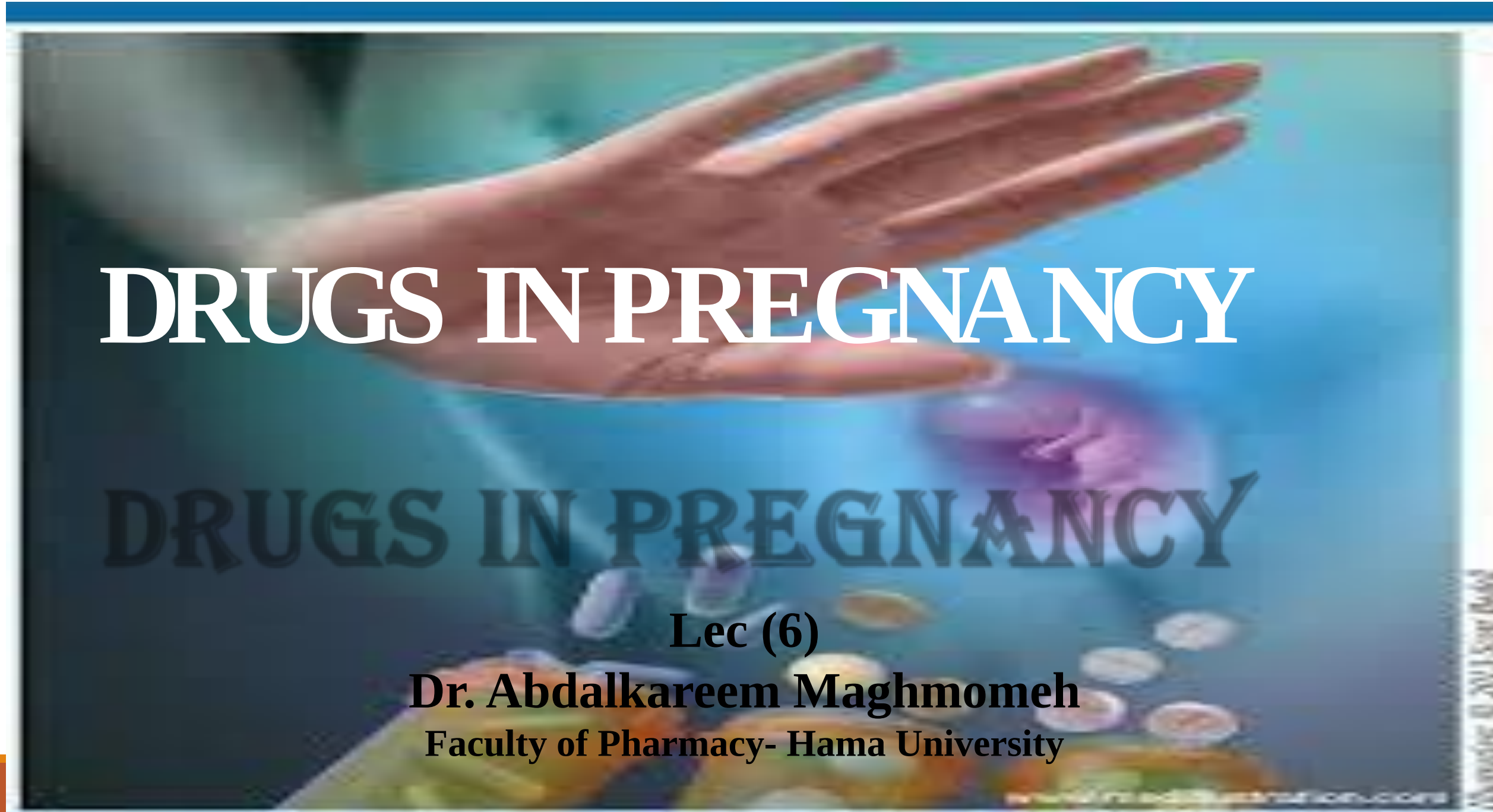

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INTRODUCTION

- The use of drugs in pregnancy is complicated by
  1. The harmful effects on the growing fetus
  2. altered maternal physiology
  3. the low and difficulties of research in this field.
  4. Medications are sometime essential therapy for serious life threatening medical conditions that are superimposed on pregnancy.

- About 2 to 3 % of all birth defects result from the use of drugs other then alcohol

PREGNANCY STAGES

FERTILIZATION AND IMPLANTATION

Animal studies suggest that interference with the fetus before 17 days gestation causes abortion, i.e. if pregnancy continues the fetus is unharmed.

act in an all-or nothing fashion

ORGANOGENESIS/EMBRYONIC STAGE

3rd and 8th week after fertilization

At this stage, the fetus is differentiating to form major organs, and this is the critical period.

Drugs that interfere with this process can cause gross structural defects (

FETOGENIC STAGE

from week nine to delivery.

In this stage, the fetus undergoes further development and maturation.

Even after organogenesis is almost complete, drugs can still have significant adverse effects on fetal growth and development.

