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Ambition never comes to an end

YOSHIDA KENKO

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THE IMPACT OF DRUGS ON CONGENITAL ANOMALIES

by

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Submitted in fulfillment of the requirements for the
Pharm. D Degree

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Dedicated
to
MY PARENTS

For their love,
care, understanding & support

My Sincere thanks goes to all those that helped me
realize this project.

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LEBANESE AMERICAN UNIVERSITY

GRADUATE STUDIES

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* We also certify that written approval has been
obtained for any proprietary material contained
therein.

THE IMPACT OF DRUGS ON CONGENITAL ANOMALIES

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ABSTRACT

by

CHANTAL FARAH

Some abnormalities that occur in the fetus and the newborn are of genetic origin , some result of an infection , some are due directly or indirectly to incidental complications of pregnancy and in some cases the cause is unknown or due to incorrect drug intake.

Women commonly ingest medications or drugs while pregnant; some of these drugs may be teratogenic. Major malformations are usually the result of the first trimester exposure during critical periods of organogenesis. Therefore, pregnant women should be discouraged from taking Over-the-Counter drugs, and such drugs should not be taken without counseling. For prescription drugs, risks versus benefits should be taken into consideration by the physician.

The safe use of a drug in a single pregnancy or even in a large number of pregnancies does not assure that the drug is safe in all pregnancies. Very few medicinal agents can be declared safe in pregnancy. Because any drug can be teratogenic, it is important to develop effective methods to prevent fetal exposure.

Chapter 1

Introduction

Some congenital anomalies are caused by genetic factors (chromosomal abnormalities and mutant genes) and some are caused by environmental factors (infectious agents and teratogenic drugs), but most common anomalies result from complex interaction of genetic and environmental factors (multifactorial inheritance).

For decades it was believed that the placenta served as a barrier that protected the fetus from the adverse effects of the drugs. The thalidomide disaster drastically changed this perception by demonstrating that fetal exposure to the drug during critical periods of development resulted in severe limb defects and other organ dysgenesis (e.g., kidney and heart defects). Despite the high rates of malformations (20 to 30 percent) and their characteristic pattern, the teratogenicity of thalidomide was not suspected for years. The suffering it caused has prompted the belief that every drug has the potential to be a new thalidomide.

Before marketing a new drug, the manufacturer almost never tests the product in pregnant women to determine its effect on the fetus. Consequently, most drugs are not labeled for use during pregnancy. Typically, descriptions of drugs that appear in the Physician's Desk Reference and similar sources contains statements such as, « Use in pregnancy is not recommended unless the potential benefits justify the potential risks to the fetus ». The safe use of a drug in a single pregnancy or even in a large number of pregnancies does not assure that the drug is safe in all pregnancies. Very few medicinal agents can be declared as « safe in pregnancy ». (16) Since the risk has been adequately established for only a few drugs, physicians caring for pregnant women have very little information to help them decide whether the potential benefits to the mother outweigh the risks to the fetus.

Pregnancies are not always planned, hundred of thousands of women therefore expose their fetuses to drugs before they know they are pregnant. About 2% to 3% of infants have congenital abnormalities. At one year of life, this incidence rises to 7.5% indicating that many anomalies are minor in nature and are not detected until later in life. (35)

Teratogenesis is defined as the dysgenesis of fetal organs as evidenced either structurally or functionally (e.g. brain functions). The typical manifestations of teratogenesis are restricted growth or death of the fetus, carcinogenesis, and malformations, defined as defects in organ structure or function. These abnormalities vary in severity.

Major malformations may be life-threatening and require major surgery or may have serious cosmetic or functional effects.

There are drugs that have teratogenic effects in animals when administered in high doses that are not teratogenic in humans given in clinically relevant doses. For example, high doses of glucocorticoids or benzodiazepines can cause oral clefts in animals, but clinically relevant doses in humans have no such effects. Similarly, salicylates cause cardiac malformations in animals but not in humans. Such discrepancies have led to unwarranted anxiety on the part of women, their families, and physicians and may have contributed to unnecessary terminations of pregnancies. Although studies in animals may identify teratogenic effects, it can be difficult to extrapolate these effects to humans. (68)

1.1 - Timing of exposure :

Pregnant women should be discouraged from taking over-the-counter drugs, and such drugs should not be taken without counseling, since many factors, including the stage of pregnancy, can influence the risk to the fetus.

During the first two weeks of development, teratogenic agents may kill the embryo, but they do not cause congenital anomalies. During the organogenetic period, teratogenic agents may cause major congenital anomalies.

During the fetal period, teratogens may produce minor morphological and functional abnormalities, particularly of the brain and the eyes. (Mental retardation may result from the teratogenic actions of infectious agents, high levels of radiations, and alcohol abuse). (85)

The two weeks after conception are considered an « all-or-nothing » period, during which the insult is significant enough to result in loss of the embryo, or the conceptus is able to overcome minor damage and develop to term unaffected. For example, a nonsteroidal antiinflammatory drug may be taken safely for pain during the first trimester of pregnancy, but there is increasing evidence that some nonsteroidal antiinflammatory drugs constrict or even close the fetal ductus arteriosus during late pregnancy (68).

The stage of development of the embryo determines its susceptibility to teratogens. The most critical period in the development of an embryo or in the growth of a particular tissue or organ is during the time of most rapid cell division.

Some agents are dangerous only when the exposure occurs around the time of delivery. Administration of drugs near term poses another potential threat to the fetus. Before birth, the fetus relies on maternal system for drug elimination. After birth, the infant must rely on its own metabolic and excretory capabilities, which have not yet fully developed. Drugs given near term or during birth, especially those with long half-lives, may have an even more prolonged action in the neonate.

For example, some sedating agents do not cause birth defects or abnormalities of body growth or maturation of the central nervous system but can cause lethargy and respiratory depression at the time of delivery.(28)

Women commonly ingest medications during pregnancy. Besides prenatal vitamin and mineral supplements, commonly used drugs include antiemetics, antacids, antihistamines, analgesics, antimicrobials, tranquilizers, hypnotics, and diuretics. Although some of these are prescribed, many are taken either without physician advice or prior to realization of pregnancy. Both patient and physician are primarily concerned with whether a drug or medication causes congenital anomalies or is a teratogen.(111)

1.2- Dosage and chronicity of the exposure:

Higher doses of the agent will have a greater therapeutic impact on the woman but also will present more of an exposure to the fetus. There generally is a « threshold » dose below which teratogenic effects do not occur.

Also important is the concept that some agents are harmful only if given in sufficient amounts over prolonged periods.

Whether a chemical or a drug and its metabolites have fetal access in quantities sufficient to cause developmental anomalies is important. To minimize the fetal risk, drug doses at the lower end of therapeutic range should be prescribed during pregnancy. (68)

1.3- Effect of maternal factors:

Apart from drug therapy, many medical conditions themselves increase fetal risks. For example, pregnant women with hypertension or cancer are more likely to have infants with intrauterine growth retardation, and pregnant women with epilepsy or diabetes mellitus are more likely to have infants with malformations.

Maternal absorption and metabolism, protein binding and storage, molecular size, electrical charge, and lipid solubility are factors that may determine the degree of placental transfer. (4)

Many pregnant women require drug therapy because of pregnancy-induced conditions such as nausea and vomiting, chronic conditions diagnosed before pregnancy, or acute conditions (e.g., those that require surgical treatment with the use of anesthetic agents).

Several principles should guide the selection of therapy during pregnancy.

Because of increased body weight and more rapid clearance of many drugs (e.g., lithium, digoxin, and phenytoin) during late pregnancy, some women may need higher-than-normal doses.(68)

1.4- Fetal susceptibility:

It is not just dose and maternal metabolism that determine whether a fetus will show adverse effects from an exposure. For example, a women who takes the same dose of phenytoin as treatment for epilepsy in two pregnancies may have one child who shows serious damage and another child who is unaffected.

Individual variation in susceptibility to a constant dose of a given agent also influences teratogenic effect. Each child of a chronic alcoholic may display different manifestations of fetal alcohol syndrome, possibly because of genotypic differences in sensitivity to alcohol. This may also explain why high doses of a known teratogen have no effect on some exposed fetuses. The occurrence of threshold phenomena can explain why low doses of some agents have no teratogenic effect.(111)

The experience with thalidomide led drug regulators, drug manufacturers, and the medical community to believe that appropriate labeling of teratogenic drugs, with warning not to take them around the time of conception, would be effective in preventing fetal exposure to the drugs. The naïvety of this belief became evident after isotretinoin was introduced for the treatment of acne. For years before its clinical introduction, this drug has been known to cause malformations in animals.

Despite explicit warning labels, scores of children with retinoid embryopathy were born in the years after the drug was introduced. Such warnings are not sufficient, because women taking isotretinoin may not plan their pregnancies, or their birth-control methods may fail. In addition, some women and men are functionally illiterate, and they may not read or understand the content of a drug-label.

The initial experience with isotretinoin led to the development of a more comprehensive program to prevent teratogenesis.

The Retinoid Pregnancy Prevention Program includes explicit and detailed printed warnings as well as a line drawing of a malformed child, and as a part of the program, women are asked to sign a consent form indicating that they agree to use two effective methods of contraception before therapy is started.

For all these reasons, we have thought of undertaking this study in order to evaluate the effect of drugs taken during pregnancy in the Lebanese population.

Chapter 2

Embryology

2.1 Definition of embryology and Fertilization:

Human embryology is the science concerned with the origin and development of a human being from a zygote to the birth of an infant.

Human development begins at conception or fertilization when an oocyte (ovum) from a female is fertilized by a sperm from a male to form a zygote. The zygote contains chromosomes and genes derived from both the mother and the father. Development involves many changes that transform a single cell, the zygote (fertilized ovum), into a multicellular human being.

Fertilization of the ovum normally takes place within the ampulla of a Fallopian tube and must occur within 12 to 24 hours of ovulation, since this is the period of ovum viability. Ideally, this period corresponds to day 14 of the menstrual cycle.

2.2 - Cleavage:

Cell division by mitosis begins immediately after the ovum and sperm nuclei have fused.

As the zygote passes down the uterine tube, a cleavage furrow develops around its equator, while the anaphase and telophase steps of mitosis are being completed. The cells divide approximately every 12 hours. Equal numbers of maternal and paternal chromosomes pass to each of the daughter cells. The daughter cells and their progeny are called blastomeres. (106)

About three days after fertilization, a ball of 12 or more blastomeres, called a morula, enters the uterus. The morula is propelled into the endometrial cavity by the rhythmic contractions of the tubal musculature.(86)

After the morula reaches the uterus, some cells will have migrated to the outer surface, leaving a fluid-filled cavity called the blastocoele, while a small cluster of cells, called the inner cell mass, will have collected at one side or pole of the cavity. This stage of development is called a blastocyst. It's formed at about 50-60 blastomeres.

2.3 - Implantation:

At the stage of 107 cells, the blastocyst is ready for implantation. Implantation or embedding of the blastocyst in the endometrium is completed during the second week. As this important process takes place, changes occur in the inner cell mass or embryoblast that produce a thick, two-layered plate called the embryonic disc that will differentiate into the embryo. The amniotic cavity, amnion, yolk sac, connecting stalk, and chorion also develop during the second week. (85)

The amniotic cavity is formed between the inner cell mass and the trophoblast. The epithelial layer lining the cavity is derived from the inner cell mass and is called the amnion. The amniotic cavity enlarges by accumulation of fetal fluids. (86) The fluid in the amniotic fluid, resembles the fetal extracellular fluid, and it buffers mechanical disturbances and temperature variations.(118)

a. Amniotic fluid:

The amniotic cavity is filled with a clear, watery fluid that is produced, in part, by amniotic cells but is derived primarily from maternal blood. During the early months of pregnancy, the embryo is suspended by its umbilical cord in this fluid, which serves as a protective cushion. The fluid absorbs jolts, prevents adherence of the embryo to the amnion, and allows for fetal movements. The volume of amniotic fluid is replaced every 3 hours. From the beginning of the 5th month, the fetus swallows its own amniotic fluid, and it is estimated that it drinks about half of the total amount. Fetal urine is added daily to the amniotic fluid in the 5th month, but this urine is mostly water, since the placenta is functioning as an exchange for metabolism wastes.(102) The yolk sac becomes visible on day 28 (6.0-6.5 weeks menstrual age) and persists through 9 menstrual weeks.

THE FIRST WEEK OF HUMAN DEVELOPMENT

Diagrammatic summary of the ovarian cycle fertilization and human blastocyst development during the first week.

b- Embryonic circulation:

On embryonic days 14 to 15, primitive vessels begin to sprout, forming a contiguous network of tiny capillaries.(86)

The third week of development follows the first missed menstrual period, and is characterized by the formation of the primitive streak, notochord, and three germ layers from which all embryonic tissues and organs develop.

Rapid development of the embryo occurs the third week.(85)

By the end of this week of development, the embryo has become too large to be nourished by diffusion of nutrients from the yolk sac. For this reason, the cardiovascular system makes an early appearance, and an embryonic circulation begins to function early in the 4th week. (39)

Fetal cardiac activity first commences on about embryonic day 22 (5 weeks menstrual age). (86)

The developing heart drives three circulatory systems. One system collects red blood cells from the wall of the yolk sac and returns there for more; one collects oxygen and nutrients from the placenta and returns there with waste products; and one is contained entirely within the embryo in order to nourish it.

The fetoplacental circulation is established by the end of the first month (6 weeks menstrual age) and is essentially completed by 2 months (10 menstrual weeks).

This simple nutritive system, however, is adequate to provide for the embryo only during the first few weeks, when it is very small. The structure taking over this function is the placenta. (118)

During the fourth week the embryo grows rapidly, tripling its size.

The third to eighth week constitute most of the embryonic period. This is a critical period of development because the primordia of all major external and internal structures develop during this time. As the organs develop, the shape of the embryo gradually changes. By the end of the eighth week, the embryo has a remarkably human appearance.

Because the organ systems develop during the fourth to eighth week, exposure of embryos to teratogens during this period (e.g., drugs and viruses) may induce or raise the incidence of congenital anomalies. They act during the stage of active differentiation of an organ or tissue.

The developmental period from the beginning of the ninth week after fertilization to full term (38 weeks after last normal menstrual period) is known as the *fetal period*. It is characterized by maturation of the tissues and organs and rapid growth of the body. At nine weeks the human embryo is referred to as a fetus to signify that it has developed into a recognizable human being.

In addition, the fetus is less vulnerable than the embryo to the teratogenic effects of drugs, viruses, and radiation.

The transformation of an embryo to a fetus is not abrupt, but the name change is intended to signify the change from embryonic to fetal development. Development during the fetal period is primarily concerned with the growth and differentiation of tissues and organs that appeared during the embryonic period. Very few new structures appear during the fetal period. The rate of body growth during the fetal period is remarkable, especially between the ninth and sixteen weeks, and weight gain is phenomenal during the terminal months.(85)

We differentiate generally between embryonic and fetal periods of development and draw the dividing line at roughly 8 weeks' gestation when the fetus is approximately 2 cm long.

c - Estimation of gestational period:

During a pregnant woman's first visit to a physician, the age of the embryo or fetus is estimated. The date of the last normal menstrual period is a time-honored guide to establishing gestational age, and it is reliable in most cases. To determine the fertilization age (developmental age) of the embryo, two weeks must be deducted from the gestational age because development does not begin until about two weeks after last normal menstrual period.

