

# Effects of Prenatal Opiates Exposure on Human Pregnancy and Breastfeeding

Antoine Malek\*

University Hospital Zurich, Department of Obstetrics, Research Division, Frauenklinikstr 10, 8091 Zurich, Switzerland

## Abstract

Opiates like heroin, morphine and their semisynthetic and synthetic analogs act to relieve pain, as well as produce tolerance and physical dependence, by mimicking the various endogenous opioids and by binding to an opioid receptor. Substance use (alcohol, nicotine and illegal drugs including opiates/opioids) and substance use disorders are not uncommon amongst women of reproductive age and during pregnancy. Opioids include naturally occurring, semi-synthetic and synthetic drugs which are used as analgesics; and prescription use of this class of drugs increases during pregnancy over the past decade. Opiates like heroin and methadone are the most commonly used forms by pregnant women. The synthetic opiates such as methadone and buprenorphine are used as substitution therapy for the abused drug like heroin. This class of drugs is both transported to the fetus and alters the placental function. This review summarizes the impact of opiates on the human pregnancy and breastfeeding.

**Keywords:** Opiates; Maternal exposure; Prenatal exposure; Human placenta; *Ex vivo* perfusion; Breastfeeding

## Introduction

The effect of the endogenous opioid system as analgesics was not identified until the early 1970's [1]. Since the 3rd century BC, however, it has been known that opium as the main compound of opiates, harvested from the juice of the opium poppy was of use in managing pain, as well being addictive [1,2]. The introduction in 1680 of Sydenham's Laudanum, a mixture of opium with sherry wine and herbs, saw opium widely accepted in the UK as a medicinal compound and thus freely available [3]. Diacetylmorphine was first synthesized in 1874, but it would be almost 25 years before 'heroin' was first marketed by the Bayer Company in Germany. Initially used to treat the distressing cough associated with tuberculosis and as a cure for morphine addiction, heroin was quickly recognized to be itself highly addictive, and legislation to curtail its use ensued. Beginning in the 1970s, the endogenous opioid peptides and their various receptors were described and their functions characterized. The action of heroin, morphine and their semisynthetic and synthetic analogs act to relieve pain, as well as produce tolerance and physical dependence is produced by mimicking the various endogenous opioids and by binding to an opioid receptor (Table 1). The recent reviews provide more details on the appropriate use of opioids and opiates for pain management during pregnancy, parturition and post-partum [4,5].

Substance use (alcohol, nicotine and illegal drugs) and substance use disorders (which include, but are more complex than, physical dependence and tolerance [2]) are not uncommon amongst women of reproductive age and during pregnancy. A nationally representative survey conducted in the USA noted that ~74% of nonpregnant women of reproductive age reported substance use, and ~20% reported a substance use disorder. During pregnancy, the numbers decrease to ~63% reporting use and ~15% having a substance use disorder [6]. Illicit drug use disorder (predominantly opioids and analgesics) was observed amongst ~2% of women, whether pregnant or not (this is of interest because nicotine and alcohol substance use disorders typically decrease during pregnancy). In England approximately 46,500 female heroin addicts are receiving treatment, the vast majority are of childbearing age [7]. Illicit substance use continues to be a major public

health problem in the UK [8]. Around 10% of adults aged 16-59 years, 22% aged 16-24 years and 8% aged 24-29 years reported using any illicit drugs in 2008/2009 in England and Wales [9]. Substance-using women are mostly of childbearing age, and 18% of women between 16 and 24 years of age report drug use [9]. Quite apart from the erratic lifestyle of drug misusing women (of whom a significant proportion engage in prostitution to fund their drug dependence) opiate use is associated with menstrual irregularity, and so unplanned pregnancy is common. In Scotland, around 1% of births are recorded as having a problem drug-using mother, but this is almost certainly an underestimate [10]. Because women with substance use disorders frequently engage in a broad range of risky behaviors (multiple drug use, poor nutrition, risky sexual behavior, inadequate antepartum care, etc.) pregnancy outcomes are complicated [11-15]. Illicit substance use in pregnancy particularly those of opiates such as heroin and methadone continues to be associated with significant maternal and neonatal morbidity, and the socio-clinical profile in the last decade appears unchanged in the UK [16]. This review summarizes the experimental approaches for evaluating human placental disposition and the impact of opiates/opioids (Malek and Mattison 2010 [17] for more detailed information