DELIVERY

Some drugs given late in pregnancy or during delivery may cause particular problems.

PREGNANCY PHYSIOLOGY AND ITS EFFECTS ON PHARMACOKINETICS

Absorption

1. Gastrointestinal motility is decreased but there appears to be no major affect in drug absorption except that reduced gastric emptying delays the appearance in the plasma of orally administered drugs, especially during labor.
2. Vomiting associated with pregnancy may make oral drug administration impractical غير عملي
3. Absorption from an intramuscular site is likely to be efficient because tissue perfusion is increased due to vasodilatation.

Distribution:

1. Total body water increases by up to 8 Liters. For water-soluble drugs this increases the apparent volume of distribution and, although clearance is unaltered, their half-life is prolonged.
2. As a result of haemodilution, plasma albumin declines and there competition for binding sites is increased due to competition by endogenous ligands, such as increased hormone levels. Thus there is scope for increased free concentration of drugs that bind to albumin.
3. These factors alter the total amount of bound drug and the apparent volume of distribution. However, the concentration of free drug usually remains unaltered, because a greater volume of distribution of free drug is accompanied by increased clearance of free drug.
4. In practice, these changes are rarely of pharmacological significance. They may cause confusion in monitoring of plasma drug levels,

Metabolism

- **Hepatic metabolism increases due to enzyme induction, but not the blood flow to liver.**
- **So, increased clearance of drugs such as phenytoin and theophylline (elimination rate depends on liver enzyme activity)**
- **Drugs that are so rapidly metabolized that their elimination rate depends on their delivery to the liver, i.e. on hepatic blood flow, have unaltered clearance, e.g. pethidine.**

Elimination:

- **Renal plasma flow almost doubles and the glomerular filtration rate increases by two-thirds during pregnancy.**
- **So there is rapid loss of drugs that are excreted by kidney. This has been documented for digoxin, lithium, ampicillin, cephalexin and gentamicin.**
- **e.g. amoxycillin, dose of which should be doubled for systemic infections (but not for urinary tract infections as penicillins are highly concentrated in urine)**

PLACENTAL TRANSFER OF DRUGS

- The placenta is not a perfect barrier to drugs and chemicals administered to mother. In the placenta, maternal blood is separated from fetal blood by a cellular membrane
- Most drugs with a molecular weight of less than 1000 can cross the placenta.
- The rate of diffusion depends on

1. the concentration of free drug
2. the lipid solubility of the drug, which is determined in part by the degree of ionization. Diffusion occurs if the drug is in the unionized state.

- Placental function is also modified by changes in blood flow, and drugs which reduce placental blood flow can reduce birth weight.

FACTORS AFFECTING PLACENTAL DRUG TRANSFER & FETAL TISSUE

(1) Physicochemical properties of drug

(2) Rate at which drug crosses placenta & amount of drug reaching the fetus

(3) Duration of exposure to drug

(4) Distribution characteristics in different fetal tissues

(5) Stage of placental & fetal development at time of exposure to the drug

(6) Effects of drugs used in combination

HOW CAN DRUG AFFECT FETEUS

- Drugs that a pregnant woman takes during pregnancy can affect the fetus in several ways:

1. They can act directly on the fetus, causing damage, abnormal development (leading to birth defects), or death.)
2. They can alter the function of the placenta, usually by causing blood vessels to narrow (constrict) and thus reducing the supply of oxygen and nutrients to the fetus from the mother. Sometimes the result is a baby that is underweight and underdeveloped
3. They can cause the muscles of the uterus to contract forcefully, indirectly injuring the fetus by reducing its blood supply or triggering preterm labor and delivery.

FDA Pharmaceutical Pregnancy Categories

Category A	Adequate and well-controlled human studies demonstrate no risk.
Category B	Animal studies demonstrate no risk, but no human studies have been performed. OR Animal studies demonstrate a risk, but human studies have demonstrated no risk.
Category C	Animal studies demonstrate a risk, but no human studies have been performed. Potential benefits may outweigh the risks.
Category D	Human studies demonstrate a risk. Potential benefits may outweigh the risks.
Category X	Animal or human studies demonstrate a risk. The risks outweigh the potential benefits.

Risk category of drugs during pregnancy

Category		Examples
A	Adequate studies in pregnant women have failed to demonstrate a risk to the foetus	Inj. Mag. sulfate, thyroxine
B	Adequate human studies are lacking, but animal studies have failed to demonstrate a risk to the foetus o r Adequate studies in pregnant women have failed to demonstrate a risk to the foetus, but animal studies have shown an adverse effect on the foetus	Penicillin V, amoxicillin, cefactor, erythromycin, paracetamol, lignocaine
C	No adequate studies in pregnant women and animal studies are lacking or have shown and adverse effect on foetus, but potential benefit may warrant use of the drug in pregnant women despite potential risk	Morphine, codeine, atropine, corticosteroids, adrenaline, thiopentone, bupivacaine
D	There is evidence of human foetal risk, but the potential benefits from use of the drug may be acceptable despite the potential risk	Aspirin, phenytoin, carbamazepine, valproate, lorazepam
X	Studies in animals or humans have demonstrated foetal abnormalities, and potential risk clearly outweighs possible benefit	Estrogens, isotretinoin, ergometrine

MEDICINES WITH KNOWN TERATOGENIC EFFECTS

Retinoids

- **Vitamin A – essential nutrients is prototype retinoic acid**

  APP 10,000 IU Vitamin A is recommended in pregnant women.

