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Placental control of drug delivery☆

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ABSTRACT

The placenta serves as the interface between the maternal and fetal circulations and regulates the transfer of oxygen, nutrients, and waste products. When exogenous substances are present in the maternal bloodstream—whether from environmental contact, occupational exposure, medication, or drug abuse—the extent to which this exposure affects the fetus is determined by transport and biotransformation processes in the placental barrier. Advances in drug delivery strategies are expected to improve the treatment of maternal and fetal diseases encountered during pregnancy.

Contents

1. Introduction

Although most pregnant women use medications during pregnancy, the majority of drug trials to date have excluded the enrollment of pregnant women [1]. It is imperative that more studies be carried out in order to fully assess the risks of fetal exposure to these medications. A better understanding of the function of the placenta in controlling the maternal-fetal transfer of drugs will help scientists and clinicians to make informed decisions to improve the health of new moms and newborns.

Given the risks of thalidomide and other teratogenic substances, some pregnant women may be reluctant to use any medications. However, for women with chronic conditions, or women who develop a temporary febrile illness, medications which maintain maternal health can improve neonatal outcomes [2,3]. In 2008, more than 93% of

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pregnant women took at least one over-the-counter or prescription medication at any time during pregnancy, and more than 50% took 4 or more medications [4]. Fig. 1 highlights some disorders that may require medication during pregnancy. Between 2004 and 2008, the most common drugs prescribed to pregnant women included antibiotics, albuterol, progesterone, levothyroxine, and ondansetron [4]. From data collected between 1997 and 2004, the most common over-the-counter medications used during pregnancy were acetaminophen, ibuprofen, and pseudoephedrine [5]. Drugs of abuse are also of special concern, as data from 2013 report that 15.4% of women smoked, 9.4% drank alcohol, and 5.4% used illicit drugs during pregnancy [6].

The potential effects of drugs on fetal development are dependent on various factors, including gestational age, dose, dosing frequency, route of administration, and drug clearance [7,8]. Therefore, it is important to consider those physiological changes associated with the progression of pregnancy which can alter the pharmacokinetics of various drugs. Together with an increase in maternal blood volume during pregnancy, maternal serum albumin concentrations decrease. For drugs with high protein binding, the decreased albumin concentrations may result in a higher proportion of free drug, and hence, greater bioactivity [9,10]. The pH of maternal arterial blood increases slightly during pregnancy. This results in a shift of the oxy-hemoglobin dissociation curve, promoting the dissociation of oxygen and its transplacental transfer. This change in pH could also affect drug-protein binding. Pregnancy-associated increases in glomerular filtration can accelerate the renal clearance of many medications. Drug absorption during pregnancy could be reduced by progesterone-induced delays in gastric emptying, nausea and vomiting, or an increase in gastric pH [9]. The expression and function of drug metabolizing enzymes can also change significantly during pregnancy, some as the result of increased estrogen levels [11]. It is important to consider whether dose adjustments would be necessary to account for the pregnancy-associated changes affecting the pharmacokinetics of certain medications [12].

This review focuses on drug transport processes within the placenta which determine maternal-to-fetal transfer rates. Although the placenta is unlikely to prevent completely the transfer of typical small molecule compounds, the placenta may reduce the transfer of certain drugs based on properties such as size, lipophilicity, and affinity for transporter proteins [13]. Following a summary of human placental structure and function, mechanisms of drug transport across the placenta and drug metabolizing enzymes within the placenta will be discussed. Continued research and advances in these areas will lead us to a greater understanding and ability to control drug delivery across the placenta in order to improve the treatment of maternal and fetal diseases encountered during pregnancy.

