PLACENTAL TRANSFER OF DRUGS

An Essay

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By

Amal Maher Ibrahim
(M.B, B. CH)

Under Supervision of

Prof. Dr. Nermin Sadek Nasr
Professor of Anesthesia and Intensive Care
Faculty of Medicine - Ain Shams University

Dr. Fady Adib Abd El Malek
Lecturer of Anesthesia and Intensive care
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
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إنتقال الأدويه خلال المشيمه

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توطئة للحصول على درجة الماجستير في التخدير

مقدمة من

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الأستاذة الدكتورة / نرمين صادق نصر

أستاذ التخدير والرعاية والمركزة

كلية الطب - جامعة عين شمس

دكتور/ فادي أديب عبد الملك

مدرس التخدير والرعاية والمركزة

كلية الطب - جامعة عين شمس

كليـــــــــة الطب

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First thanks to **GOD** *to whom I relate any success in achieving any work in my life.*

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Amal Maher Ibrahim

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List of Abbrevation

CABA : Chloroaminobenzoic acid

CS : Cearean section

CTG : Cardiography tocography

FSH : Follicular stimulating hormone

hcc : human chorionic corticotropine

hcFSH : human chorionic follicular stimulating

hCG : Human chroinic gonadotrophin

hCT : human chorionic thyrotropine hormone

hPL : Human placental lactogen

LH : Utilizing hormone

MA : Maternal artery

MRI : Magnetic resonance image

MV : Maternal venous

OECD : Test guidelines for reproductive toxicity testing include prenatal developmental studies

PCA : Patient controlled analgesia

PLGF : placental growth factor

TSH : Thyroid stimulating hormone

UV : Umblical venous

VEGF : vascular endothelial growth factor

INTRODUCTION

Mammalians have barriers that regulate and limit the distribution of a broad variety of compounds and xenobiotics. Among these, the placental barrier, which forms during embryogenesis. To protect the developing fetus, the placenta is composed of several layers of cells acting as a barrier for the diffusion of substances between the maternal and fetal circulatory systems. Lipid soluble molecules can readily cross while the transfer of large molecular-weight molecules is limited *(Ghoshoa and Marchi ٢٠٠٩).*

The question that really matters is: what effect does a certain drug have on the baby whether fetus or new born? Such a question may in certain respects be more important than how much drug has passed to the fetus, because drugs affect the baby not only because they cross the placenta but also indirectly by affecting the mother's physiology and biochemistry in many ways. Because direct drug effects are not always easily quantifiable, and because they are assumed to be related to bodily concentrations, it seemed that drug essay is an essential starting point for elucidating the likelihood of measurable effects occurring in different clinical situation *(Rynolds, ١٩٩٨).*

Functionally, the placenta constitutes the region through which exchanges take place between maternal and fetal organisms.

Oxygen, nutrients, water, electrolytes, vitamins and antibodies are transported to the fetus. Carbon dioxide and excretory substances are transferred to the mother. In addition to this role as an essential link between mother

and fetus, the placenta has a wide range of enzymatic activities, and also serves to produce certain hormones and to inactivate and degrade others. With respect to the of actions it performs, the placenta is unique, being at once lung, intestine, liver, kidney and endocrine gland *(Marx, ١٩٩١).*

Several factors influence the placental transfer of drugs, including the physiochemical structure of the drugs themselves, maternal drug concentrations in the plasma, properties of the placenta, and hemodynamic events within the feto-maternal unit *(Santos et al., ١٩٩٦).*

Drug transmission depends on molecular weight (less than ٥٠٠ daltons are unimpeded in crossing the placenta), lipid solubility, degree of ionization, ph of mother and fetus and concentration gradient of drug between mother and fetus *(Duvaldestin et al., ١٩٧٨).*

Chapter ١

ANATOMY AND HISTOLOGY OF PLACENTA AND UTERUS

Anatomy of the uterus

The uterus is a thick-walled, muscular organ situated in the pelvis between the urinary bladder and the rectum. It lies posterior to the bladder and uterovesical space and anterior to the rectum and recto-uterine pouch. It is mobile, which means that its position varies with distension of the bladder and rectum *(Standring et al., ٢٠٠٨).*

