transfer of drugs are available elsewhere (Mirkin and Singh, 1976; Nandakumaran and Olive, 1983).

PROBLEM OF DRUG USE IN FIRST TRIMESTER

As mentioned earlier, drugs are potential teratogens when used in the first pregnancy trimester and hence it is customary to limit the use of drugs during this period to only emergency situations. Some of the established teratogenic agents in man are thalidomide, the antibiotic tetracyclines, anticonvulsants (trimethadione and phenytoin), folic acid antagonists (methotrexate and aminopterin), alcohol, diethylstilbesterol and radiochemicals (Goldman, 1980; Iams and Rayburn, 1982). Tuchmann- Duplessis (1975) and Shepard (1983) have done extensive surveys of the teratogenic agents in man. The analgesics (salicylates, narcotics and acetaminophen), the antibiotics (penicillin, cephalosporins and sulfonamides), antiemetics (Bendectin, promethazine), corticosteroids and heparin are not known to have teratogencity in humans at customary dosages (Iams and Rayburn, 1982). However, no drug should be considered 100% safe for first trimester use and adequate dose for the drug given at a sensitive period of gestation to a pregnant woman, is capable of inducing a deformity in a genetically predisoposed or susceptible foetus.

DRUG USE IN LATER GESTATION

Use of drugs in the second or third pregnancy trimester is usually not associated with organ malformation, but drugs are capable of inducing effects as jejunoileal atresia or vascular lesions of brain, etc. when administered during those periods. Although intrauterine growth retardation (IUGR) is considered is considered to be characteristic drug effect at this stage (Redmond, 1980), drugs are also capable of inducing a variety of functional disturbances (Tables 1, 2, 3, 4, 5 and 6) in the foetus or neonate when administered in late gestation or around time of delivery. The probable effect of drug on receptor modulation or development in the foetus is poorly investigated. Giacoia and Yaffe (1981) and Nandakumaran and Olive (1983) have published extensive surveys of the foetal / neonatal effects associated with drug use in pregnancy.

Tables 1: *Adverse foetal / neonatal effects of some commonly used drugs in pregnancy.*

AGENT	FOETAL / NEONATAL	REFERENCES
Salicylates	Bleeding tendencies, prolonged pregnancy & labour; may cause premature closure of ductus arteriosus	Lietman & Niebyl (1982)
Narcotics	Neonatal depression; withdrawal signs	Shute & Davis (1933) Shnider et al. (1966)
Phenacetin	Methemoglobinemia or hemolytic anemia, nephrotoxic.	Ledward & Hawkins (1983) Lietman & Niebyl
Anesthetics General Local	Neonatal depression Neonatal depression, bradycardia, seizures.	Nandakumaran & Olive (1983) Nandakumaran & Olive (1983)
Anorexic agent Amphetamines Phenmetrazine	Possible cardiac defects, irritable poor feeding. Skeletal Anomalies	Iams and Rayburn (1982) Iams and Rayburn (1982)

Tables 2

AGENT	FOETAL / NEONATAL	REFERENCES
Antidepressants Lithium	Occasionally cyanosis, lethargy, hypotonia, poor suckling in neonate.	Nora et al. (1974) Ledward & Hawkins (1983)
Anti-infection agents Aminoglycosides	Ototoxicity	Nandakumaran & Olive (1983) Ledward & Hawkins (1983)
Chloramphenicol	'Grey baby' Syndrome (ashen grey cyanosis, hypothermia, flaccidity leading to cardiovascular collapse, respiratory failure & cardiac arrest); possibility of bone marrow depression.	Scott & Warner (1960) Hamod & Khouzami (1982
Sulphonamides (Long-acting)	Neonatal jaundice; Kernicterus	Moya & Thorndike (1962)
Tetracyclines	Impaired bone growth, stained deciduous teeth	Cohlan et al, (1963) Gibbons & Reichelderfer (1960)

Trimethoprim	Hyperbilirubinemia	Iams& Rayburn (1982)

Tables 3

AGENT	FOETAL / NEONATAL	REFERENCES
Anticoagulants Dicoumarol	Bleeding tendancies	Kraus et al. (1949) Goldberg (1982)
Phenindione &Warfarin	Bleeding tendancies, Foetal Warfarin Syndrome	Goldberg (1982)
Anticonvulsants Phenytoin	IUGR, craniofocal abnormalities, bleeding dyscrasias, may lower serum folate level, foetal hydantoin syndrome.	Ledward & Hawkins (1983) Hanson & Smith (1975)
Trimethadione	Mental retardation, hemorrhagic tendancies.	Stempel & Moore (1982)
Barbiturates	Bleeding tendancies, withdrawal signs	Nandakumaran & Olive (1983)
Carbamazepine	Bleeding, withdrawal	Stempel & Moore (1982) Iams& Rayburn (1982)