Receptor	Response on activation
$\mu$	Analgesia, respiratory depression, miosis, euphoria, reduced gastrointestinal motility
$\kappa$	Analgesia, dysphoria, psychotomimetic effects, miosis, respiratory depression
$\delta$	Analgesia

Table 1: Putative effects mediated by activation of opioid receptors.

\*Corresponding author: Dr. Antoine Malek, University Hospital Zurich, Department of Obstetrics, Research Division, Frauenklinikstr 10, 8091 Zurich, Switzerland, Tel: +41-044-255 51 48; Fax: +41-044-255 90 66; E-mail: [antoine.malek1@gmail.com](mailto:antoine.malek1@gmail.com)

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on maternal physiological changes, placental function and drug disposition during pregnancy).

## Definition and Action of Opiate and Opioid

The described definition of an opiate or an opioid is derived from Wikipedia (the free encyclopedia). An opioid is a chemical that works by binding to opioid receptors, which are found principally in the central and peripheral nervous system and the gastrointestinal tract. The receptors in these organ systems mediate both the beneficial effects and the side effects of opioids. Opioids are among the world's oldest known drugs; the use of the opium poppy for its therapeutic benefits predates recorded history. The analgesic (painkiller) effects of opioids are due to decreased perception of pain, decreased reaction to pain as well as increased pain tolerance. The side effects of opioids include sedation, respiratory depression, constipation, and a strong sense of euphoria. Opioids can cause cough suppression, which can be both an indication for opioid administration and an unintended side effect. Opioid dependence can develop with ongoing administration, leading to a withdrawal syndrome with abrupt discontinuation. Opioids are well known for their ability to produce a feeling of euphoria, motivating some to recreationally use opioids. Although the term opiate is often used as a synonym for opioid, the term opiate is properly limited to the natural alkaloids found in the resin of the opium poppy (*Papaver somniferum*). In some definitions, the semi-synthetic substances that are directly derived from the opium poppy are considered to be opiates as well, while in other classification systems these substances are simply referred to as semi-synthetic opioids. Based on these definitions, opiate is a specific term that is used to describe drugs derived from the juice of the opium poppy such as morphine, methadone (a synthetic analgesic drug) is, strictly speaking, not an opiate [18], however based on the ATC classification methodology they belong to the same class of drugs (anatomic, therapeutic and chemical class, see <http://www.fmrc.org.au/atc/> for more information on ATC classifications, accessed 26 September 2011). "Narcotic" is commonly used to describe morphine-like drugs and other drugs for which substance use disorders occurs [2,12]. In this review, the opioids will be used in the generic sense according to in the ATC classification.

Endogenous and synthetic opioids produce their effects by combining with opioid receptors. There are four classes of opioid (or morphine) receptors;  $\mu$  (mu),  $\kappa$  (kappa),  $\delta$  (delta) and nociceptin/orphanin FQ receptors and the effects mediated by the three major class of receptors are summarized on Table 1 [1,2,19]. Table 2 lists some example opioids by action at the three primary receptors [19,20]. Opioids receptors are found in several area of the central nervous system, particularly in the periaqueductal grey matter, and throughout

	$\mu$ receptor	$\delta$ receptor	$\kappa$ receptor
Morphine	+		+
Levorphanol	+		
Methadone	+		
Fentanyl	+		
Buprenorphine	+		-
Pentazocine	+		+
Butorphanol	+		+
Nalbuphine	-		+
Naloxone	-	-	-
Naltrexone	-	-	-

+ binding as agonist, - binding as antagonist, Modified from [1]

**Table 2:** Classification of opioids as agonist, agonist-antagonist and antagonist with specific receptors.

the spinal cord [21]. Our understanding of opioid receptor function and the determination of the molecular pharmacology of opioids were mainly obtained from investigation with animal models. These function properties were provided by the cloned receptors in the "knockout" animals [19,20].