  High doses, beginning at 15, 000 IU per day are associated with risk of malformation (تشوه)

- **Both isotretinoin and itretinoin are derivatives of vitamin A.**

  Isotretinoin is utilized for cystic acne And etretinate is used primarly for psoriasis.

ANTICONVULSANTS

Increased risk of congenital anomalies has been reported to be associated with anti convulsants. e.g Phenytoin, carbamazepine and valproic acid.

ANTICOAGULANTS

Warfarin a coumarin anticoagulant is relatively small molecule and readily cross plcants.

PSYCHOTROPICS

Lithium is used primarily to treat affected mental disorders.

This agent used in early gestation(الحمل المبكر) is associated with increased risk of cardiovascular disease.

USE OF SOME COMMON MEDICATION DURING PREGNANCY

ANTI MICROBIAL

All the Penicillin are apparently safe for use during pregnancy in patients not allergic to these drugs.

Cephalosporins also cross placenta to similar degree like penicillin resulting in significant fetal levels similar to that in mother.
There is no controlled scientific studies regarding cephalosporins use in pregnancy.
Second and third generation cephalosporins contain N-methyl thio tetrazole (MTT) side chain that was reported to be associated with testicular hypoplasia in new born animals.
Cefoxitin a commonly used 2nd generation have no MTT side chain, this apper to be rational choice when therapy with broad spectrum cephalosporins if indicated during pregnancy.

Erythromycin a macrolide antibiotic is not associated with adverse fetal effects. This agent does't not cross placenta.

All aminoglycosides cross the placenta to some degree and result in significant level.

A drug is this class streptomycin, has been associated with 8th cranial nerve damage (sensor neural deafness) in fetus whose mothers received it for a significant time during pregnancy

Clindamycin is utilized primarily for anaerobic infections and known to cross placenta. There are no scientific studies regarding its use in pregnancy, it effects on the developing fetus are unknown

Sulfonamide and trimethoprim are often used in combination primarily to treat UTI.

Sulfonamides is utilized during late gestation can cause neonatal hyperbilirubinemia.

Trimetroprim is weak folate antagonist but is not associated with increased risk of anomalies

Nitrofurantion نتروفورانتوين also safe to use in pregnancy.

Fluoroquinilona (cipro and norfloxacin) are also used to treat UTI. There are no scientific studies ,but can cause irreversible arthopathy اعتلال مفصلي in dogs whose mothers were given drug during pregnancy.

ANTIFUNGALS

clotrimazole, miconizole nestatin and Amphotericin B.

The use of these drugs is not associated with increased risk of malformations

griseoflavin

utilized for the treatment of mycoticفطرية infection of skin and nails has been repeates of increased central nervous system and skeletal anomalies in animal studies

ASTHMA

- The prevalence of asthma diseases among pregnant women is approximatly 3-5%.
- Two major classes are used in asthma bronchodilators and immunosuppressant. These are relativity safe in pregnancy.
- Theophylline, terbutaline, salbutamol, albuterol, have no significant teratogenic or fetal effects.
- Epinephrine is another bronchodilator. It is reserved for a cute asthmatic attacks. An increased frequency of non major malformations is reported with its use.

ANTIHISTAMINES:

Chlorphenaranine, Laratadine, doxylamine, bromphenerine diphenlydramine are low risk during pregnancy.

ANALGISC (NSAIDS)

The frequency of congenital anomalies is not increased if given during first trimester.

ACITAMENOPHEN

is the preferred analgesic for use in pregnancy.

MANAGEMENT OF THE PREGNANT PATIENT WITH MEDICATION EXPOSURE

- Management of patient who has been exposed to medication during pregnancy especially during critical period of organogenesis present challenge to clinical. There are several important questions that will arise:

1. Is the medication was known taratogen?
2. Are there potential adverse effects?
3. What is risk to mother with use of medications or if it is withheld?
4. Are there other factors that may be important than medication such as disease being treated?
5. How should the patient be counseled?

PRESCRIBING IN PREGNANCY

Prescribing in pregnancy is a balance between the risk of adverse drug effects on the fetus and the risk of leaving maternal disease untreated.

1. **minimize prescribing;**
2. **use the smallest effective dose**
3. **remember that the fetus is most sensitive in the first trimester;**
4. **discuss the potential risks of taking or withholding therapy with the patient;**
5. **seek guidance on the use of drugs in pregnancy in the British National Formulary, Drug Information Services**
6. **warn the patient about the risks of smoking, alcohol, over-the-counter drugs and drugs of abuse.**

QUESTIONS????