Tables 4

AGENT	FOETAL / NEONATAL	REFERENCES
Hypogycemic Agents Chloropropamide	Neonatal hypoglycemia	Giacoia & Yaffe (1981)
Tolbutamide	Thrombocytopenia	Giacoia & Yaffe (1981)
Antimalarial drugs Quinine	Risk of abortion; other foetal abnormalities with overdosage	Ledward & Hawkins (1983)
Chloroquine	Foetal cochlear and retinal damage in high doses.	Giacoia & Yaffe (1981) Ledward & Hawkins (1983)

Tables 5

AGENT	FOETAL / NEONATAL	REFERENCES
Antihypertensive agents Methyldopa	Hemolytic anemia , ileus	Iams& Rayburn (1982)
Hydralazine	Tachycardia	Vink et al. (1980)
Propranolol	IUGR, bradycardia, hypoglycemia	Nandakumaran & Olive (1983)
Reserpine	Lethargy, nasal stuffiness	Desmond et al. (1957)
Diazoxide	Disturbed foetal hair formation, neonatal hypoglycemia	Niebyl & Merkatz (1982)
B-Sympathomimetics (Ritodrine, Salbutamol, Isoxsuprine, Terbutamine)	Tachycardia, foetal hyperglycemia, neonatal hypoglycemia	Nandakumaran & Olive (1983)
Magnesium sulfate	Respiratory depression due to hypermagnesemia	Lipsitz (1971)
Diuretics Furosemide	Death from sudden hypoperfusion	Iams& Rayburn (1982)
Thiazides	Thrombocytopenia, hypokalemia, hyponatremia, hyperbilirubinemia	Kelly (1977) Garnet (1963)

Tables 6

AGENT	FOETAL / NEONATAL	REFERENCES
Immunosuppressive agents Azathioprine	Risk of maternal & foetal viral infection, particularly herpes genitalis & cytomegalovirus	Ledward & Hawkins (1983)
Corticoids	Growth delay; increased risk of foetal / neonatal infection	Zuspan, Arwood & Cordero (1982)
Miscellaneous Vitamin A (high doses)	Urogenital anomalies	Iams& Rayburn (1982)
Vitamin D (high doses) & other analogues	Mental retardation, facial cleft, skeletal abnormalities.	Iams& Rayburn (1982)
Antithyroid drugs	Goiter, mental retardation.	Peterson & Young (1952) Iams& Rayburn (1982)

Alcohol (high doses)	Intoxication, hypotonia, respiratory depression; foetal alcohol syndrome	Niebyl & Merkatz (1982) Clarren & Smith (1978)

DRUG IN BREAST MILK – RISK FOR THE BABY

A variety of drugs and environmental pollutants have been reported to be secreted or excreted into the breast-milk which ultimately can find their way into the baby. Diffusion is thought to be the major mechanism for transfer of drugs from plasma to milk (Berlin, 1980). As in the case of placental transfer, large molecular weight, high degree of ionization and low liposolubility tend to limit plasma to milk transfer of drugs while the reverse factors facilitate the process (Gardner and Rayburn, 1982).

Some of the drugs that are contraindicated in the nursing mother are lithium, isoniazid, antimetabolites, radioactive pharmaceuticals, phenindione, propylthiouracil and chloramphenicol (Berlin, 1980). Besides, some drugs as bromocriptine, dopamine, pyridoxine, alcohol, nicotine, estrogens, androgens and diuretics are capable of inhibiting lactation by diverse mechanisms. (Ledward and Hawkins, 1983). In the light of some pharmacokinetic data, Berlin (1980) recommends that nursing women should avoid all drugs and chemicals as far as possible. When medication seems necessary the risk for infant from milk-excreted drug could be minimized by, adjusting the following precautions: firstly, time the dose to just after nursing and / or at least 4 hours prior to another nursing; Secondly, to take the drug after the last evening feeding of the baby, in the case of once-daily medication. Nursing mothers on long-term medication are perhaps best advised not to breast-feed during the period of treatment.

CONCLUSION

Use of drugs in pregnancy has to be instituted with utmost caution. Although it is true that the first trimester of pregnancy is the most vulnerable period for drug induced malformations, it is not safe to assume that drugs cannot effect malformations later in pregnancy. The benefit-to-risk ratio for the mother as well as the baby need be carefully evaluated before deciding on the appropriate drug regimen. A thorough appraisal of the advantages and drawbacks of available therapeutic agents may be necessary to assure the best possible therapy, with minimum of attendant risks for the baby. Evidently, this is not to recommend a therapeutic nihilism in pregnant woman; an untreated or delayed therapeutic intervention of the maternal disease may cause (or does) incalculable harm for the mother as well as the baby. It seems advisable not to take recourse to recently introduced drugs with poorly established or theoretical advantages than resorting to established therapeutic agents with considerable clinical experience and data. Long-term well planned prospective studies need to be planned for potentially harmful therapeutic agents in pregnancy to evaluate any possible untoward effect on behavioral or personality development, as a result of drug exposure *in*

utero. Finally, it seems advisable for nursing women to avoid drugs and chemicals in order to minimize untoward drug effects for the baby; if a medication seems necessary, the potential hazards are best reduced by following a revised dosing schedule.

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