The uterus is divided into two main regions: the body of the uterus (corpus uteri) which forms the upper two-thirds, and the cervix (cervix uteri) which forms the lower third. In the adult nulliparous state the cervix tilts forwards relative to the axis of the vagina (anteversion), and the body of the uterus tilts forward relative to the cervix (anteflexion). In ١٠ to ١٥٪ of women the whole uterus leans backwards at an angle to the vagina and is said to be retroverted. A uterus that angles backwards on the cervix is described as retroflexed *(Standring et al., ٢٠٠٨).*

Body:

The body of the uterus is pear shaped and extends from the fundus superiorly to the cervix inferiorly. Near its upper end, the uterine tubes enter the uterus on both sides at the uterine cornua. Inferoanterior to each cornu is the round ligament and inferoposterior is the ovarian

ligament. The dome-like fundus is superior to the entry points of the uterine tubes and covered by peritoneum which is continuous with that of neighbouring surfaces *(Delancey, ٢٠٠٠)*.

The fundus is in contact with coils of small intestine and occasionally by distended sigmoid colon. The lateral margins of the body are convex, and on each side their peritoneum is reflected laterally to form the broad ligament, which extends as a flat sheet to the pelvic wall. The anterior surface of the uterine body is covered by peritoneum which is reflected onto the bladder at the uterovesical fold. This normally occurs at the level of the internal os, the most inferior margin of the body of the uterus *(Balen et al., ٢٠٠٤)*.

The vesico-uterine pouch between the bladder and uterus is obliterated when the bladder is distended, but may be occupied by small intestine when the bladder is empty *(Burton et al., ١٩٩٩)*.

The posterior surface of the uterus is convex transversely. Its peritoneal covering continues down to the cervix and upper vagina and is then reflected back to the rectum along the surface of the recto-uterine pouch (of Douglas), which lies posterior to the uterus. The sigmoid colon and occasionally the terminal ileum lie posterior to the uterus. The cavity of the uterine body usually measures ٦ cm from the external os of the cervix to the wall of the fundus and is flat in its anteroposterior plane. In coronal section, it is triangular, broad above where the two uterine tubes join the uterus, and narrow below at the internal os of the cervix *(Balen et al., ٢٠٠٤)*.

There may be failure in fusion of the paramesonephric (Müllerian) ducts, which results in a uterus that is not pear shaped. There may just be a

septum (septate uterus) or partial clefting of the uterus (bicornuate uterus); the most extreme example is a septate vagina, two cervices, and two discrete uteri, each with one uterine tube (uterus didelphys) *(Standring et al., ٢٠٠٨)*.

Cervix:

The adult, non-pregnant cervix is narrower and more cylindrical than the body of the uterus and is typically ٢,٥ cm long. The upper end communicates with the uterine body via the internal os and the lower end opens into the vagina at the external os *(Jones and Jauniaux, ١٩٩٥)*.

In nulliparous women, the external os is usually a circular aperture, whereas after childbirth it is a transverse slit. Two longitudinal ridges, one each on its anterior and posterior walls, give off small oblique palmate folds that ascend laterally like the branches of a tree (arbor vitae uteri): the folds on opposing walls interdigitate to close the canal *(Balen et al., ٢٠٠٤)*.

The narrower isthmus forms the upper third of the cervix. Although unaffected in the first month of pregnancy, it is gradually taken up into the uterine body during the second month to form the 'lower uterine segment'. In non-pregnant women the isthmus undergoes menstrual changes, although these are less pronounced than those occurring in the uterine body *(Balen et al., ٢٠٠٤)*.

The external end of the cervix enters the upper end of the vagina, thereby dividing the cervix into supravaginal and vaginal parts. The supravaginal part is separated anteriorly from the bladder by cellular connective tissue, the parametrium, which also passes to

the sides of the cervix and laterally between the two layers of the broad ligaments *(Dalencey, ٢٠٠٠)*.

Pelvic ligaments and peritoneal folds:

The uterus is connected to a number of 'ligaments'. Some are true ligaments in that they have a fibrous composition and provide support to the uterus, some provide no support to the uterus, and others are simply folds of peritoneum *(Burton et al., ١٩٩٩)*.