2. Placental structure and function

2.1. Development of the maternal-fetal interface

The placenta is a unique organ of fetal origin that provides nutrients and oxygen to the developing fetus and also serves as the avenue for carbon dioxide and other fetal waste products to be eliminated via the maternal circulation [14]. The placenta starts to develop soon after blastocyst implantation. The outer blastocyst trophoblast cells facing the uterine epithelium fuse to form multinucleated syncytiotrophoblast. Proliferation of the syncytiotrophoblast comes about by fusion of precursor cytotrophoblast cells. Lacunae emerge within the interior of the trophoblastic complex and trophoblast invasion leads to the remodeling of maternal spiral arteries within the uterine wall. As the maternal endometrial vessel walls are eroded, maternal blood cells reach the lacunae. Arterial inlets into the lacunar system and venous outlets from

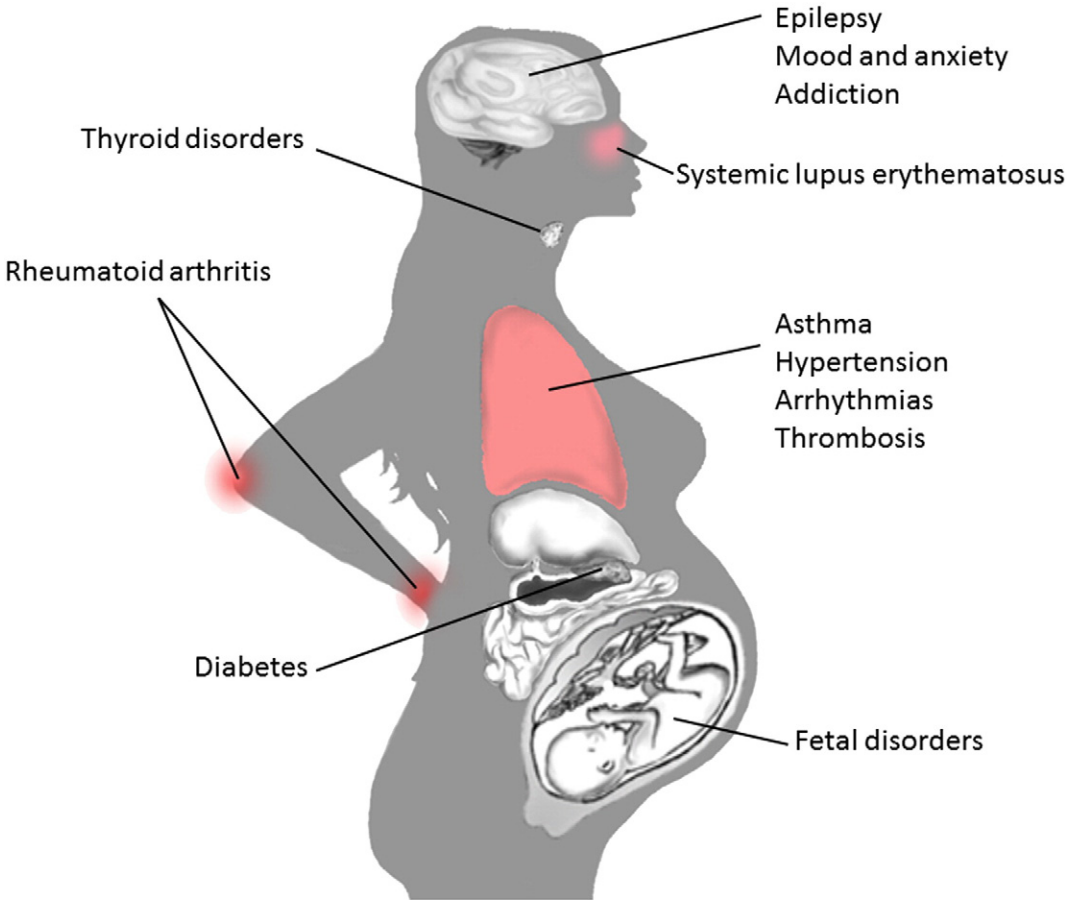

Fig. 1. Selected disorders that may require pharmacotherapy during pregnancy.