## Complications of Opioid use and Abuse in Human Pregnancy

Among substance use disorders in the US, opioid and analgesic abuse is second most common following marijuana and leading cocaine [2,14]. Similar observations were noted in European Union [9,10]. In contrast to European Union, much higher prevalence of illicit substance use in pregnant women has been reported from US and Australia [22,23]. Opioids include naturally occurring, semi-synthetic and synthetic drugs which are used as analgesics; and prescription use of this class of drugs increases during pregnancy [24]. Both historical and recent research suggests that this class of drugs is both transported to the fetus and alters placental function [25,26].

Use of opioids/narcotics during pregnancy is not rare; a significant fraction of pregnant women use opioids for pain relief [24], others are dependent upon opioids during pregnancy, and treatment of opioid substance use disorders involves use of synthetic opioids like methadone and buprenorphine which are used as substitution therapy for the abused drug [2,12,27-31].

The drug class of opioids, which contains opiates, are natural or semi-synthetic morphine-like substances, as well as the fully synthetic opioids. Morphine, codeine and heroine are opiates, while meperidine, fentanyl, propoxyphene, and methadone are synthetic opioids [32]. Most of the information available regarding the effects of opioids on pregnancy is derived from studies of patients who have used heroin or methadone. There has been a recent increase in the use of prescription opioid analgesics, such hydromorphone and oxycodone, during pregnancy. The prevalence of opiate use in pregnant women ranges from 1% to 21% [33]. The higher number reflects use in at-risk populations and does not represent overall use in a more standard obstetric population. Heroin is the most commonly abused illicit opiate and crosses the placenta readily. Heroin enters the fetal tissues within 1 hour of maternal use [34]. Women who use heroin are likely to use other harmful substances, such as tobacco, alcohol, and cocaine, all of which have their own potential adverse effects on pregnancy. Therefore, it is difficult to separate the effects of heroin from these other substances. Heroin can be mixed with other substances, including amphetamines, which can have independent detrimental effects on the pregnancy and fetus. In addition, intravenous drug use is a risk factor for many infectious diseases, including cellulitis, endocarditis, chorioamnionitis, and human immunodeficiency virus (HIV) infection, which can further complicate pregnancy.

Opioids like heroin and methadone are the most commonly used forms by pregnant women [35,36]. Over the past decade, heroin abuse has been on the increase. It is estimated that approximately 7000 opiate-exposed births, from women with substance use disorders, occur annually [37]. While obstetrical complications associated with opioid use in pregnancy vary greatly, there has been up to a 6-fold increase in obstetrical complications associated with this phenomenon [38].

The complications of heroin use include respiratory depression, which is dependent upon the dose of heroin and the user's degree of tolerance. Fatal respiratory depression is most common after intravenous injection, and lesser degrees of respiratory depression

coupled with cigarette smoking contribute to the high incidence of pneumonia, bronchospasm and pulmonary hypertension among regular users. The infective complications of intravenous drug use are well described and greatly increased by the use of shared needles. Infections include blood borne viruses, particularly HIV and hepatitis B and C, as well as a plethora of bacteria, fungi and parasites. Around 50% of drug misusing mothers are hepatitis C antibody positive, of whom two thirds have active infection [39,40]. Unprotected sexual contact is another source of infection. Heroin addiction is expensive, and frequently funded by criminality and prostitution, leading regular users to a life of poverty and social deprivation.

Heroin is not considered teratogenic, at least in terms of gross congenital abnormality. However it readily crosses the placenta and untreated heroin use during pregnancy is associated with spontaneous abortion, intrauterine growth restriction, and premature rupture of the membranes, antepartum haemorrhage, preterm delivery and stillbirth [41,42]. All of these complications are compounded by the effects of deprivation and poor antenatal care. Acute heroin withdrawal is generally not thought to carry a significant risk of death to the individual, but may increase perinatal mortality. Live born infants are likely to show early signs of narcotic withdrawal [42] and have increased neonatal morbidity and mortality. The newborn may be at risk of perinatally acquired HIV, hepatitis C and/or hepatitis B infection and the incidence of sudden infant death is significantly increased [42,43].