Peritoneal folds:

The parietal peritoneum is reflected over the upper genital tract to produce anterior (uterovesical), posterior (rectovaginal) and lateral peritoneal folds. The lateral folds are commonly called the broad ligaments *(Delancey, ٢٠٠٠)*.

Uterovesical and rectovaginal folds:

The anterior or uterovesical fold consists of peritoneum reflected onto the bladder from the uterus at the junction of its cervix and body. The posterior or rectovaginal fold consists of peritoneum reflected from the posterior vaginal fornix on to the front of the rectum, thereby create the deep recto-uterine pouch of Douglas. The pouch of Douglas is bounded anteriorly by the uterus, supravaginal cervix and posterior vaginal fornix, posteriorly by the rectum and laterally by the uterosacral ligaments *(Delancey, ٢٠٠٠)*.

Broad ligaments:

The lateral folds or broad ligaments extend on each side from the uterus to the lateral pelvic walls, where they become continuous with the peritoneum covering those walls. The upper border is free and the lower border is

continuous with the peritoneum over the bladder, rectum and pelvic side-wall. The borders are continuous with each other at the free edge via the uterine fundus and diverge below near the superior surfaces of levatores ani. A uterine tube lies in the upper free border on either side *(Balen et al., ٢٠٠٤)*.

The broad ligament is divided into an upper mesosalpinx, a posterior mesovarium and an inferior mesometrium *(Delancey, ٢٠٠٠)*.

The mesosalpinx is attached above to the uterine tube and posteroinferiorly to the mesovarium. Superior and laterally it is attached to the suspensory ligament of the ovary and medially it is attached to the ovarian ligament. The fimbria of the tubal infundibulum projects from its free lateral end. Between the ovary and uterine tube the mesosalpinx contains vascular anastomoses between the uterine and ovarian vessels, the epoophoron, and the paroophoron *(Jones and Jauniaux, ١٩٩٥)*.

The mesovarium projects from the posterior aspect of the broad ligament, of which it is the smaller part. It is attached to the hilum of the ovary and carries vessels and nerves to the ovary *(Burton et al., ١٩٩٩)*.

The mesometrium is the largest part of the broad ligament, and extends from the pelvic floor to the ovarian ligament and uterine body. The uterine artery passes between its two peritoneal layers typically ١,٥cm lateral to the cervix: it crosses the ureter shortly after its origin from the internal iliac artery and gives off a branch that passes superiorly to the uterine tube, where it anastomoses with the ovarian artery *(Jones and Jauniaux, ١٩٩٥)*.

Between the pyramid formed by the infundibulum of the tube, the upper pole of the ovary, and the lateral pelvic

wall, the mesometrium contains the ovarian vessels and nerves lying within the fibrous suspensory ligament of the ovary (infundibulopelvic ligament). This ligament continues laterally over the external iliac vessels as a distinct fold. The mesometrium also encloses the proximal part of the round ligament of the uterus, as well as smooth muscle and loose connective tissue *(Delancey, ٢٠٠٠)*.

Ligaments of the pelvis:

The ligaments of the pelvis consist of the round, uterosacral, transverse cervical and pubocervical ligaments.

Round ligament:

The round ligaments are narrow, somewhat flattened bands ١٠-١٢cm long. Each is attached medially to the upper part of the uterus just below and anterior to the lateral cornua. From here, each passes laterally within the upper part of the broad ligament to the pelvic side-wall. At the start of the inferior epigastric artery, the round ligament enters the deep inguinal ring. It traverses the inguinal canal and splits into strands that merge with the surrounding connective tissue before terminating in the mons pubis above the labium majus *(Burton et al., ١٩٩٩)*.

Near the uterus the round ligament contains a considerable amount of smooth muscles but this gradually diminishes and the terminal portion is purely fibrous. The round ligament contains blood vessels, nerves and lymphatics *(Jones and Jauniaux, ١٩٩٥)*.

These lymphatics drain the uterine region around the entry of the uterine tube to the superficial inguinal lymph nodes. In the fetus a projection of peritoneum (processus vaginalis) is carried with the round ligament for a short