Reasonable estimates of the age of embryos in utero can be determined by making early ultrasounds (by measuring the Crown Rump length between the 8th and 12th of gestation). (85)

TIMETABLE OF HUMAN PRENATAL DEVELOPMENT

1 to 6 weeks

EARLY DEVELOPMENT OF OVARIAN FOLLICLE									
MENSTRUAL PHASE									
COMPLETION OF DEVELOPMENT OF FOLLICLE									
CONTINUATION OF PROLIFERATIVE PHASE									
SECRETORY PHASE OF MENSTRUAL CYCLE									
midcycle									
ovulation									
oocyte									
Stage 1									
fertilization									
Stage 2 begins									
zygote divides									
morula									
Stage 3 begins									
early blastocyst									
late blastocyst									
Stage 4									
Implantation begins									
inner cell mass									
Stage 5 begins									
Stage 6 begins									
primary villi									
extraembryonic mesoderm									
coelom									
Primitive placental circulation established.									
Blastocyst completely implanted									
epithelium growing over surface defect									
Lacunae appear in syncytiotrophoblast									
primary yolk sac									
amniotic cavity									
bilaminar disc									
Stage 7									
dorsal aspect of embryo									
prochordal plate									
embryonic disc									

AGE (weeks)

1

2

TIMETABLE OF HUMAN PRENATAL DEVELOPMENT

7 to 38 weeks

43	CR: 16.0 mm	44 Stage 18 begins	CR: 17.0 mm	45 Tip of nose distinct. Digital rays appear in foot plates.	46 Loss of villi Smooth chorion forms.	47 urogenital membrane anal membrane ♀ or ♂	48 Stage 19 begins	49 CR: 18 mm
50	Upper limbs longer & bent at elbows. Fingers distinct.	51 Anal membrane perforated Urogenital membrane degenerating. Testes and ovaries distinguishable.	52 Stage 21 begins	53 External genitalia still in sexless state but have begun to differentiate.	54 Stage 22 begins	55 genital tubercle urethral groove anus ♀ or ♂	56 Stage 23	57 Beginning of fetal period.
58		59 Genitalia show some ♀ characteristics but still easily confused with ♂.	60 phallus urogenital fold labioscrotal fold perineum ♀	61 Genitalia show fusion of urethral folds. Urethral groove extends into phallus.	62 phallus urogenital fold labioscrotal fold perineum ♂	63 CR: 50 mm	69 glans penis urethral groove scrotum ♂	70 CR: 61 mm
64	Face has human profile. Note growth of chin compared to day 44.	65	66 Face has human appearance.	67 clitoris labium minus urogenital groove labium majus ♀	68 Genitalia have ♀ or ♂ characteristics but still not fully formed.	69

9 12 16 20 24 28 32 36 38 FULL TERM

THE NINTH TO THIRTY-EIGHTH WEEKS OF HUMAN DEVELOPMENT

FERTILIZATION AGE IN WEEKS

Diagram illustrating the changes in size of the human fetus when drawn to scale.

Chapter 3

Placenta

3.1 Placental Physiology:

The placenta is a fetomaternal organ, i.e., it consists of fetal and maternal components. The larger fetal portion develops from the chorionic sac, and the smaller maternal portion is derived from the endometrium. The placenta functions primarily as an organ that permits the exchange of materials carried in the blood streams of the mother and embryo/fetus. It allows nutritional materials and oxygen to reach the embryo/fetus and provides a route for the disposal of waste products and carbon dioxide.

The chorion, amnion, yolk sac, and allantois constitute the fetal membranes. They develop from the zygote but do not form parts of the embryo or fetus, except for the yolk sac and allantois.

The placenta and fetal membranes perform the following functions and activities: protection, nutrition, respiration, excretion, and hormone production. At birth, the placenta and fetal membranes are separated from the fetus; and, shortly after birth, the placenta membranes are expelled from the uterus as the afterbirth.

The term «decidua» is applied to the functional layer of the (pregnant) endometrium. For descriptive purposes, three regions of the «decidua» are named according to their relation to the implantation site:

- (1) the part of the «decidua» deep to the conceptus that forms the maternal component of the placenta is the «decidua basalis»,
- (2) the superficial portion overlying the conceptus is known as the «decidua capsularis»

(3) all the remaining endometrium lining the uterine wall is the « decidua parietalis », or 'decidua vera ». These decidual regions, clearly recognizable during ultrasonography, are important in diagnosis early pregnancy.

The fetal component of the placenta is formed by « villous chorion ».

The maternal component of the placenta is formed by the « decidua basalis ». By the end of the fourth month, the « decidua basalis » is almost entirely replaced by the fetal component of the placenta (i.e., the fetal part of the placenta is larger than the maternal part).

The fetal portion of the placenta (villous chorion) is attached to the maternal portion of the placenta (decidua basalis) by the « cytotrophoblastic shell ».

The fetus, floating in the amniotic cavity, is attached by the umbilical cord to the placenta.

The umbilical cord: The vessels of the umbilical cord provide a very extensive circulation of blood between the fetus and placenta. The cord contains two umbilical arteries, which originate from the fetal iliac arteries, and these carry deoxygenated blood to the placenta. Following the transfer of nutrients and excretory products a single umbilical vein returns the blood to the fetus, where the vein branches to join the portal vein (which conveys blood to the liver) and the inferior vena cava (which conveys blood to the heart). (3,25)

Relation of the villous chorion (fetal part of the placenta) to the decidua basalis (maternal part of the placenta).

3.2 Placental transfer:

At one time and until the middle of this century it was thought that the placenta presented a barrier to the passage of any chemical to the fetus and that the uterus provided a protective environment for the fetus and served as a barricade against harm from the external environment. It is now known, that any chemical substance in the blood stream including medications is able to cross the placenta to some extent unless it is destroyed or altered during passage. In general most medications cross the placenta to the fetus and we can say that what the mother consumes also is consumed by the fetus.

Movement of the compounds in the placenta is generally bi-directional, although the net transfer occurs from the mother to the fetus in most instances. It is important to note that even though every substance cross the placenta, of great importance is whether the rate and extent of transfer are sufficient to result in a significant concentration within the fetus.

Several factors influence the rate of drug transfer across the placenta including:

- * Drug factors: molecular weight, lipid solubility, ionization, protein binding
- * Maternal factors: uterine and umbilical blood flow, maternal disease.

Drugs with molecular weights (MW) less than 600 cross easily, while those greater than 1000 (e.g., heparin) cross with difficulty or not at all. But since most drugs have MW less than 600, it is safe to assume that most drugs reaching the mother's circulatory system also will reach the fetus.

The penetration of highly protein - bound drugs is inhibited; only the free unbound drugs cross the placenta. Changes in plasma protein concentrations during pregnancy may affect the degree of binding and, thus the amount of unbound drug. Despite an increase in production of serum albumin, the increase in intracellular and intravascular volumes in pregnancy cause the serum albumin concentrations to decrease.(12)

Placental circulation: The maternal blood enters placental sinuses via the uterine artery, percolates through them, and exits via the uterine veins. Simultaneously, blood flows from the fetus into the capillaries of the chorionic villi via the umbilical arteries and out of the capillaries back to the fetus via the umbilical vein.

Five weeks after implantation, the placenta has become well established, the fetal heart has begun to pump blood, and the entire mechanism for nutrition of the fetus and excretion of its waste products is in operation.

The fetal blood acquires nutrients and oxygen from the maternal blood. Waste products formed within the embryo are carried by the umbilical arteries to the placenta where they are transferred to the maternal blood. It must be emphasized that there is an exchange of materials between the two bloodstreams but no actual mingling of the fetal and maternal blood.(118)

Placental blood flow is critical to oxygen supply, since the amount of oxygen reaching the fetus is primarily dependent on delivery and not diffusion.

3.3 Placental functions and activities:

It is incorrect to regard the placenta simply as an organ designed for the transport of substrates and respiratory gases between the mother and fetus.

The placenta has three main functions and activities: (1) endocrine secretion, (2) metabolism, and (3) transport of substances (e.g., oxygen and carbon dioxide).

a - Hormone production: By the end of the 4th month, the placenta produces progesterone in sufficient amounts to maintain pregnancy in case the corpus luteum is removed or fails to function properly.

In addition to progesterone, the placenta produces increasing amounts of estrogenic hormones until just before the end of pregnancy, when a maximum level is reached. These high levels of estrogens stimulate uterine growth and development of the mammary gland. (102)

b - Placental metabolism: the placenta, particularly during early pregnancy, synthesizes glycogen, cholesterol and, fatty acids, which serve as sources of nutrients and energy for the embryo/fetus. (35)

c - Placental transport of substances:

The placenta plays an essential role in growth and development of the fetus and in regularly maternal adaptation to pregnancy.

Transfer of materials across the placental membrane is governed by molecular weight, solubility and the ionic charge of the substance involved. Actual transfer is achieved by simple diffusion, facilitated diffusion, active transport and pinocytosis.

Simple diffusion: Small molecules generally cross the placenta by simple diffusion.

Facilitated diffusion: This system pertains to glucose transport.

Active transport: This process occurs with essential amino acids and water-soluble vitamins.

Pinocytosis: This process applies to the transfer of globulins, phospholipids and lipoproteins and is of particular importance in the transfer of immunologically active material.

Transport of intact cells: Fetal red cells are commonly seen in the maternal circulation, particularly following delivery.

* Gases: Oxygen, carbon dioxide, and carbon monoxide cross the placental membrane by simple diffusion. Interruption of oxygen transport for even a few minutes will endanger embryonic/fetal survival.

At term, the fetus extracts 20-30 mL of oxygen per minute from the maternal circulation.

* Nutritional substances: Water is rapidly and freely exchanged by the mother and her fetus by simple diffusion and in increasing amounts as pregnancy advances. There is little or no transfer of maternal cholesterol, triglycerides, or phospholipids. There is transport of free fatty acids, but the amount transferred appears to be relatively small. Vitamins cross the placenta and are essential for normal development.

* Hormones: Protein hormones do not reach the embryo/fetus in significant amounts except for a slow transfer of thyroxine and triiodothyronine. Testosterone and certain synthetic progestins cross the placenta and may cause external masculinization of female fetuses.

* Electrolytes: They are freely exchanged across the placenta in significant quantities, each at its own rate.

* Antibodies: Some passive immunity is conferred upon the fetus by transplacental transfer of maternal antibodies.

Maternal antibodies confer fetal immunity to such diseases as diphtheria, smallpox, and measles or chickenpox. The fetus has a poor capacity to produce antibodies until well after birth.

The only Immunoglobulin that crosses the placenta is the IgG.

* Waste products: Carbon dioxide, the major waste product, diffuses across the placenta even more rapidly than oxygen. Urea and uric acid pass the placental membrane by simple diffusion, and bilirubin is quickly cleared. (39)

The placenta has a much higher oxygen consumption than the fetus as a whole, and its metabolic rate has been compared with that of the brain.

Glucose is the principal substrate for oxidative metabolism by placental tissue. Of the total amount of glucose that leaves the maternal compartment to nourish the uterus and its contents, as much as 70% may be consumed by the placenta. This statement refers to glucose uptake on a net basis, considering the mother as the sole supplier of sugar and the placenta and fetus as recipients who will partition glucose between them.(41)

C → F : 5th to 22nd week

Photograph of a 6-week embryo.

Schematic representation of a human embryo at the beginning of the 2nd month of development.

Photograph of a 19-week-old fetus in its natural position in the uterus

Photograph of a 23-week-old fetus in the uterus.

10th week. The fetus measures a dozen cms. The umbilical cord reaches the placenta. The fetus has a human form.

13th week. The arms started to move. we distinguish already the fingers ;the ears and the nose become visible.

6th month. The Amniotic cavity fills all the uterus and the mother feels the movements of the fetus. The proportions of the fetus are close to that of the newborn.

At the end of the 7th month, all sense organs function.

**At the 9th, the functioning of the organs and
their final form are aquired.**

The baby remains in this position in the uterus until birth.

Chapter 4

Prenatal Diagnosis

Prenatal testing may sometimes be indicated. After patients are fully informed of the risks, some request pregnancy termination. Psychologic support of the patient's decision should be provided.

Amniocentesis, a procedure that is accurate in detecting fetal chromosomal abnormalities, does not provide much information regarding drug exposures because most agents do not damage the fetal chromosomes.

Maternal serum alpha-fetoprotein (AFP) testing detects 85% of all open neural tube defects and may be of use if the patient was exposed to a hazardous agent during the 3rd-4th week after conception (the time of neural tube closure). A detailed ultrasound will provide important information regarding fetal growth and structure but is rarely able to detect all problems potentially attributable to a drug exposure. For example, an ultrasound might be able to detect malformations of growth retardation associated with maternal use of alcohol but would rarely be able to detect the more subtle damage to the central nervous system that results in cognitive and behavioral abnormalities. (28)

Patients should be counseled that ultrasonography can never exclude the presence of teratogenic effects.

The most critical period for brain development is from three to 16 weeks. Anomalies develop during the third and fourth weeks. Teratogens (e.g. alcohol) may also produce mental retardation during the fetal period. The brain is growing rapidly at birth and continues to do so throughout the first two years after birth; hence, mental retardation can also result from injury during infancy.

Environmental disturbances during the first two weeks after fertilization may interfere with cleavage of the zygote and implantation of the blastocyst and/or cause early death and spontaneous abortion of the embryo, but they are not known to cause congenital anomalies in human embryos.

Recognition of human teratogens offers the opportunity for the prevention of some congenital anomalies; for example, if women are made aware of the harmful effects of alcohol and certain drugs and viruses, most of them will not expose their embryos to these teratogenic agents.(85)

Chapter 5

Classification of drugs:

In 1979, the United States Food and Drug Administration (FDA) established five categories for drugs and medications with regards to possible adverse fetal effects, ranging from Class A drugs (which are designed as safe for use during pregnancy) to Class X drugs (which are contra-indicated during pregnancy because of proven teratogenicity).

This system is used by manufacturers to rate their products for use during pregnancy and are reported in the Physician Desk Reference (PDR) to guide physicians in the interpretation of the teratogenic risk associated with prescription drugs.

- **Category A:** Category A drugs are those for which controlled studies in humans have demonstrated no fetal risks in the first trimester (and there's no evidence of a risk in later trimesters). There are few category A drugs, and examples include multivitamins or prenatal vitamins, but not « megavitamins ». Vitamin C is an example of a category A substance when its use does not exceed the recommended daily allowance.

- **Category B:** With category B drugs, animal studies indicate no fetal risks, but there are no human studies; or adverse effects have been demonstrated in animals, but not in well-controlled human studies. Several classes of commonly used drugs, an example of which is the penicillins, are in this category.

- **Category C:** Drugs for which there are no adequate studies, either animal or human, or drugs in which there are adverse fetal effects in animal studies but no available human data, are classified in category C. Drugs should be given only if the potential benefit justifies the potential risk to the fetus. Zidovudine is an example.

- **Category D:** There is positive evidence of human fetal risk, but the benefits from use in pregnant women are thought to outweigh the risk (e.g., the drug is needed for a life-threatening condition or for a serious disease for which safer drugs cannot be used or are ineffective). Phenytoin and Carbamazepine are an example of a category D drug.

- **Category X:** Studies in animals or human beings have demonstrated fetal abnormalities, or evidence exists of fetal risk based on human experience, and the risk in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.(111)

The acne medication isotretinoin, which may cause multiple central nervous system, facial, and cardiovascular anomalies, is an example of a category X drug.