The signs and symptoms associated with overdose of opioids (e.g., coma, circulatory collapse, pinpoint pupils, bradycardia, hypothermia, and severe respiratory depression) are similar in pregnant and nonpregnant women [44]. Opioid withdrawal may be difficult to distinguish from other more commonly observed syndromes, such as upper respiratory infections. The lipophilic opioids have a rapid transplacental passage (less than 60 minutes), and maternal and fetal withdrawal is likely to begin 6 to 48 hours after last usage among opioid abusers [45]. The maternal opioid withdrawal syndrome is characterized by influenza-like symptoms (e.g., myalgias) and signs (e.g., rhinorrhea and lacrimation), as well as by anorexia that can result in impaired fetal growth. The stress state that characterizes withdrawal may also have an adverse impact on the fetus; some studies show increased epinephrine in amniotic fluid [46].

Neonatal abstinence syndrome (NAS), a withdrawal from opioids after birth, has been well-characterized and may last up to 10 weeks following delivery and require management in an intensive care unit. NAS includes wakefulness, irritability, tremulousness, and temperature dysregulation, as well as a disorganized suck and subsequent failure to thrive. Seizures have also been reported [46,47]. The recent study by Goel et al. [16] demonstrated that in UK methadone and heroin are among the frequent drugs used in pregnancy. Heroin use was high in a population with low socioeconomic status and polydrug use was common, despite an active methadone management program [16]. While higher doses of methadone or other opiates during pregnancy are associated with more severe manifestations of NAS, withdrawal during pregnancy is associated with worse outcomes for the fetus overall [12-15,37,46-48]. Although the mechanism of fetal death in connection with withdrawal is uncertain, it may involve hyperactivity secondary to premature contractions, hypoxia, or possibly meconium aspiration. Therefore, it is the current standard of care to maintain opioid-dependent women on long-acting narcotics during pregnancy rather than initiate any type of withdrawal protocol [4,12,37,47]. Since the early 1970s methadone has been the drug of choice for treating the pregnant opioid-dependent patient. Other opioids like buprenorphine

[49,50] and naltrexone [51,52] have been suggested as an alternative; they appear equally safe as methadone [43,49,51,52]. Additionally, several opioids are used for pain management during pregnancy and labor, including: pethidine (meperidine), morphine, diamorphine, fentanyl and remifentanyl. [1,2,53,54]. Although there are methods available for monitoring opioids in urine, sweat, placenta and meconium [55-58], monitoring maternal abuse of opioids is beyond the scope of this review.

## Exploring Methods of Human Placental Function

*In vivo* information obtained at the time of delivery, through comparison of maternal and fetal (umbilical cord) concentrations of any molecule or medication, provides information on concentrations at a particular time point without indicating the mechanism(s) involved in the exchange between maternal and fetal compartments. Placental structure and function show a higher inter-species diversity than observed in any other mammalian organ. Differences between species have been described in placental permeability, transport, blood flow and even metabolic activities [59,60]. In addition, differences in fetal susceptibility to teratogens also exist between species [61] as do rates and extent of fetal development during pregnancy. The animal species that most closely mimic human placental characteristics have a hemochorial histological organization such as primarily primates and rodents. Clearly, primates would be the species of choice, but they are expensive and can be difficult to work with, so rats and mice are more commonly used. While the human placenta is hemomonochorial in classification, composed of a single layer of trophoblast (syncytium) in direct contact with the maternal blood, rats and mice have three trophoblast layers (hemotrichorial) in a labyrinthine placenta [60]. This anatomical difference is reflected by different diffusion patterns between maternal and fetal circulations, with concomitant differences in permeability to various substances. Possible immunological differences between the two species have been reviewed [62]. Mouse and human placental endocrine functions vary strongly [63]. In addition, in humans the yolk sac is present only very early in pregnancy, whereas in rodents it persists throughout gestation, encloses the fetus, and performs important transport functions [64]. For example, the transfer of IgG from maternal to fetal circulations in humans occurs via Fc receptors in the placenta, which can be readily demonstrated using *ex vivo* perfusion [65], while in mice the yolk sac is the organ responsible for IgG materno-fetal transport [66,67]. The fetus/placenta weight ratio of the mouse reaches 30:1 at birth, higher than that of man which is 6:1 [68]. The higher ratio would indicate that the smaller placenta can more efficiently nourish the fetus per unit of placental weight.