APPENDIX

A. ACIDIFYING AGENTS

Ammonium Chloride (B)

B. ANESTHETICS

1. Local

Lidocaine (C)

C. ANTIHISTAMINES

Antazoline (C)

Azatadine (B_M)

Bromodiphenhydramine (C)

Brompheniramine (C_M)

Bucizine (C)

Carbinoxamine (C)

Chlorcyclizine (C)

Chlorpheniramine (B)

Cinnarizine (C)

Clemastine (C)

Cyclizine (B)

Cyproheptadine (B_M)

Dexbrompheniramine (C)

Dexchlorpheniramine (B_M)

Dimenhydrinate (B_M)

Dimethindene (C)

Dimethothiazine (C)

Diphenhydramine (C)

Doxylamine (B)

Hydroxyzine (C)

Meclizine (B_M)

Methdilazine (C)

Pheniramine (C)

Phenyltoloxamine (C)

Promethazine (C)

Pyrilamine (C)

Terfenadine (C_M)

Trimeprazine (C)

Tripelennamine (B)

Tripolidine (C_M)

D. ANTI-INFECTIVES

1. Amebicide

Carbarsone (D)

Iodoquinol (C)

2. Aminoglycosides

Amikacin (C)

Gentamicin (C)

Kanamycin (D)

Neomycin (C)

Streptomycin (D)

Tobramycin (D_M)

3. Anthelmintics

Gentian Violet (C)

Mebendazole (C_M)

Piperazine (B)

Pyrantel Pamoate (C)

Pyvinium Pamoate (C)

Thiabendazole (C_M)

4. Antifungals

Amphotericin B (B)

Butoconazole (C_M)

Ciclopirox (B_M)

Clotrimazole (B)

Fluconazole (C_M)

Flucytosine (C)

Griseofulvin (C)

Ketoconazole (C_M)

Miconazole (C_M)

Nystatin (B)

Terconazole (C_M)

5. Antimalarials

Chloroquine (C)

Hydroxychloroquine (C)

Mefloquine (C_M)

Primaquine (C)

Pyrimethamine (C)

Quinacrine (C)

Quinidine (C)

Quinine (D/X)

6. Antituberculosis

para-Aminosalicylic Acid (C)

Cycloserine (C)
 Ethambutol (B)
 Isoniazid (C)
 Pyrazinamide (C)
 Rifampin (C)

7. Antivirals

Acyclovir (C_M)
 Amantadine (C_M)
 Idoxuridine (C)
 Ribavirin (X_M)
 Vidarabine (C_M)
 Zidovudine (C_M)

8. Cephalosporins

Cefaclor (B_M)
 Cefadroxil (B_M)
 Cefamandole (B_M)
 Cefatrizine (B)
 Cefazolin (B_M)
 Cefonicid (B_M)
 Cefoperazone (B_M)
 Ceforanide (B_M)
 Cefotaxime (B_M)
 Cefotetan (B_M)
 Cefoxitin (B)
 Ceftazidime (B_M)
 Ceftizoxime (B_M)
 Ceftriaxone (B_M)
 Cefuroxime (B)
 Cephalexin (B_M)
 Cephalothin (B_M)
 Cephapirin (B_M)
 Cephradine (B_M)
 Moxalactam (C_M)

9. Fluoroquinolones

Ciprofloxacin (C_M)

10. Iodine

Iodine (D)
 Povidone-Iodine (D)

11. Anti-infectives

Bacitracin (C)
 Chloramphenicol (C)
 Clavulanate Potassium (B_M)
 Clindamycin (B)
 Clofazimine (C_M)
 Colistimethate (B)
 Erythromycin (B)
 Furazolidone (C)
 Hexachlorophene (C_M)
 Lincomycin (B)
 Novobiocin (C)
 Oleandomycin (C)
 Paromomycin (C)
 Pentamidine (M)

Polymyxin B (B)
 Spectinomycin (B)
 Spiramycin (C)
 Trimethoprim (C_M)
 Troleandomycin (C)
 Vancomycin (C_M)

12. Penicillins

Amoxicillin (B)
 Ampicillin (B)
 Bacampicillin (B_M)
 Carbenicillin (B)
 Cloxacillin (B_M)
 Cyclacillin (B_M)
 Dicloxacillin (B_M)
 Hetacillin (B)
 Methicillin (B_M)
 Nafcillin (B)
 Oxacillin (B_M)
 Penicillin G (B)
 Penicillin G, Benzathine (B)
 Penicillin G, Procaine (B)
 Penicillin V (B)
 Piperacillin (B_M)
 Ticarcillin (B)

13. Scabicide/Pediculicide

Lindane (B_M)
 Pyrethrins with Piperonyl Butoxide (C)

14. Sulfonamides

Sulfasalazine (B/D)
 Sulfonamides (B/D)

15. Tetracyclines

Chlortetracycline (D)
 Clomocycline (D)
 Demeclocycline (D)
 Doxycycline (D)
 Methacycline (D)
 Minocycline (D)
 Oxytetracycline (D)
 Tetracycline (D)

16. Trichomonacides

Metronidazole (B_M)

17. Urinary Germicides

Cinoxacin (B_M)
 Mandelic Acid (C)
 Methenamine (C_M)
 Methylene Blue (C_M/D)
 Nalidixic Acid (B)
 Nitrofurantoin (B)

E. ANTILIPEMIC AGENTS

Cholestyramine (C)
 Clofibrate (C)

Appendix

Dextrothyroxine (C)
Lovastatin (X_M)
Niacin (A/C)

F. ANTINEOPLASTICS

Aminopterin (X)
Asparaginase (C_M)
Azathioprine (D)
Bleomycin (D)
Busulfan (D)
Chlorambucil (D_M)
Cisplatin (D)
Cyclophosphamide (D)
Cytarabine (D_M)
Dacarbazine (C_M)
Dactinomycin (C_M)
Daunorubicin (D_M)
Doxorubicin (D)
Fluorouracil (D)
Hydroxyurea (D)
Laetrile (C)
Leuprolide (X_M)
Mechlorethamine (D)
Melphalan (D_M)
Mercaptopurine (D)
Methotrexate (D)
Plicamycin (Mithramycin) (D)
Procarbazine (D)
Teniposide (D)
Thioguanine (D_M)
Thiotepa (D)
Vinblastine (D)
Vincristine (D)

G. ANTITUSSIVES AND EXPECTORANTS

1. Antitussives

Codeine (C/D)

2. Expectorants

Guaifenesin (C)
Hydriodic Acid (D)
Iodinated Glycerol (X_M)
Potassium Iodide (D)
Sodium Iodide (D)

H. AUTONOMICS

1. Parasympathomimetics (Cholinergics)

Acetylcholine (C)
Ambenonium (C)
Bethanechol (C_M)
Carbachol (C)
Demecarium (C)

Echothiophate (C)

Edrophonium (C)

Isoflurophate (C)

Neostigmine (C_M)

Physostigmine (C)

Pilocarpine (C)

Pyridostigmine (C)

2. Parasympatholytics (Anticholinergic)

Anisotropine (C)

Atropine (C)

Belladonna (C)

Benztropine (C)

Biperiden (C_M)

Clidinium (C)

Cycrimine (C)

Dicyclomine (B)

Diphenamil (C)

Ethopropazine (C)

Glycopyrrolate (B_M)

Hexocyclium (C)

Homatropine (C)

l-Hyoscyamine (C)

Isopropamide (C)

Mepenzolate (C)

Methantheline (C)

Methixene (C)

Methscopolamine (C)

Orphenadrine (C)

Oxyphencyclimine (C)

Oxyphenonium (C)

Piperidolate (C)

Procyclidine (C)

Propantheline (C_M)

Scopolamine (C)

Thiphenamil (C)

Tridihexethyl (C)

Trihexyphenidyl (C)

3. Skeletal Muscle Relaxants

Baclofen (C)

Chlorzoxazone (C)

Cyclobenzaprine (B_M)

Dantrolene (C_M)

Decamethonium (C)

Methocarbamol (C)

Orphenadrine (C)

4. Sympathomimetics (Adrenergic)

Albuterol (C_M)

Cocaine (C)

Dobutamine (C)

Dopamine (C)

Ephedrine (C)

Epinephrine (C)

Fenoterol (B)
 Isoetharine (C)
 Isoproterenol (C)
 Isoxsuprine (C)
 Levarterenol (D)
 Mephentermine (C)
 Metaproterenol (C_M)
 Metaraminol (D)
 Methoxamine (C_M)
 Oxymetazoline (C)
 Phenylephrine (C)
 Phenylpropanolamine (C)
 Pseudoephedrine (C)
 Ritodrine (B_M/X)
 Terbutaline (B)

5. Sympatholytics

Acebutolol (B_M)
 Atenolol (C_M)
 Betaxolol (C_M)
 Bisoprolol (C_M)
 Carteolol (C_M)
 Doxazosin (B_M)
 Ergotamine (D)
 Esmolol (C_M)
 Guanabenz (C_M)
 Guanadrel (B_M)
 Labetalol (C_M)
 Mepindolol (C)
 Metoprolol (B_M)
 Nadolol (C_M)
 Oxprenolol (C)
 Penbutolol (C_M)
 Pindolol (B_M)
 Prazosin (C)
 Propranolol (C_M)
 Sotalol (B_M)
 Terazosin (C_M)
 Timolol (C_M)

I. CARDIOVASCULAR DRUGS

1. Angiotensin-Converting Enzyme Inhibitors

Benazepril (D_M)
 Captopril (D_M)
 Enalapril (D_M)
 Fosinopril (D_M)
 Lisinopril (D_M)
 Quinapril (D_M)
 Ramipril (D_M)

2. Antihypertensives

Acebutolol (B_M)
 Atenolol (C_M)
 Clonidine (C)

Diazoxide (C_M)
 Esmolol (C_M)
 Guanfacine (B_M)
 Hexamethonium (C)
 Hydralazine (C_M)
 Labetalol (C_M)
 Mepindolol (C)
 Methyldopa (C)
 Metoprolol (B_M)
 Minoxidil (C_M)
 Nadolol (C_M)
 Oxprenolol (C)
 Pargyline (C_M)
 Phenoxybenzamine (C)
 Phentolamine (C)
 Pindolol (B_M)
 Prazosin (C)
 Propranolol (C_M)
 Reserpine (D)
 Sodium Nitroprusside (C)
 Timolol (C_M)
 Trimethaphan (C)

3. Calcium Channel Blockers

Amlodipine (C_M)
 Bepridil (C_M)
 Diltiazem (C_M)
 Felodipine (C_M)
 Isradipine (C_M)
 Nicardipine (C_M)
 Nifedipine (C_M)
 Nimodipine (C_M)
 Verapamil (C_M)

4. Cardiac Drugs

Acetyldigoxin (C)
 Adenosine (C_M)
 Amiodarone (C)
 Amrinone (C_M)
 Bretylium (C)
 Deslanoside (C)
 Digitalis (C)
 Digitoxin (C_M)
 Digoxin (C_M)
 Disopyramide (C)
 Encainide (B_M)
 Flecainide (C_M)
 Gitalin (C)
 Lanatoside C (C)
 Lidocaine (C)
 Mexiletine (C_M)
 Milrinone (C_M)
 Moricizine (B_M)
 Ouabain (B)
 Procainamide (C_M)

Appendix

Propafenone (C_M)

Quinidine (C)

Tocainide (C_M)

5. Vasodilators

Amyl Nitrite (C)

Cyclandelate (C)

Dioxyline (C)

Dipyridamole (C)

Erythryl Tetranitrate (C)

Flosequinan (C_M)

Isosorbide Dinitrate (C)

Isosorbide Mononitrate (C_M)

Isoxsuprine (C)

Nicotinyl Alcohol (C)

Nitroglycerin (C_M)

Nylidrin (C_M)

Pentaerythritol Tetranitrate (C)

Tolazoline (C)

Dibenzepin (D)

Dothiepin (D)

Doxepin (C)

Fluoxetine (B_M)

Imipramine (D)

Ipindole (D)

Iproniazid (C)

Isocarboxazid (C)

Maprotiline (B_M)

Mebanazine (C)

Nialamide (C)

Nortriptyline (D)

Opipramol (D)

Phenelzine (C)

Protriptyline (C)

Sertraline (B_M)

Tranylcypromine (C)

Trazodone (C_M)

4. Hallucinogens

Lysergic Acid Diethylamide (C)

Marijuana (C)

Phencyclidine (X)

5. Narcotic Analgesics

Alfentanil (C_M)

Alphaprodine (C_M/D)

Anileridine (B/D)

Butorphanol (B/D)

Codeine (C/D)

Dihydrocodeine Bitartrate (B/D)

Fentanyl (B/D)

Heroin (B/D)

Hydrocodone (B/D)

Hydromorphone (B/D)

Levorphanol (B/D)

Meperidine (B/D)

Methadone (B/D)

Morphine (B/D)

Nalbuphine (B/D)

Opium (B/D)

Oxycodone (B/D)

Oxymorphone (B/D)

Pentazocine (B/D)

Phenazocine (B/D)

6. Narcotic Antagonists

Cyclazocine (D)

Levallorphan (D)

Nalorphine (D)

Naloxone (B_M)

7. Nonsteroidal Anti-inflammatory Drugs

Diffunisal (C_M/D)

Fenoprofen (B/D)

Ibuprofen (B/D)

J. CENTRAL NERVOUS SYSTEM DRUGS

1. Analgesics and Antipyretics

Acetaminophen (B)

Aspirin (C/D)

Aspirin, Buffered (C/D)

Ethoheptazine (C)

Phenacetin (B)

Propoxyphene (C/D)

2. Anticonvulsants

Aminogluthethimide (D_M)

Bromides (D)

Carbamazepine (C_M)

Clonazepam (C)

Ethosuximide (C)

Ethotoin (D)

Magnesium Sulfate (B)

Mephenytoin (C)

Mephobarbital (D)

Metharbital (B)

Methsuximide (C)

Paramethadione (D_M)

Phenobarbital (D)

Phensuximide (D)

Phenytoin (D)

Primidone (D)

Trimethadione (D)

Valproic Acid (D)

3. Antidepressants

Amitriptyline (D)

Amoxapine (C_M)

Bupropion (B_M)

Clomipramine (D)

Desipramine (C)

Indomethacin (B/D)
Ketoprofen (B_M/D)
Meclofenamate (B/D)
Naproxen (B_M/D)
Oxyphenbutazone (D)
Phenylbutazone (D)
Piroxicam (B/D)
Sulindac (B/D)
Tolmetin (C_M/D)

8. Sedatives and Hypnotics

Alprazolam (D_M)
Amobarbital (D/B)
Aprobarbital (C)
Butalbital (C/D)
Chloral Hydrate (C_M)
Chlordiazepoxide (D)
Clorazepate (D)
Diazepam (D)
Ethanol (D/X)
Ethchlorvynol (C_M)
Ethinamate (C_M)
Flunitrazepam (D)
Flurazepam (X_M)
Lorazepam (D_M)
Mephobarbital (D)
Meprobamate (D)
Methaqualone (D)
Metharbital (D)
Midazolam (D_M)
Oxazepam (D)
Pentobarbital (D_M)
Phenobarbital (D)
Propofol (B_M)
Secobarbital (D_M)
Temazepam (X_M)
Triazolam (X_M)

9. Stimulants

Amphetamine (C_M)
Caffeine (B)
Dextroamphetamine (C_M)
Diethylpropion (B)
Fenfluramine (C)
Mazindol (C)
Methamphetamine (C_M)
Methylphenidate (C)
Phendimetrazine (C)
Phentermine (C)

10. Tranquilizers

Acetophenazine (C)
Butaperazine (C)
Carphenazine (C)
Chlorpromazine (C)
Chlorprothixene (C)

Droperidol (C_M)
Flupenthixol (C)
Fluphenazine (C)
Haloperidol (C)
Hydroxyzine (C)
Lithium (D)
Loxapine (C)
Mesoridazine (C)
Methotrimeprazine (C)
Molindone (C)
Perphenazine (C)
Piperacetazine (C)
Prochlorperazine (C)
Promazine (C)
Tetrabenazine (C)
Thiopropazate (C)
Thioridazine (C)
Thiothixene (C)
Trifluoperazine (C)
Triflupromazine (C)
Zuclopenthixol (C)

K. COAGULANTS/ANTICOAGULANTS

1. Anticoagulants

Anisindione (D)
Coumarin Derivatives (D/X_M)
Dicumarol (D)
Diphenadione (D)
Enoxaparin (B_M)
Ethyl Biscoumacetate (D)
Heparin (C)
Nicoumalone (D)
Phenindione (D)
Phenprocoumon (D)
Warfarin (D)

2. Antiheparin

Protamine (C)

3. Hemorrheologic

Pentoxifylline (C_M)

4. Hemostatics

Aminocaproic Acid (C)
Aprotinin (C)

5. Thrombolytics

Streptokinase (C)
Urokinase (B_M)

L. DIAGNOSTIC AGENTS

Diatrizoate (D)
Ethiodized Oil (D)
Evans Blue (C)
Gadopentetate Dimeglumine (C_M)
Indigo Carmine (B)
Iocetamic Acid (D)

Appendix

Iodamide (D)
Iodipamide (D)
Iodoxamate (D)
Iopanoic Acid (D)
Iothalamate (D)
Iodate (D)
Methylene Blue (C_M/D)
Metrizamide (D)
Metrizoate (D)
Sodium Iodide I¹²⁵ (X)
Sodium Iodide I¹³¹ (X)
Tyropanoate (D)

M. DIURETICS

Acetazolamide (C)
Amiloride (B_M)
Bendroflumethiazide (D/C)
Benzthiazide (D)
Bumetanide (D/C_M)
Chlorothiazide (D)
Chlorthalidone (D)
Cyclopenthiazide (D)
Cyclothiazide (D)
Dichlorpenamide (C_M)
Ethacrynic Acid (D)
Furosemide (C_M)
Glycerin (C)
Hydrochlorothiazide (D)
Hydroflumethiazide (D)
Indapamide (D)
Isosorbide (C)
Mannitol (C)
Methazolamide (C)
Methyclothiazide (D)
Metolazone (D)
Polythiazide (D)
Quinethazone (D)
Spironolactone (D)
Triamterene (D)
Trichlormethiazide (D)
Urea (C)

N. ELECTROLYTES

Potassium Chloride (A)
Potassium Citrate (A)
Potassium Gluconate (A)

O. GASTROINTESTINAL AGENTS

1. Antidiarrheals

Bismuth Subsalicylate (C)
Diphenoxylate (C_M)
Kaolin/Pectin (C)
Loperamide (B_M)

Paregoric (B/D)

2. Antiemetics

Bucizine (C)
Cyclizine (B)
Dimenhydrinate (B)
Doxylamine (B)
Droperidol (C_M)
Meclizine (B_M)
Metoclopramide (B_M)
Ondansetron (B_M)
Prochlorperazine (C)
Trimethobenzamide (C)

3. Antiflatulents

Simethicone (C)

4. Anti-inflammatory Bowel Disease Agents

Mesalamine (B_M)
Olsalazine (C_M)
Sulfasalazine (B/D)

5. Antisecretory Agents

Cimetidine (B_M)
Famotidine (B_M)
Misoprostol (X_M)
Nizatidine (C_M)
Omeprazole (C_M)
Ranitidine (B_M)
Sucralfate (B_M)

6. Gallstone Solubilizing Agents

Chenodiol (X_M)
Ursodiol (B_M)

7. Laxatives/Purgatives

Casanthranol (C)
Cascara Sagrada (C)
Danthron (C)
Docusate Calcium (C)
Docusate Potassium (C)
Docusate Sodium (C)
Lactulose (C)
Mineral Oil (C)
Phenolphthalein (C)
Senna (C)

8. Stimulants

Metoclopramide (B_M)

P. GOLD COMPOUNDS

Aurothioglucose (C)
Gold Sodium Thiomalate (C)

Q. HEAVY METAL ANTAGONISTS

Deferoxamine (C_M)
Penicillamine (D)
Trientine (C_M)

R. HEMATOPOIETIC AGENTSEpoetin Alfa (C_M)**S. HORMONES****1. Adrenal**

Beclomethasone (C)

Betamethasone (C)

Cortisone (D)

Dexamethasone (C)

Prednisolone (B)

Prednisone (B)

2. Androgens

Danazol (X)

3. Antidiabetic Agents

Acetohexamide (D)

Chlorpropamide (D/C)

Glyburide (D/B_M)

Insulin (B)

Tolazamide (D/C)

Tolbutamide (D/C)

4. Antiprogestogen

Mifepristone (X)

5. Antithyroid

Carbimazole (D)

Methimazole (D)

Propylthiouracil (D)

Sodium Iodide I¹³¹ (X)**6. Estrogens**Chlorotrianisene (X_M)Clomiphene (X_M)

Dienestrol (X)

Diethylstilbestrol (X_M)

Estradiol (X)

Estrogens, Conjugated (X_M)

Estrone (X)

Ethinyl Estradiol (X)

Hormonal Pregnancy Test

Tablets (X)

Mestranol (X)

Oral Contraceptives (X)

7. Pituitary

Corticotropin/Cosyntropin (C)

Desmopressin (B_M)Leuprolide (X_M)Lypressin (C_M)

Somatostatin (B)

Vasopressin (B)

8. Progestogens

Ethisterone (D)

Ethinodiol (D)

Hydroxyprogesterone (D)

Lynestrenol (D)

Medroxyprogesterone (D)

Norethindrone (X_M)Norethynodrel (X_M)Norgestrel (X_M)

Oral Contraceptives (X)

9. Thyroid

Calcitonin (B)

Iodothyronine (A)

Levothyroxine (A_M)Liothyronine (A_M)

Liotrix (A)

Protirelin (C)

Thyroglobulin (A)

Thyroid (A)

Thyrotropin (C_M)**T. NUTRIENTS**

Hyperalimentation, Parenteral (C)

Lipids (C)

L-Lysine (C)

U. SERUMS, TOXOIDS, AND VACCINES**1. Serums**Immune Globulin Intramuscular (C_M)Immune Globulin Intravenous (C_M)Immune Globulin, Hepatitis B (C_M)Immune Globulin, Rabies (C_M)Immune Globulin, Tetanus (C_M)

Immune Globulin, Varicella Zoster (Human) (C)

2. Toxoids

Tetanus/Diphtheria Toxoids (Adult) (C)

3. VaccinesBCG (C_M)Cholera (C_M)*Escherichia coli* (C)Group B *Streptococcus* (C)Hemophilus b Conjugate (C_M)Hepatitis B (C_M)Influenza (C_M)Measles (X/C_M)

Meningococcus (C)

Mumps (X_M)Plague (C_M)Pneumococcal Polyvalent (C_M)Poliovirus Inactivated (C_M)Poliovirus Live (C_M)

Rabies Human (C)

Rubella (X/C_M)

Smallpox (X)

Tularemia (C)

Appendix

Typhoid (C)
Yellow Fever (D)

V. SPASMOLYTICS

Aminophylline (C)
Dyphylline (C_M)
Oxtriphylline (C)
Theophylline (C)

W. TOXINS

Ciguatoxin (X)

X. VAGINAL SPERMICIDES

Nonoxynol-9 (C)
Octoxynol-9 (C)

Y. VITAMINS

β-Carotene (C)
Calcifediol (A/D)
Calcitriol (A/D)
Cholecalciferol (A/D)
Dihydrotachysterol (A/D)
Ergocalciferol (A/D)
Etretinate (X_M)
Folic Acid (A/C)
Isotretinoin (X_M)
Leucovorin (C_M)
Menadione (C_M/X)
Niacin (A/C)

Niacinamide (A/C)
Pantothenic Acid (A/C)
Phytonadione (C)
Pyridoxine (A/C)
Riboflavin (A/C)
Thiamine (A/C)
Tretinoin (B_M)
Vitamin A (A/X)
Vitamin B₁₂ (A/C)
Vitamin C (A/C)
Vitamin D (A/D)
Vitamin E (A/C)
Vitamins, Multiple (A)

Z. MISCELLANEOUS

Allopurinol (C)
Aspartame (B)
Bromocriptine (C_M)
Camphor (C)
Colchicine (C_M)
Cromolyn Sodium (B_M)
Cyclamate (C)
Cyclosporine (C_M)
Disulfiram (C)
Electricity (D)
Nutmeg (C)
Phenazopyridine (B_M)
Probenecid (B)
Saccharin (C)

Chapter 6

Drugs

Yet 35 years after the recognition of thalidomide associated embryopathy, fewer than 30 drugs have been proved to be teratogenic in humans when used in clinically effective doses, and even fewer are currently in clinical use. Many other commonly used drugs, including salicylates, glucocorticoids, and spermicides, were once thought to be teratogenic but have been shown to be safe in subsequent studies that were larger and better controlled than the initial studies.

The clinician and patient must weigh the benefits to mother and fetus of using the agent against the theoretical or known risks of the agent. In some situations, the decision is relatively easy, such as in treatment of an infection that presents a significant hazard to the mother and fetus with an antibiotic that has been well studied and presents minimal risk to the fetus.(28)

While almost any chemical substance may cross the placenta and concentrate in the fetus, some do so more readily than others. The effect of a chemical or a drug upon the fetal tissues depends on:

- 1 - when it is administered during the gestation period,
- 2 - the duration of the exposure,
- 3 - the dosage administered,
- 4 - the type of chemical agent,
- 5 - the genetic makeup of both the mother and the fetus,
- 6 - and the coexistence of other chemicals and their interactions with the chemical in question.

Some agents may produce damage to organ systems and cause abnormal development; others may change the growth patterns of a tissue; while still others may cause subtle behavioral or intellectual changes that may only become manifest long after birth.

Chemical agents and drugs undergo various interactions in the body before combining with specific tissue receptors to manifest their pharmacologic effect. This effect may be modified by the extent and rate of absorption, the volume of distribution, the nature and rate of metabolic degradation, and the interactions of the chemical with other compounds.

Those physiochemical aspects of the drug that determine the amount and rate of absorption (i.e., its bioavailability), in the case of the oral route, are:

- (1) the dissolution and solubility of the drug,
- (2) the gastric and intestinal pH,
- (3) the gastric emptying time,
- (4) the intestinal transit time,
- (5) the presence of other agents that may compete with or block the drug, and
- (6) the mesenteric blood flow.

The fetal circulation is such that the distribution of a drug may vary considerably in different situations. In hypoxic conditions, for example, the peripheral circulation, including the hepatic circulation, may be shut down; thus, the chemical may bypass the liver entirely and instead attain high concentrations in the fetal brain and heart. Fetal plasma proteins provide a lesser degree of binding of a drug than the plasma proteins of the adult organism, which allows more free drug to be available to the fetus. Drug distribution is also affected to some extent by the change in the total body water content of the fetus, which decreases from 94% at 4 months gestation to 76% at term. Furthermore, in early pregnancy, there is no fat present in the fetus, whereas in the last trimester, fat accounts for about 15% of the body weight at term.

There are 4 elimination routes for the fetus:

- (1) the placenta,
- (2) the fetal kidney,
- (3) the fetal skin, and
- (4) the fetal lungs.

The placenta is the primary organ for the excretion of fetal waste products. However, the fetal kidneys, lung, and skin offer some intriguing problems: the passage of chemicals via these organs may allow them to be recirculated, added to, or preferentially partitioned in the fetus or in the amniotic fluid. (35)

COMMON DRUGS INITIALLY THOUGHT TO BE TERATOGENIC BUT SUBSEQUENTLY PROVED SAFE.

DRUG	INITIAL EVIDENCE OF RISK	SUBSEQUENT EVIDENCE OF SAFETY
Diazepam*	Oral clefts ⁹	No increase in risk in large cohort and case-control studies ^{10,12}
Oral contraceptives	Birth defects involving the vertebrae, anus, heart, trachea, esophagus, kidney, and limbs ¹³ ; masculinizing effects on female fetuses resulting in pseudohermaphroditism ¹⁴	No association between first-trimester exposure to oral contraceptives and malformations in general or external genital malformations in two meta-analyses ^{15,16}
Spermicides	Limb defects, tumors, Down's syndrome, and hypospadias ¹⁷	No increase in risk in a meta-analysis ¹⁸
Salicylates	Cleft palate ¹⁹ and congenital heart disease	No increase in risk in large cohort studies ^{20,21}

DRUGS WITH PROVEN TERATOGENIC EFFECTS IN HUMANS.*

DRUG	TERATOGENIC EFFECT
Aminopterin†, methotrexate	CNS and limb malformations
Angiotensin-converting-enzyme inhibitors	Prolonged renal failure in neonates, decreased skull ossification, renal tubular dysgenesis
Anticholinergic drugs	Neonatal meconium ileus
Antithyroid drugs (propylthiouracil and methimazole)	Fetal and neonatal goiter and hypothyroidism, aplasia cutis (with methimazole)
Carbamazepine	Neural-tube defects
Cyclophosphamide	CNS malformations, secondary cancer
Danazol and other androgenic drugs	Masculinization of female fetuses
Diethylstilbestrol‡	Vaginal carcinoma and other genitourinary defects in female and male offspring
Hypoglycemic drugs	Neonatal hypoglycemia
Lithium	Edstein's anomaly
Misoprostol	Moebius sequence
Nonsteroidal antiinflammatory drugs	Constriction of the ductus arteriosus‡, necrotizing enterocolitis
Paramethadione†	Facial and CNS defects
Phenytoin	Growth retardation, CNS deficits
Psychoactive drugs (e.g., barbiturates, opioids, and benzodiazepines)	Neonatal withdrawal syndrome when drug is taken in late pregnancy
Systemic retinoids (isotretinoin and etretinate)	CNS, craniofacial, cardiovascular, and other defects
Tetracycline	Anomalies of teeth and bone
Thalidomide	Limb-shortening defects, internal-organ defects
Trimethadione†	Facial and CNS defects
Valproic acid	Neural-tube defects
Warfarin	Skeletal and CNS defects, Dandy-Walker syndrome

*Only drugs that are teratogenic when used at clinically recommended doses are listed. The list includes all drugs proved to affect neonatal morphology or brain development and some of the toxic manifestations predicted on the basis of the pharmacologic actions of the drugs. Data are from Briggs et al.⁸ CNS denotes central nervous system.

†The drug is not currently in clinical use.

‡Sulindac probably does not have this effect.

Teratogenic drugs

6.1 - Antibiotics:

A number of bacterial, viral, fungal, and parasitic infections are commonly encountered during pregnancy. Virtually, all antimicrobial and chemotherapeutics agents used for these infections readily cross the placenta.

A large number of antimicrobial agents are available , but there have been few studies regarding their efficacy and safety during pregnancy . Most of the antibiotics used cross the placenta and expose the fetus to their effects. (19)

a - Aminoglycosides:

Class: C

Aminoglycosides are active against aerobic gram negative bacilli. Transplacental passage has been demonstrated to result in 3 to 11 percent rate of ototoxicity in exposed infants . Although hearing loss appears to be dose related, these agents should be avoided if possible during pregnancy. (43) In cases requiring these drugs for serious infections , their use should be restricted to as shorter time as possible and maternal serum levels should be monitored (43,95)

b - β -Lactam antibiotics:

Class : B

β -Lactam antibiotics, Penicillins and Cephalosporins , have been widely used in pregnancy and are probably the « safest » antimicrobial to use during pregnancy.. Penicillins with newer broad spectrum activity such as piperacillin and mezlocillin as well as those combined with the β -Lactamase inhibitors, clavulanic acid and sulbactam, are also included in this group (43,95,103).

c - Clindamycin:

Class : B

Clindamycin has a broad spectrum of anaerobic activity. There have been no studies of potential adverse embryofetal effects from its use during pregnancy, clinical experience suggests that this drug seems relatively safe (95,103).

d - Chloramphenicol:

Class: C

Chloramphenicol use should be restricted to potentially life-threatening situations because of the possibility of drug-induced aplastic anemia. The « gray baby syndrome» manifested by cyanosis , vascular collapse , and death , has been reported with large dose of chloramphenicol administered to preterm neonates , but it seems unlikely that fetal levels obtained from maternal administration would cause this syndrome (76,95,103).

e - Macrolides:

Class: B

Erythromycin is a macrolide antibiotic used in penicillin-allergic patients . It is effective against gram-positive bacteria and mainly used for the treatment of maternal chlamydial and mycoplasmal infections . It is apparently safe in pregnancy since only small amounts of the drug gain fetal access (95,103). There are no studies available about the safety of the new macrolide Azithromycin.

f- Quinolones:

Class: C

Quinolones are relatively new antimicrobials that are especially useful for the treatment of urinary tract infections . Fluoroquinolones should not be used during pregnancy unless needed for resistant infections (95,103).

g- Sulfonamides:

Class B/D:

Sulfonamides readily cross the placenta, but fetal blood levels appear to be lower than maternal levels . These drugs compete for bilirubin -binding sites and may be associated with hyperbilirubinemia if used close to term.

Trimethoprim is often used in association with sulfonamides , and since it is a folate antagonist, it should be avoided during pregnancy (76,95,103).

h - Tetracycline:

Class : D

Tetracycline is a broad spectrum antibiotic frequently used for the treatment of respiratory tract infections and acne . Tetracyclines are contraindicated in pregnancy throughout the 3 trimesters of gestation. Why? (42,76).

The administration of these agents during the period of osseous organogenesis in animals may result in hypoplasia of the anterior limb buds and other skeletal abnormalities (76,103). Tetracyclines are effective chelators of heavy metals. They are competitive at the osteoblastic level with calcium in the areas of new bone formation. This action results in the inhibition of bone growth.

While bone is the major fetal site of tetracycline action, it is not the sole target organ. In teeth , the binding of tetracycline to calcium forms a calcium - tetracycline -orthophosphonate complex which is responsible for the brown permanent discoloration in teeth. However, the degree of discoloration is dose dependent. In spite of that , it is still contraindicated (19,43,103).

Large doses of tetracycline 2 g/day intravenously , used for the treatment of pyelonephritis , resulted in maternal hepatotoxicity that should be fatal. The symptoms include jaundice, azotemia, acidosis and terminal, irreversible shock.

The fetus may not be directly affected but as a result of maternal pathology , still born infants and premature birth are common (19,76,103).

i - Vancomycin:

Class:C

Vancomycin is the drug of choice for *Clostridium difficile* pseudomembranous colitis. Although there are no available human reproductive studies, vancomycin has been associated with maternal nephrotoxicity and ototoxicity, and it may cause the same effects in the human embryo or fetus (95,103).

6.2 - Anticonvulsants:

Anticonvulsants drugs have been shown to induce teratogenic effects in the developing fetus when administered during pregnancy: the Fetal Hydantoin Syndrome, the Fetal Valproate Syndrome, as well as other structural and functional defects related to exposure to carbamazepine and trimethadione. In more than 90 % of patients who received antiepileptic drugs a successful pregnancy outcome was observed. The potential teratogenesis is decreased by administering a single antiepileptic drug with the minimal effective dose (22,81).

a - Phenytoin:

Class : D

The frequency of major malformations among the children of epileptic women treated with phenytoin during pregnancy is about twice as great as the frequency of such anomalies in the general population. The risk of malformations in the offspring is probably even greater if the mother requires treatment with other anticonvulsants in addition to phenytoin during pregnancy (42).

The use of Phenytoin during pregnancy is also associated with minor anomalies in the offspring. A « Fetal Hydantoin Syndrome », which consists of an unusual and characteristic pattern of anomalies, has been described in about 10 % of infants born to epileptic women who took phenytoin during pregnancy (19,42,53).

The basic syndrome consists of variable degrees of hypoplasia and ossification of the distal phalanges and craniofacial abnormalities. The facial anomalies of this syndrome include poorly developed midface, a broad low nasal bridge, cleft palate, congenital heart disease, microcephaly, developmental delay, and prenatal and postnatal growth retardation may also occur. Limb defects consist mainly of digital and nail hypoplasia (19,42,53,59).

Exposure to Phenytoin during pregnancy has also been associated with an increased risk of tumor development in humans. Exposed children must be closely evaluated for several years since tumors may take that long before appearing (19,42,59).

Use of Phenytoin and other anticonvulsants during the third trimester increases the risk of hemorrhagic disease in the newborn due to induction of fetal liver microsomal enzymes (by depletion of vitamin K dependent coagulation factors) and induced thrombocytopenia.

Phenytoin may also induce folic acid deficiency in the epileptic patient by impairing gastrointestinal absorption or by increasing hepatic metabolism of the vitamin. Low maternal folate levels, have been proposed as one possible mechanism for the increased incidence of defects observed in infants exposed in utero to phenytoin (19,59).

There are also other possible mechanisms of phenytoin teratogenesis:

- 1 - A direct teratogenic effect of one or more arene oxide products of phenytoin metabolism.
- 2- The production of teratogenic free radicals during phenytoin metabolism.
- 3- Fetal hypoxia secondary to phenytoin-induced cardiodepression.
- 4- A direct effect of seizures
- 5- A developmental effect associated with the genotype of epilepsy (53,123,42).

The use of phenytoin during pregnancy involves significant risk to the fetus. The risk to the mother, however, is also great if the drug is not used to control her seizures. The benefit risk ratio, in this case, favors continued use of the drug during pregnancy. Frequent determinations of phenytoin levels are recommended to maintain the lowest level required to prevent seizures and to possibly decrease fetal anomalies (19).

b - Valproic acid.

Class: D

Valproic acid is known to cross the placenta and is present in higher concentration in the fetus than in the mother. A « Fetal Valproate Syndrome » has resulted with characteristic facial features, associated with some minor and major congenital malformations.

This syndrome involves postnatal growth retardation , microcephaly , developmental delay , midface hypoplasia , short nose , broad nasal bridge , thin upper lip and thick lower lip (19,26,42,123).

Other frequent major congenital malformations include neural tube defects , congenital heart defects , oral clefts , genital abnormalities , and limb defects. Other less frequent abnormalities include abdominal wall defects, tracheomalacia and strabismus.

Anencephaly is rarely seen, but most reports have been of spina bifida suggesting that valproate affects primarily the lowest closure site of the neural tube (26,42,16,19).

The actual mechanism of valproic acid teratogenicity is unknown . Several mechanisms have been proposed : a direct teratogenic effect of the parent drug alteration in intracellular pH , interference with lipid metabolism , alteration in zinc concentrations, or disruption of folate use. (26,42)

Since valproic acid is a potent teratogen , it should be used with caution during pregnancy. The patient should be followed by serum α -fetoprotein determinations ultrasonography and amniocentesis (22).

c - Carbamazepine:

Class: C

Carbamazepine was considered a relatively safe alternative to the teratogenic risk associated with other anticonvulsants . However , several reports have shown an association between carbamazepine exposure and fingernail and toenail hypoplasia, or reduced birth weight, length and head circumference (98).

The drug was known to cross the placenta with fetal levels reaching approximately 50-80% of maternal serum concentration (19).

A Fetal Carbamazepine Syndrome has been described consisting of dysmorphic features

short nose , distal digital hypoplasia and microcephaly . Developmental delay has also been found in 20 % of exposed children (123).

Recently carbamazepine was discovered to be associated with 1 % risk of spina bifida. This defect results from drug exposure early in pregnancy before the closure of the neural tube (2 to 3 weeks after conception) (42,66,107).

Two possible mechanisms have been suggested for carbamazepine teratogenesis

- 1) the formation of an intermediate teratogenic metabolite , or
- 2) decreased serum folate levels (66).

Although the data were insufficient for a definitive estimation , carbamazepine does appear to present a significant risk to the fetus (98).

The patient should be monitored by ultrasonography and serum alpha-fetoprotein levels for possible congenital malformations (107).

6.3 - Thyroid disorder drugs

Iodine deficiency during pregnancy is the most common preventable cause of fetal mental deficits.

The most severe effect of iodine deficiency is endemic cretinism which is characterized by the combination of mental deficiency deaf-mutism , and motor rigidity or less commonly , by severe hypothyroidism . The two forms are often referred to as neurologic cretinism and hypothyroid cretinism respectively (52). Iodine deficiency in the beginning of the third trimester causes irreversible abnormalities in head growth and neurologic development. But in areas with severe iodine deficiency the iodine supplementation before pregnancy prevented cretinism but supplementation during pregnancy did not (65,52,122).

In areas with a moderate degree of iodine deficiency maternal and fetal goiter formation , maternal hypothyroxinemia and an increased frequency of neonatal hypothyroidism and hyperthyrotropinemia have been reported(10). The administration of 300 ug KI / day during pregnancy with moderate iodine deficiency prevents the development of fetal thyroid enlargement (65).

Therefore thyroid hormone deficiency in the fetus and neonate can result in developmental retardation . The severity , duration , and time of onset of thyroid hormone deficiency interact in determining the degree and potential reversibility of any brain damage (10).

** Hyperthyroidism:*

Iodide acutely inhibits the release of stored thyroid hormone and can be of great value in severely thyrotoxic patients when it is used in conjunction with antithyroid drugs (15). Iodide readily crosses the placenta.

Exposure to excess iodine for prolonged periods or close to term is an important cause of fetal neonatal hypothyroidism and goiter . Iodine may accumulate in the fetus following intravenous , oral , topical or mucosal absorption of topical iodine preparation applied to the umbilical cord (10).

Short-term use, such as a 10-day preparation course for maternal thyroid surgery, does not carry this risk and is apparently safe (19).

Radioactive iodine is a mainstay in the treatment of thyrotoxicosis in non-pregnant women , but is absolutely contraindicated in pregnancy . This agent crosses the placenta and can cause fetal hypothyroidism if administered after 10 or 12 weeks of gestation (33).

6.4 - Anticoagulants:

Anticoagulants are administered for the treatment of established deep venous thrombosis or pulmonary embolism occurring during pregnancy, and for prophylaxis against venous thromboembolism. Also anticoagulant treatment is continued in women with mechanical heart valve prostheses who become pregnant. Anticoagulant therapy in pregnancy carries several risks , including the potential for teratogenic and hemorrhagic complications in the fetus and newborn, the dangers of life -threatening maternal hemorrhage at parturition (46,47).

a - Warfarin:

Class : D

Warfarin is a vitamin K antagonist that act through inhibition of the carboxylation step of glutamic acid residues in the vitamin-K dependent clotting factors . Hemorrhage is one of the common side-effects of warfarin therapy.

However, oral anticoagulant drugs cross the placenta and enter the fetal circulation . This may result in two major side-effects: Warfarin embryopathy and fetal CNS anomalies (46,47).

Use of warfarin in the first trimester of pregnancy has been associated with a characteristic pattern of defects known as the Fetal Warfarin Syndrome. The susceptible period seems to be between the sixth and ninth week of gestation.

Consistent features are nasal hypoplasia with depression of the nasal bridge, which may be sufficiently marked to result in neonatal respiratory distress due to upper airway obstruction . Hypoplasia of the extremities, with short fingers have also been noted in about 50 % of affected neonates. Less common features are reduced birth weight, eye and ear defects, development retardation, congenital heart disease, laryngeal calcification and death (19,30,47,59,77,98)

b - Heparin:

Class:C

Heparin is a large molecule and does not cross the placenta to the fetus. The risk of teratogenesis and fetal hemorrhage seen with warfarin therapy should therefore not be present when heparin is administered during pregnancy. However, two heparin related serious side-effects have given cause for concern: osteopaenia and severe thrombocytopenia. The risk of maternal hemorrhage at delivery also exists (19,30,47,59,53).

6.5 - Diethylstilbestrol

Class: X

Diethylstilbestrol (DES) , the first orally active estrogen is mainly used for the treatment of ovarian insufficiency and in combination with progestins for oral contraception (46). Large doses of DES were given during pregnancy in attempt to prevent threatened or habitual abortion . (59,74).

In 1970 it was reported that young women whose mothers has been given DES during the first trimester of pregnancy had an increased incidence of vaginal adenocarcinoma. Subsequent studies showed that most of the vaginal adenocarcinomas in the daughters occurred after age 14 and only in those exposed before week 18 of gestation. There is a 75 % risk for vaginal adenosis for exposures occurring before the ninth week of pregnancy, however , the risk of developing adenocarcinoma is extremely low (1 in10000) (42,77,94,98).

Vaginal epithelium changes are under the influence of several factors : 1) timing of the onset of exposure to DES, 2) total dose of DES, 3) duration of exposure, and 4) age of the DES-daughter at the time of surveillance for adenosis (74).

There have been reports that males exposed to DES in utero exhibited genital lesions and abnormal spermatozoa. Some studies suggest that epididymal cyst, hypoplastic testes, cryptorchidism, and abnormalities on semen analysis are more frequent among sons of mothers treated with DES during pregnancy. About 25 % of males exposed to DES in utero exhibited genital lesions and low sperm counts, but an increased incidence of malignant neoplasia has not been reported (42,74,94,98).

6.6 - Androgens and Progestogens

Class : D

Any hormone that has androgenic activity may affect the fetus, producing masculinization of the female external genitalia. Clitoromegaly and sometimes fusion of the labia minora have been reported following maternal exposure to large doses of testosterone and methyltestosterone. Since differentiation of the external genitalia is usually complete by the twelfth week of gestation, hormone treatment after that time could have little effect on these organs (77,117).

Progesterone is a hormone essential for pregnancy. In addition to being secreted in moderate quantities by the corpus luteum at the beginning of pregnancy, it is secreted in tremendous quantities by the placenta. Progestins have been widely used for the prevention of abortion since progesterone has a special effect on decreasing the contractility of the gravid uterus, thus preventing uterine contractions from causing spontaneous abortion (48, 105).

Maternal use of high doses of synthetic progesterones (norethindrone, norethynodrel) medroxyprogesterone and hydroxyprogesterone has been associated with the occurrence of masculinization of the external genitalia in female infants.

The genital anomalies observed include various degrees of clitoral hypertrophy with or without labioscrotal fusion. Internal genitalia and pubertal development were not affected. Labioscrotal fusion is associated with exposure between the seventh and thirteenth week of gestation, but clitoral hypertrophy can develop at this time and late in pregnancy (19,42,98).

An association between exposure to female sex hormones and congenital neural tube defects, limb defects and congenital heart disease have been reported.

Further re-evaluation of these data failed to support an association between female sex hormones and non-genital malformations (19,98).

Because oral contraceptives are primarily combination products , it is difficult to separate entirely the fetal effects of progestogens and estrogens . The acronym VACTERL (Vertebral, Anal, Cardiac, Tracheal , Esophageal , Renal or Radial , and Limb) has been used to described the fetal malformations produced by oral contraceptives . The incidence of these malformation is very low and is estimated to occur in only 0.07 % of the pregnancies exposed to oral contraceptives (19).

6.7 - Angiotensin-converting enzyme ACE inhibitors

Class D:

ACE inhibitor prevent the conversion of inactive angiotensin I to the active form, angiotensin II. Commonly used ACE inhibitors have been shown to cross the placenta, and the teratogenic effects of maternal therapy have been reported (117). However, the direct effect of ACE inhibitors on the fetus are difficult to determine since these drugs are usually administered to women with high risk pregnancy.

Oligohydramnios, premature labor, IUGR, fetal and neonatal renal failure, bony limb contractures pulmonary hypoplasia, respiratory distress syndrome, prolonged hypotension and neonatal death have been observed after maternal treatment with ACE inhibitors.

Prolonged anuria associated with renal failure and hypotension in the newborn and the unique skull ossification defect in neonates are very likely to be related to ACE inhibitors therapy. Because of the frequency and consistency of the reported fetal complications, ACE-inhibitors should be avoided during gestation (8,19,105) Each woman being treated with ACE inhibitors should have a second antihypertensive regimen to which she may switch once pregnancy is diagnosed (70).

6.8 - Lithium Carbonate:

Class : D

Lithium is the most commonly used agent for bipolar disorders. It was first associated with human congenital malformations (98).

Its use during the first trimester of gestation may be related to an increased incidence of congenital defects, particularly the cardiovascular system: Ebstein's anomaly (malattachment of the tricuspid leaflets leading to tricuspid insufficiency, right ventricular dilation, and occasionally a ventricular septal defect) has been associated with prenatal lithium exposure (19,55,62).

Given the small number of studies and the small sample sizes, the risk of lithium induced Ebstein's anomaly may be very small but, cannot be ruled out. Therefore, lithium therapy should be stopped during the first trimester of pregnancy (1,38,55,62).

However, reintroduction of the drug in the second and third trimester may be also associated with an increased risk of malformations mainly polyhydramnios, and neonatal toxicity.

Polyhydramnios resulting from lithium-induced nephrogenic diabetes insipidus in the fetus. Neonatal toxicity can occur even when the mother's serum level is therapeutic, and it may result in abnormal respiratory patterns, cyanosis, hypotonia, decreased suckling and reflexes hypoglycemia, thrombocytopenia and convulsions (38,42,62). Neonatal hypothyroidism has also been reported.

The mechanism of lithium teratogenic action is unknown. It crosses the placenta freely and maternal and fetal plasma concentrations are similar (1,19).

Treatment of the bipolar disorder during pregnancy depends on the severity of the mother's illness. For modest to moderate severity, lithium dosage should be tapered to stop the drug before conception. Women with more severe bipolar disorder may benefit most from lithium therapy continued throughout pregnancy. The risk of relapse is so great that maintenance of lithium during attempts to conceive and pregnancy can be justified.

Patients who have taken lithium during the first trimester of pregnancy are followed by ultrasound examination for prenatal detection of congenital anomalies such as Ebstein's anomaly (55).

6.9 - Retinoids (Isotretinoin, Tretinoin)

Class: X

Isotretinoin , a synthetic retinoid , used for oral treatment of severe recalcitrant acne, is now considered one of the most severe human teratogen (100).

Approximately 25 to 30 percent of exposed fetuses had birth defects , the so-called Retinoic Acid Embryopathy consisting of craniofacial, heart, central nervous system, cardiovascular and thymus defects (70,54,100,115). Central nervous system defects include hydrocephalus, and structural malformations of the cerebral cortex and cerebellum. Neurobehavioral deficits may also be expected (54,100,115). Limb reduction defects may occasionally occur (99,42).

The mechanism by which isotretinoin produces developmental toxicity remain unresolved (32,19).

Tretinoin is a topical retinoid that is related to isotretinoin . Topical application of a low dose preparation of tretinoin results in minimal systemic levels of the agent. There have been few reports of malformations after topical use of tretinoin, and pregnant women should be counseled to avoid use of the agent (30).

In summary, isotretinoin has proven to be one of the most potent human teratogens and a high percentage of the recipients of this drug are women in their child-bearing years. Therefore, pregnancy must be excluded and prevented in these patients before isotretinoin use, and therapy should be stopped at least one month prior to conception(19).

6.10 - Vitamin A:

Class: A/X

Vitamin A (retinol) is a fat soluble nutrient required for the maintenance of normal epithelial tissue and for growth and bone development, vision, and reproduction (19,42) Beta-carotene and other carotenoids are plant-synthesized precursors fo vitamin A that are partially converted to retinol during or after absorption. However, experiments in animals have shown that retinoids, but not carotenoids can be teratogenic (101).

The Recommended Dietary Allowance (RDA) for normal pregnant women is 5000IU/day. Chronic intake of vitamin A that greatly exceeds the recommended daily allowance leads to clinical manifestations of hypervitaminosis A with toxic effects to the central nervous system, liver, bone and skin (116).

It is estimated that 1 in every 57 infants is born with a birth defect attributable to the high vitamin A intake (10000IU/day) of the mother (101).

The spectrum of defects following maternal hypervitaminosis A was similar to that found among infants exposed to isotretinoin, consisting mainly of malformations of the central nervous system, spina bifida, ear ocular defects, cleft palate, cardio-vascular defects, intestinal atresia, urogenital and skeletal defects (100,51).

Mild to moderate vitamin A deficiency has been associated with increased incidence of prematurity and intrauterine growth retardation. Severe vitamin A deficiency has also been associated with increased rate of birth defects (19).

6.11 - Alcohol

Class D/X

Alcohol is a central nervous system depressant widely consumed in beverages. The chronic ingestion of excessive amounts is a major social and medical problem.

In 1973, Jones and Smith described a distinct pattern of congenital anomalies called the Fetal Alcohol Syndrome (FAS), in infants exposed to chronic alcohol ingestion during pregnancy (113). It is the third most common cause of birth defects (behind Down syndrome and spina bifida) but is the only one that is preventable (17,19,68).

The manifestations of FAS may vary depending on the amount of alcohol consumed. In mild cases, the term «fetal alcohol effects» or «alcohol related birth defects» is used to describe mild physiologic and neurologic findings. Signs include poor attention focusing, mild developmental delay, and sometimes hyperreactivity (17).

With greater intake of alcohol , progressive dysmorphogenesis is seen . Characteristic features include growth deficiencies, abnormal facial features and neurologic disorders (17,108,111).

Both prenatal and postnatal growth deficiencies have been reported with maternal alcohol use. Characteristic facial anomalies visible at birth include microcephaly, short palpebral fissures, short nose, maxillary hypoplasia, elongated midface, and thin upper lip (17,19,42,68,111).

Central nervous system manifestations consist mainly of developmental delays hyperreactivity , attention deficit-disorder, seizures and severe mental retardation.

Cardiac septal defects (particularly ventricular septal defect), limb abnormalities, and aberrant fingerprints can also occur.

Various ocular finding are associated with FAS, including microphthalmia, strabismus and visual impairment. Glaucoma, cataract, retinal and optic nerve anomalies may also be present. Maternal alcohol use during pregnancy has also been associated with increased risk of miscarriage and stillbirth (17,42,68,111).

Newborns who have been exposed to alcohol in utero just before birth may show signs of withdrawal after delivery, including tremors, seizures, irritability, low apgar scores, autonomic instability, increased respiratory rate, abnormal reflexes , increased muscle tone , hypotonia , less vigorous and increased activity decreased sucking, and disturbed sleep patterns (17,68).

Diagnosis of FAS and fetal alcohol effects is made clinically and based on maternal history of alcohol consumption during pregnancy . In the most severely affected children , FAS can be diagnosed at birth , but physical characteristics are most distinguishable between 8 months and 8 years . However , physical features become less pronounced with age , but unfortunately , developmental and cognitive delays persist throughout life (17,108).

6.12 - Tobacco

Tobacco smoking is a significant problem among human beings. It is associated with a wide variety of cancers and chronic diseases , most notably respiratory and cardiovascular disorders.

Maternal smoking is one of the few known preventable causes of perinatal morbidity and mortality. Carbon monoxide and nicotine are thought to be the main ingredients in cigarette smoke responsible for adverse fetal effects . Carbon monoxide has 200 times greater affinity for adult hemoglobin than does oxygen and an even higher affinity for fetal hemoglobin resulting in a decrease in oxygen-carrying capacity.

Relative hypoxia is induced by increased carboxyhemoglobin levels in the fetus. Nicotine's action on the adrenal glands results in increased levels of circulatory norepinephrine, epinephrine and acetylcholine, which leads to a decrease in uteroplacental perfusion. Nicotine crosses the placenta and increases the blood pressure in the fetus , either directly or indirectly through the adrenal gland , and also decreases fetal breathing .

It may also affect the gastrointestinal, genital, urinary and central nervous system . Fetal, neonatal and infant mortality is increased, birth weight and length decreased, gestation shortened and frequency of fetal breathing is reduced.

Complications of pregnancy also may occur such as abruptio placenta, premature rupture of membranes, amnionitis and placenta previa . Changes in the uterine and placental oxygenation or blood flow may be the cause of infant death, prematurity or spontaneous abortions.

Complications in infancy and childhood may present as deficits in long term physical growth or intellectual and behavioral performance.

The effect on the placenta, uterus , fetus and infant are dose related . Smokers have a 3.5 - 4 fold increase in small -for-gestational-age infants compared with nonsmokers. But women who stop smoking before 16 weeks of gestation have infants with birth weights similar to those babies of women who never smoked.

All women should be encouraged to stop smoking while pregnant , and smoking cessation programs designed for pregnant women may be beneficial (53,98).

Warfarin embryopathy or fetal warfarin syndrome; nasal hypoplasia and depressed nasal bridge.

Fetal hydantoin syndrome. (*Upper*) Facial features including upturned nose, mild midfacial hypoplasia, and long upper lip with thin vermilion border. (*Lower*) Distal digital hypoplasia.

Isotretinoin embryopathy:
Bilateral microtia or anotia with stenosis
of external ear canal (*left*). Flat depressed
nasal bridge, ocular hypertelorism (*right*).

A

B

C

Fetal alcohol syndrome. Male child. A. At 2 years 6 months. B, C. At 12 years.

Chapter 7

Routine Drug Use In Pregnancy

7.1 - Vitamin and Mineral supplementation:

A carefully chosen diet can provide adequate nutrition during pregnancy without supplementation. However, women who are unlikely to consume an adequate diet and women who are in high - risk categories should take a daily multivitamin-mineral supplementation (31). Most of the available multivitamin-mineral preparations contain sufficient amounts to meet the Required Dietary Allowances (RDA)

1 - Vitamins

a-Folic acid.

Folic acid is important for growth of maternal, fetal and placental tissues because of its role in DNA synthesis. Fetal demands , impaired maternal absorption, and defective use are related to the increased folate requirements during pregnancy (62).

Since folate deficiency has been associated with megaloblastic anemia, administration of folic acid is necessary for certain patients who are at special risk of developing folate deficiency.

The recommended daily intake for folate during pregnancy is 400 μ (31,62).

Folate supplementation before conception and during early pregnancy has been shown to reduce the risk of recurrent neural tube defects . Women who have had a previous baby with neural tube defects should be given a supplement of 4mg of folic acid daily for 1-3 months prior to conception and throughout the first trimester of gestation. This supplementation may be also beneficial for women treated with drugs such as diphenylhydantoin, valproic acid, methotrexate to decrease the risk of having a baby with neural tube defect (3,71).

b- Vitamin B-12:

Vitamin B-12 deficiency during pregnancy is rare. Since vitamin B-12 is present only in foods of animal origin, patients who are strict vegetarians may give birth to infants whose vitamin B-12 stores are low. Therefore, vitamin B-12 supplementation at 2µg/day is recommended for complete vegetarians (61,62,95).

c- Vitamin B-6 (Pyridoxine):

Vitamin B-6 concentrations decrease in blood during pregnancy. Because of its important role in the metabolism of proteins, the need for vitamin B-6 increases during pregnancy to accommodate the greater protein intake. Women considered at high-risk of vitamin B-6 deficiency include substance abusers, pregnant adolescents, and women bearing multiple fetuses. Their supplementation with 2mg/day vitamin B-6 is recommended (61, 62, 95).

d - Vitamin C:

Vitamin C is essential for normal cell integrity and growth. The recommended dietary allowance for vitamin C during pregnancy is 70 mg per day. However, a reasonable diet should provide this amount. The ingestion of large doses of vitamin C (>1g / day) may be harmful during pregnancy leading to neonatal scurvy apparently as a result of conditioning the fetus to an elevated level of vitamin C. In addition, large doses of vitamin C may interfere with vitamin B-12 absorption and metabolism, and this may not be overcome by vitamin B-12 supplementation (31, 95, 98).

e - Vitamin A

Vitamin A is necessary for normal cellular growth, especially for epithelial cells. To provide adequate vitamin A for fetal storage, the recommended daily requirements during pregnancy is 800 µg retinol equivalents (RE). Well-nourished adults maintain hepatic stores of vitamin A sufficient to meet requirements for several months.

However, excessive intake of vitamin A has been associated with increased intracranial pressure and congenital malformations in the offspring (3,62).

j- VitaminD:

Vitamin D is important in regulating the metabolism of calcium and phosphorus. As the need for these minerals rises throughout pregnancy, vitamin D requirements also rise. The recommended daily allowance during pregnancy is 10 µg daily. (61, 62) Excessive intake has been associated with adverse fetal effects including aortic stenosis, hyperparathyroidism and other congenital anomalies (62,98).

g- VitaminE:

Vitamin E is evidently found in most diets, and deficiency in humans is rare. Specific functions for vitamin E are unclear, but it is believed to have a significant role in fatty acid metabolism. Neonatal hemoglobinopathies have been reported with vitamin E deficiency in the newborn. The recommended dietary allowance is 10 mg tocopherol equivalents (62).

h- Vitamin K:

Supplementation of the pregnant women on anticonvulsants with 10 mg vitamin k1/day from the 36 th week of gestation, has been shown to protect the infant against vitamin k1 responsive bleeding. In addition prophylactic vitamin k1, 0,5 to 1mg, must be given to the newborn to prevent this condition (19,42,53,59)

2 - Minerals

a - Iron:

Iron is an essential nutrient for humans and a constituent of hemoglobin, myoglobin and several enzymes. The requirement of iron is greatest when there is rapid expansion of tissue and red cell mass such as during infancy, childhood and pregnancy (98,119)

Approximately half of all pregnant women experience anemia. One of the factors that lead to anemia in pregnancy is iron deficiency, the other important factor is a dilutional one with greater increase in serum volume than in red cell mass. Because of the difficulty of obtaining iron from the diet, it is the one nutrient supplement usually prescribed during pregnancy (98, 119).

Iron is transported actively across the placenta to the fetus. Two thirds of this transported iron is incorporated into hemoglobin and the remainder is stored as ferritin in the fetal liver for use in the first year of life. The majority of iron transferred to the fetus occurs in the last trimester, and it is during this time that fetal iron stores are developed. For this reason premature infants have diminished stores of iron. Iron stores in the offspring of iron deficient mothers are decreased, however, neonatal serum iron levels are not changed (62, 119).

* Iron requirement for pregnancy (42):

<i>Event</i>	<i>Elemental Iron</i>
Increased red blood cell mass	450 mg
Fetus and placenta	360 mg
Vaginal delivery	190 mg

The iron requirements of normal pregnancy total about 1g. About 360 mg are actively transferred to the fetus and placenta, and about 190 mg are lost during vaginal delivery. 450 mg of iron are required for the increase in the total volume of circulating erythrocytes during pregnancy. Practically all the iron for these purposes is used during the latter half of pregnancy. Therefore, the iron requirement becomes quite large during the second half of pregnancy, averaging 6 to 7 mg/day (95).

* Elemental iron content of supplements:

<i>Supplement</i>	<i>Content (%)</i>
Ferrous fumarate	33 %
Ferrous sulfate	20 %
Ferrous gluconate	11%

30 mg of iron supplied in the form of a simple iron salt such as ferrous gluconate sulfate or fumarate , taken regularly once each day throughout the later half of pregnancy, provide sufficient iron to meet the requirements of pregnancy and to protect any preexisting iron stores (95).

Therapeutic iron is doses of 60 to 120 mg per day is prescribed for women who have diagnosed iron deficiency anemia (31).

The patient may notice black stools during iron therapy, which should not be confused with darkened tarry stools or melena that occur with gastrointestinal bleeding (53)

b- Calcium:

Calcium is necessary for the development of bones and teeth , and is also important in the maintenance of cell membrane permeability , the coagulation process and neuromuscular excitability . During pregnancy , the maternal serum concentration of calcium declines slightly.

Calcium-deficient diets during gestation have been associated with decreased bone density in the newborn infant (98). The total fetal demand for calcium is estimated to be 30g, mostly required in the later stages of pregnancy . Because of the increase calcium need during pregnancy, it is recommended that the daily intake is 1200mg (62).

A possible mode of action for calcium supplementation is that it reduces parathyroid hormone release and intracellular calcium, and so reduces small muscle reactivity. In addition, it can also reduce uterine smooth muscle contractility (21).

c- Phosphorus:

Phosphorus is primarily combined with calcium in bone formation. The recommended dietary allowance for phosphorus is 1200mg daily during pregnancy. However, its widespread availability makes deficiency unlikely (62).

d- Zinc:

Zinc is essential for growth of all tissues, because it is involved in many major metabolic pathways congenital malformations, particularly of the central nervous system, and iron deficiency anemia have been reported with Zinc deficiency. The recommended dietary allowance for Zinc during pregnancy is 15mg/day (62).

7.2 - Antiemetics:

Nausea, with or without vomiting is common in early gestation. It has been reported in 70 % of pregnancies. Typically onset is between 4 and 8 weeks gestation continuing to about 14 to 16 weeks gestation (53, 62).

The cause of nausea and vomiting during pregnancy is unknown. Relaxation of the smooth muscle of the stomach is a probable factor, as well as elevated levels of sex steroids and human chorionic gonadotropin (53,62,95).

Symptoms may vary from slight nausea, to persistent vomiting throughout the day, in other women (62,95).

Mild symptoms are managed supportively with reassurance and avoidance of precipitating factors (7, 53).

If drug therapy is required, meclizine is a reasonable drug of choice because it is associated with low teratogenic risk. Daily doses of 25 to 50mg p.o are usually effective.

If symptoms are not controlled, Promethazine in low doses (50 mg/day in two to four divided doses) for a reasonable duration of time is generally considered safe. Adverse effects to the human fetus following use have not been reported; however neither is recommended for routine use during pregnancy . If nausea and vomiting persists, Metoclopramide 5 to 10 mg 3 times daily may be used. The drug appears to be safe in pregnancy. No congenital defects or other fetal or newborn complications following its use have been reported , although the drug crosses the placenta and produces substantial fetal blood levels . Phenothiazines such as chlorpromazine should be avoided because of the potential for embryotoxicity , jaundice , and prolonged extrapyramidal effects in neonates (7,31, 53).

Hyperemesis gravidarum is a pernicious form of nausea and vomiting of pregnancy and is associated with weight loss, electrolyte imbalance , dehydration and possible hepatic and renal damage . Hospitalization with parenteral replacement of fluids , electrolytes , and calories may be necessary (31, 62).

7.3 - Laxatives:

Pregnant women frequently complain of abdominal bloating and constipation. Constipation is a common problem because of the decreased motility of the colon, increased water absorption from the colon , and mechanical pressure from the gravid uterus (53, 62).

The use of laxatives during pregnancy may have serious side effects to both mother and fetus. The safest agents are bulk - forming preparations containing fibers because no systemic absorption occurs. Lactulose , sorbitol and glycerine are not teratogenic in animals and thus are safe in pregnancy . Castor oil can initiate premature uterine contractions . Saline laxatives such as milk of magnesia may produce sodium retention in the mother . Excessive use of mineral oil can decrease maternal absorption of fat soluble vitamins resulting in neonatal hypothermia and hemorrhage .

Stimulant laxatives such as phenolphthalein and bisacodyl appear safe during pregnancy. But excessive use , long term or overdosage can lead to electrolyte imbalance and dehydration (53). Therefore, increasing dietary fibers content or using bulk agents is the preferred treatment for constipation (7, 53).

7.4 - Antacids:

Heartburn is a painful, retrosternal burning sensation that is caused by regurgitation of acidic gastric content into the esophagus . It is estimated to occur in 30% to 50% of all pregnancies . This regurgitation results from the upward displacement of the stomach by the enlarging uterus , relaxation of the lower esophageal sphincter by progesterone and delayed gastric emptying (7,26,62).

Nonsystemic drug therapy with antacids is the first step in treating the pregnant patient who does not respond to lifestyle modifications . They are generally safe if not taken in excess. Adverse effects of antacids include interference with iron absorption and metabolic and electrolyte alterations such as hypercalcemia , hypermagnesemia, hypophosphatemia and others.

Sucralfate like antacids appears to be safe, since none of the drug is absorbed.

The mainstay of symptomatic management for severe cases of reflux is inhibition of acid secretion by using H₂-receptor antagonists . Their use in pregnancy appears to be safe despite transfer of the drug across the placenta . Information on omeprazole is limited to animal studies where it have shown an increased rate of congenital malformations. Therefore, it should not be used in pregnancy (7,24,62).

7.5 - Tocolytics

Preterm labor is one of the most common complication occurring during the third trimester of pregnancy . It is defined as the onset of labor in patients with intact membranes before 37 weeks

Tocolysis is both a prophylactic and a therapeutic mean of managing prematurity. Tocolytics are therapeutic agents used to decrease or inhibit uterine contractions. These agents include β - sympathomimetics , magnesium sulfate , prostaglandin synthetase inhibitors, calcium channel blockers and others

a- Beta - sympatbomimetic agents

β - sympathomimetic agents with β_2 selectivity appear to be the most widely used drugs for the management of preterm labor . These agents bind selectively to β_2 - receptors in uterine smooth muscles leading to their relaxation . Oral therapy is used for mild forms of preterm labor while intravenous therapy is used for the management of established preterm labor (5).

Terbutaline and Ritodrine are the most frequently used agents.

Intravenous therapy and high dosage may predispose the patient to several side effects including tachycardia, a rise in systolic blood pressure and a decrease in diastolic blood pressure. A rare more serious side effect is the development of pulmonary edema which is usually rare in young healthy women with single pregnancy but more common in pregnancies with multiple gestation. Metabolic complications , such as hypokalemia , hyperglycemia , and an increase in fatty acids due to lipolysis , are common (98).

Placental transfer of β -adrenergic agents does occur , however , the effects on uteroplacental perfusion are controversial : some studies show an increase , others a decrease. The common effects on the neonate have been limited primarily to hypoglycemia and fetal tachycardia. Long term follow-up have revealed no significant problems in child development (43, 98).

b- Magnesium sulfate:

Magnesium sulfate is an effective tocolytic agent and is the drug of choice for patients with diabetes mellitus or heart disease. It has been suggested that magnesium acts by competition with calcium either at the motor end plate , reducing excitation , or at the cell membrane, reducing calcium influx into the cell at depolarization (43).

Magnesium sulfate is administered intravenously to achieve therapeutic blood levels between 6 to 8 mEq/l . Common minor side effects include feeling of warmth and flushing. Other side effects such as pulmonary edema, hypothermia, and neuro-muscular toxicity are frequent with elevated blood levels (5,43, 98).

Magnesium concentration in the fetus and the neonate are similar to maternal levels. This may lead to decreased long - term fetal heart rate variability , central nervous system depression, and hypocalcemia in the neonate . Infants of mothers treated with intravenous magnesium sulfate shortly before delivery may be hypotonic at birth and require respiratory support until magnesium is eliminated (5)

c- Calcium channel blockers

The calcium channel blocker, Nifedipine has been used to inhibit preterm labor . Its tocolytic activity is due to a reduction of calcium influx into uterine smooth muscle.

Its most common side effects include hypotension and tachycardia secondary to vasodilation. It is, therefore, the drug of choice for patients with chronic hypertension and preterm contractions (5,43).

The effects of Nifedipine on the fetus are limited only to animal studies . No human studies have documented significant adverse effects on the fetus due to careful administration of Nifedipine. The drug is apparently safe in pregnancy (98).

RECOMMENDATIONS OF INTERVALS FOR ROUTINE AND
INDICATED TESTS AND PROCEDURES DURING PRENATAL CARE

Time (wk)	Assessment
Initial (as early as possible)	Hemoglobin or hematocrit Urinalysis, including microscopic examination and infection screen Blood group and D type Antibody screen Rubella antibody titer Syphilis screen Cervical cytology Hepatitis B virus screen
8-18	Ultrasound Amniocentesis Chorionic villus sampling
16-18	Maternal serum alfafetoprotein
26-28	Diabetes screening
28	Repeat hemoglobin or hematocrit Repeat antibody test for unsensitized D-negative patients Prophylactic administration of anti -D immune globulin
32-36	Ultrasound Testing for sexually transmitted disease Repeat hemoglobin or hematocrit

Chapter 8

Study details

1- Introduction:

Drugs taken during pregnancy are classified according to teratogenicity potential around the world; we thought of assessing the use of drugs during pregnancy, and evaluate the existing association between teratogenic drugs and malformations in Lebanon. This would be a first step towards a further full evaluation of this issue.

2- Material and methods:

21- Objective of the study:

This is a case-control study design; its objective is to evaluate the association between the use of drugs during pregnancy and child abnormalities, in a country like Lebanon, where no statistics exist to assess drug intake or congenital abnormalities.

22- Population of the study:

The source populations are women who delivered in two different hospitals in Beirut (Rizk and Makassed Hospitals), taken as to represent different socioeconomic status of the Lebanese population.

Cases were chosen from registered malformations in the obstetrics services, with the following exclusion criteria: gestation duration of less than 20 weeks, associated abortions, malformations of known origin (toxoplasmosis, rubella), premature rupture of membrane, intrauterine fetal distress, cerclage failure, and toxemia.

Controls were also taken from the same registers, taken by hazard from normal children deliveries.

$$N = \frac{2.487}{2[\text{Arc sin } P1 - \text{Arc sin } P0]}$$

N: Minimal number of patients in the study

P0: Percentage of the general population (0.03)

P1: Percentage in patients taking high risk drugs (0.06)

23- Data collection:

Women between 1996-1998 were taken, and retrospective information was retrieved from medical files. Standardized questionnaires were filled by the interviewer; missing information was then completed by telephone interviews for both cases and controls. Data were then computerized on Epi Aid CDC program (Atlanta).

Results were given by Epi Aid and Excel programs.

Problems during data collection.

We faced many problems during data collection some of which are the following:

Initially we started with n1=61 cases and n2=39 controls with a total of 100 patients. We ended up actually with n1=46 cases and n2=37 controls with a total of 83 patients.

Many reasons stand behind this difference in number. First of all at Makassed Hospital there was no filing system until 10/1997. The total number of birth from 10/1997 till 12/1998 includes 1125 birth. Whereas at Rizk Hospital the study was conducted for the last three years (1996 till 1998) with a total number of 1924 deliveries.

One more problem that we faced during data collection includes the non-compliance of some doctors! to look in their records and tell us the medications their patients were taking.

For this reason incomplete files were completed by telephone calls.

Some patients were non-compliant and for some others the telephone number was not available.

3-Descriptive results of the study:

The sample size for which correct information could be taken was $n = 83$; divided into $n_1=46$ case and $n_2=37$ controls.

31- Sociodemographic characteristics and past pregnancies:

Individual sociodemographic, lifestyle and past pregnancies features were taken for both cases and controls; results are presented in the following table:

Characteristic	Cases	Controls	P value
Age			
17-34 years	31 (69%)	27 (73%)	0.43
35-45 years	14 (31%)	10 (27%)	
Pregnancies			
1-2	28 (65%)	20 (54%)	0.5
3-4	8 (19%)	15 (41%)	
5-12	7 (16%)	2 (5%)	
Viable children			
0-2	36 (84%)	30 (81%)	0.67
3-4	4 (9%)	6 (16%)	
5-13	3 (7%)	1 (3%)	
Abortions			
0-2	40 (93%)	36 (97%)	0.77
3-4	2 (5%)	1 (3%)	
5-6	1 (2%)	0 (0%)	
Consanguinity	8 (18%)	1 (3%)	0.03
Blood type			
A+	14 (39%)	19 (56%)	0.26
A-	2 (6%)	0 (0%)	
AB+	3 (8%)	1 (3%)	
B+	3 (8%)	6 (17%)	
O+	13 (36%)	7 (21%)	
O-	1 (3%)	1 (3%)	
Coffee during pregnancy			
0-5 cups/d	14 (88%)	16 (94%)	0.48
> 5 cups/d	2 (12%)	1 (6%)	
Alcohol during pregnancy			
No or occasional intake			

Regular intake	32 (100%) 0 (%)	29 (100%) 0 (0%)	-----
Smoking during Pregnancy			
0-5 cigarettes/d	14 (78%)	8 (50%)	0.09
> 5 cigarettes/d	4 (22%)	8 (50%)	

We notice that all p values are non significant ($p < 0.05$), except for consanguinity; this assures us the comparability of the cases and controls, and decreases confusion type biases due to these characteristics, except consanguinity that needs to be taken into consideration in Mantel-Haenzel adjustment analysis, in order to decrease its confusion effect.

32- Past medical history and problems during pregnancy:

In addition to sociodemographic characteristics, past medical history and problems during pregnancy were also assessed:

Characteristic	Cases	Controls	P value
Gestation			
20-35 weeks	8 (19%)	2 (6%)	0.09
35-41 weeks	35 (81%)	32 (94%)	
Past Medical history			
Infertility history	1(4%)	3 (10%)	0.25
Surgical operation	10 (38%)	16 (55%)	
Chronic diseases	10 (38%)	7 (24%)	
Others	13 (50%)	8 (28%)	
Drug allergy	5 (11%)	6 (16%)	0.36
Problems during pregnancy			
Bleeding or spotting	6 (20%)	1 (4%)	0.16
Nausea and vomiting	8 (27%)	10 (42%)	
Infection	12 (40%)	4 (17%)	
Others	14 (47%)	13 (54%)	

We notice here also the non significance of the p value for the features characterized above, confirming the comparability of cases and controls and decreasing the likelihood of confusion effect.

33- Child abnormalities:

Child abnormalities in the cases group are summarized in the table below; we notice that a child could have more than one abnormality.

Abnormality	Number	Percentage
Skin	1	2%
Central nervous system (CNS)	2	3%
Down syndrome	2	3%
Metabolism	2	3%
Genital	3	5%
Thorax and lungs	4	6%
Multiple anomalies	4	6%
Gastrointestinal	5	8%
Hydroencephalic- Myelomeningocele	6	9%
Limb malformation	6	9%
Others	7	11%
Cardiovascular	9	14%
Stillbirth due to multiple anomalies	14	22%
Total	65	100%

These malformations were found in 45 cases, compared to 37 controls.

34- Drugs taken during pregnancy:

Drugs taken during pregnancy were all evaluated in terms of name of the drug, its dosage and duration of intake. However, available information was only for type of drug, dosage and duration of intake being rarely specified. The results are presented in the table below:

Drug	Cases	Controls	P value
Abortifive agents	1 (2%)	0 (0%)	0.60
Acyclovir	1 (2%)	0 (0%)	0.62
Analgesics	25 (60%)	22 (67%)	0.29
Antacids	1 (2%)	2 (6%)	0.80
Antiepileptics	1 (2%)	1 (3%)	0.80
Antifungal	1 (2%)	1 (3%)	0.80
Antipyretics	5 (12%)	6 (18%)	0.50
Antispasmodics	3 (7%)	2 (6%)	0.36
Antivomitives	10 (24%)	8 (24%)	0.61

Benzodiazepines	3 (7%)	2 (6%)	0.64
Beta lactams	4 (10%)	2 (6%)	0.16
Calcium	24 (57%)	23 (70%)	0.48
Corticosteroids	4 (10%)	3 (9%)	0.35
Cough syrups	6 (14%)	7 (21%)	0.61
Estrogens	0 (0%)	0(0%)	-----
Fluor	1 (2%)	3 (9%)	0.50
Folic acid	0 (0%)	2 (6%)	0.33
Inhalers	3 (7%)	2 (6%)	0.69
Iron	42 (100%)	33 (100%)	-----
Laxatives	2 (5%)	0 (0%)	0.41
Magnesium	5 (12%)	2 (6%)	0.38
Neuroleptics	2 (5%)	1 (3%)	0.63
Non beta lactams	4 (10%)	3 (9%)	0.33
Plant derivatives	1 (2%)	2 (6%)	0.80
Progesterones	5 (12%)	1 (3%)	0.23
Tocolytics	2 (5%)	0 (%)	0.40
Vitamins	4 (10%)	5 (15%)	0.40
Others	6 (14%)	7 (21%)	0.60

All the p-values are expected to be non significant, since the study was not initially designed to be able to detect single drug abnormality. On the other hand, since the prevalence of abnormality is low in the general population, we can assume that the control group represent the general population; by this, we can put the table below:

Frequency	Drugs taken during pregnancy In the general population:
0-3%	Estrogens, progesterones, abortives, acyclovir, laxatives, antiepileptics, antifungals, tocolytics
4-10%	β-Lactam antibiotics, other antibiotics, folic acid, magnesium, plant derivatives, inhalers, benzodiazepines, fluorine, antispasmodics, corticosteroids, antacids
11-50%	Antipyretics, cough syrups, vitamins, antivomitives, others
51-75%	Calcium salts, analgesics
> 75%	Iron salts

35- Classification of drugs:

The drugs described above were taken by both groups; their classification into A, B, C, D, and X classes is described down here; we note that for pregnant women taking multiple drugs, the one with higher risk class was taken into consideration:

Drug class	Cases	Controls	Total
A	12	11	23
B	11	17	28
C	09	06	15
D	10	03	13
X	00	00	00
Total	42	37	79

4- Univariate analysis:

Classes of drugs were divided into 2 groups:

Group 1 containing classes C, D, and X drugs (**higher risk drugs HRD**)

Group 2 containing classes A and B drugs (**lower risk drugs LRD**)

Exposure to those drugs was calculated for cases and controls, and the following association was found:

Drugs	HRD	LRD	Total
Cases	19	23	42
Controls	9	28	28
Total	28	51	79

The odds ratio OR is equal to 2.57, with a confidence interval of $0.97 < OR < 6.95$ at 95%, and a p-value of **0.043**.

5- Mantel-Haenzel adjustment (stratified) analysis:

Since the only significant statistical difference found between cases and controls was consanguinity, adjustment by Mantel-Haenzel method is necessary to rule out the confusion effect of this factor.

The following results were obtained:

No consanguinity	HRD	LRD	Total	Analysis
Cases	18	16	34	OR = 3.94 1.38<OR<11.4 p = 0.0076
Controls	8	28	36	
Total	26	44	70	

Consanguinity	HRD	LRD	Total	Analysis
Cases	1	7	8	OR = 0 0 <OR < 11.14 p = 0.22
Controls	1	0	1	
Total	2	7	9	

Interaction test is impossible to apply, due to a null value in the second table; however, we can clearly see that we have non significant results in the second

table due to insufficient effectiveness; by this, we assume that the interaction between consanguinity and high risk drugs is quantitative, and we can calculate the adjusted ORa:

ORa = 2.76 ; $1.12 < \text{ORa} < 8.57$ is the confidence interval at 95%, and the p value is:

p = 0.023.

Adjustment on other risk factors (age, duration of gestation, problems during pregnancy, smoking and alcohol intake during pregnancy) all gave similar results for crude and weighted odds ratios.

6- Discussion:

This case-control study clearly confirms the effects of drugs on teratogenicity, based on a Lebanese population. Drug intake during pregnancy, as in other countries, is associated with higher incidence of congenital abnormalities. In fact, pregnant women of this study have approximately 3 times more risk of having abnormal children than those taking low risk drugs (p = 0.023). The significant results obtained with a low sample size demonstrates high level of drug intake by Lebanese pregnant women.

However, several limitations and validity questions can come up to mind upon evaluating internal and external validity of this study:

61- Selection bias:

This bias is possible since we have only evaluated hospitalized women, and it is possible that other deliveries may have happened without hospitalization, especially for low socioeconomic status women. In fact, these may be more or less prone to take over the counter drugs, or also non controlled prescription

drugs, and may have different childhood abnormality prevalence than closely followed women who deliver in a hospital.

In addition, missing or incorrect data from different registers or files, and from non compliant phoned women may have led us to disregard several files. Characteristics of this missing information is unfortunately impossible to evaluate, and the direction of this selection bias is impossible to predict. However, since cases and controls were comparable in all means, we can assume that this bias has a slight effect, if any, on the association we found.

62- Classification bias: This bias is likely to exist in our study, but it is not probably a non differential one. Imperfect filing and registering could lead to a classification bias, where minor abnormalities could not be reported, or drug intake was not registered for unknown reasons: imperfect file filling, inability of women to remember drug intake as such, or the names of drugs taken (low education level...). We note that this could happen for both cases and controls, leading to a non differential classification bias.

However, memory and subjectivity biases can not be out of sight: The study was not blind, and knowing the disease state of the child could lead the woman or the interviewer to unconsciously “force” the answers.

In addition, there is ample evidence of partial memory bias in the way women recall the drugs they took during pregnancy. For example, women treated with a prescribed drug for a chronic illness tends to recall their treatment better than women who took an over the counter drug.

For information concerning neuroleptic or anxiolytic drugs, alcohol intake and smoking, several social and / or religious reasons can lead some women to hide true information, while some others may become non compliant upon asking this kind of questions by the interviewer.

These none differential information biases can lead to misclassification of malformations on a hand, and of drug and other factors exposure on the other

hand. This can dilute the association between drug exposure and congenital abnormalities, reducing it toward the null.

Another possibility of classification bias may be due to the type of congenital anomalies chosen to be classified as cases: only immediately visible abnormalities were taken, and late appearance ones were considered to be in the control group, because there was no follow up of delivering women and children (data was retrieved from obstetrical registers and files, without long term observation of physiological functions of children). This non differential classification bias can further dilute the association toward the null, confirming more efficiently the strength of the association between exposure to high risk drugs and abnormalities.

63- Confusion biases: Adjustment on consanguinity was necessary to rule out confusion effect on the results obtained, and the weighted odds ratio obtained after Mantel-Haenzel analysis confirms that high risk drug intake had its own effect on the congenital abnormalities of the study population.

Other risk factors being comparable between cases and controls, and giving non significant results upon Mantel-Haenzel adjustment ($p > 0.05$), we can assume that their residual confusion effect is very weak, if any.

64- Internal causality criteria:

641 – Time sequence: this criteria was respected, since drug intake happened during pregnancy, and the abnormality detected was after delivery of the child.

642- Association strength: the OR being greater than 2, we assume that is not likely to explained by confusion biases.

643- Cause and effect specificity: This was impossible to evaluate, since drugs and abnormalities were not taken one by one and evaluated. Any way, this was not the objective of the study, which has a more descriptive orientation for general drug intake in pregnant women of Lebanon.

644- Dose-effect relationship: this was unfortunately impossible to assess, since women hardly recall dosages of drugs they were taking, and files rarely mentioned this information.

645- Internal coherence of the study: selection and classification biases were minimized as much as possible, by the greater comparability of cases and controls; residual biases due to practical feasibility could not be overwhelmed. Confusion biases were unlikely, after adjustment on several risk factors and obtaining of minimal confusion effects.

65- External causality criteria:

651- Reproducibility of the results: The results obtained were constantly found in several studies conducted on other populations all over the world, during previous periods of time, and with other study designs. This is in favor of a positive reproducibility of our results.

652- Biological plausibility: Exposure to xenobiotics in general, and drugs in particular, has long been studied in developmental toxicology, and mechanisms of actions of several drugs toxicity are already known, independently of our results. This increases the likelihood of our results.

In conclusion, high risk drugs intake is a risk factor with high causality likelihood of congenital abnormalities, in the population of our study, and most likely in the Lebanese population. This leads us to the adoption of several internationally taken measures, in order to minimize the effects of drugs, control pregnancy in all women, and decrease by this the incidence of congenital abnormalities in Lebanon.

STANDARDIZED QUESTIONNAIRE

Name of patient:

Name of attending:

Phone number:

Age:

Parity:

Duration of gestation:

Weight:

Height:

Blood type:

Family history:

Past medical history:

Present problem:

Medications (in details):

Smoking (specify):

Alcohol:

Allergies:

Consanguinity:

Drug abuse, Acute intoxication, ... :

Others:

Chapter 9

Conclusion

Physicians counseling women who are pregnant or are planning a pregnancy should make sure that they understand clearly the nature and magnitude of a risk associated with a drug. Women's attitudes toward voluntary abortion differ. The same information about the nature and magnitude of a teratogenic risk may prompt different decisions by different women, according to the clinical situation and specific circumstances. For example, women with epilepsy that have been treated effectively with phenytoin since their childhood may be glad to hear that although the drug is teratogenic, the overall risk of malformations is not high. In contrast, women who have been treated with phenytoin for a single grand mal seizure and who have normal children born before phenytoin was prescribed may find it unacceptable to continue an unplanned pregnancy after learning about the higher-than-normal risk of adverse effects.

Decisions on pregnancy testing and termination must be the couple's own; it is the duty of the counselor to support and to inform but not to persuade. Some couples refuse the option of interrupting pregnancy e.g. for religious reasons.(55)

Strategies to reduce risk: One of the most effective strategies in reducing teratogenic exposures is to have patients receive:

- 1 - Classical genetic counseling that aim to help families by giving emotional support and by disclosing and discussing the causes of certain « genetic » problems, the risks of recurrence, and the possibilities for prevention or other options.

The process of genetic counseling involves a team approach to assist families or individuals in dealing with genetic disorders and their implications for the family.(66)

It is now standard medical practice in the United States to offer prenatal chromosomal diagnosis to all women who at their expected delivery date will be 35 years or older. The most common indication for antenatal cytogenetic studies is advanced maternal age.

All chromosomal disorders are detectable in utero.(29)

2 - The other strategy includes counseling and information before conception.

It has been estimated that more than 50% of all conceptions are unplanned.

Strategies that may help reduce risk include minimizing 1st trimester exposures, avoiding polydrug regimens that may result in potentiation of teratogenesis, and using the lowest possible dose for the shortest duration of treatment.

A statement such as the following puts the exposure in perspective and often is reassuring: « if you had a baby with a birth defect, it would be much more likely to be due to the background risk than to this drug exposure ».

Many teratogens cause defects before a woman recognizes that she is pregnant, so educational efforts must begin long before pregnancy.(28)

In addition to the risk associated with fetal exposure to teratogenic drugs, there is a risk associated with misinformation about the teratogenicity of drugs, which can lead to unnecessary abortions or the avoidance of needed therapy. The medical community and drug manufacturers should make a concerted effort to protect women and their unborn babies from both risks.(68)

Chapter 10

Appendix 1: Definitions

Zygote: This cell, formed by the union of an ovum and a sperm, represents the beginning of a human being. The common expression « fertilized ovum » refers to the zygote.

Morula: When 12 or more blastomeres have formed, the ball of cells resulting from cleavage of the zygote is called a morula and resembles the berrylike fruit. The morula stage is reached about three days after fertilization, just as the developing human is about to enter the uterus from the uterine tube.

Blastocyst: After the morula passes from the uterine tube into the uterus, a cavity forms in it known as the blastocyst cavity. This converts the morula into a blastocyst.

Abortion: the term abortion is applied to all pregnancies that terminate before the period of viability, i.e., before 22 weeks.(85)

Omphalocele is persistence of gut herniation into the base of the umbilical cord.
(86)

Amniocentesis: Amniotic fluid can be sampled as early as the fourth month by inserting a needle into the amniotic cavity. A large number of genetic diseases can be diagnosed by the finding of certain chemicals either in the fluid or in cells suspended in the fluid.(118)

Hydramnios or *Polyhydramnios* is the term used to describe an excess of amniotic fluid (1500-2000 mL), whereas *oligohydramnios* refers to a decreased amount (less than 400 mL).(102)

Critical period: Period of time during development when the organism is especially responsive to and learns from a specific type of stimulant. The same stimulant at other point of development has little or no effect.

Teratogen: Any outside effect, such as a disease or a chemical whose presence significantly increases the risk of deviations or abnormalities in prenatal development.

Primipara: a primipara is a woman who has been delivered only once of a fetus or fetuses who reached viability.

Multipara: a multipara is a woman who has completed two or more pregnancies to viability, and not the number of fetuses delivered, that determines parity.

Nullagravida: a nullagravida is a woman who is not now, and never has been pregnant.

Gravida: a gravida is a woman who is or has been pregnant, irrespective of the pregnancy outcome. (102)

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