The accessibility of human placental tissue together with its resistance to hypoxia or anoxia makes the human placenta particularly well suited for *in vitro* studies [69,70], though with certain caveats including the representation of the structure and function of the mature organ which may not reflect placental function earlier in gestation. Therefore multiple models (Table 3), such as cell and tissue explant culture and *ex vivo* perfusion of human placental tissues, have been used to explore a wide variety of functions like cellular proliferation and differentiation, hormone production and endocrine function as well as permeability, transport, influx and efflux, and metabolism [17,71].

The *ex vivo* perfusion model allows the study of these parameters as well as of the kinetic profile and the chemical action on the placental tissue [17,71]. This method has been used to study the transfer of many substances such as nutrients, hormones, proteins, therapeutic

Method	Approach for preparing placental materials	Experimental data derived
Placental Membrane Preparations	Isolation of brush border and basal membranes, generally from term human placenta	Transport of solutes across brush border or basal membranes of syncytiotrophoblast. Interaction of solutes on membrane transport mechanisms. No data on solute metabolism or retention by the placenta.
Placental Cell Culture	Primary trophoblast cell culture and transformed trophoblast cell culture, across gestational ages.	Uptake, metabolism of solutes by trophoblast. Impact of solutes on trophoblast metabolism and function.
Placental explants	Isolated villi in perfusion medium, across gestational ages.	Uptake, metabolism and retention of solutes by placental villi. Impact of solutes on villous function.
Placental perfusion	Identification of intact cotyledon with perfusion of maternal and fetal portions of the placenta, generally from term human placenta. Possible to study placenta from maternal, fetal or placental disease states.	Uptake, metabolism and retention of solutes by placenta. Directionality of transport (maternal to fetal or reverse). Impact of solute on placental function, integrity of placental vasculature and vascular responses.
Maternal and fetal bloods sampled from umbilical cord	Samples taken generally at term following delivery, however some studies have sampled fetal blood in utero. Placental materials are generally not studied in these analyses.	Concentrations of parent solute and metabolites at fixed periods of time after maternal dosing.

See [17] for a more detailed discussion of these various methods for assessing placental disposition and impact of opioids

**Table 3:** Methodological approaches for studying human placental disposition of opiates and opioids.

agents and drugs of abuse, and offers an extremely useful tool for therapeutic drug development. The increasing body of experimental data on placental drug transfer has enabled clinicians to make better informed decisions about which drugs cross the placenta in significant amounts, and to develop dosage regimens that minimize fetal exposure to potentially toxic concentrations of these.

### Placental Transport Mechanisms

The syncytiotrophoblast, the outermost layer of human the placenta is the main site of exchange for drugs and metabolites, nutrients, waste products and gases between maternal and fetal circulations [72]. Efficient transfer of these molecules across the placenta is essential for fetal growth and development. There are several mechanisms by which transfer occurs, and depending on the mechanism of transfer the direction may be towards the maternal or fetal circulation [73-75]. In the human placenta the syncytiotrophoblast arises from the fusion of cytotrophoblast cells, forming a syncytium over the surface of the placenta facing the maternal blood. The plasma membranes of the syncytiotrophoblast are polarized; the brush-border membrane is in direct contact with maternal blood and the basal membrane faces the fetal circulation. The brush-border membrane possesses a microvillous structure that effectively amplifies the surface area, whereas the basal membrane lacks this structure. The placental transport mechanisms described below are derived from Malek and Mattison [17].

#### Solvent drag

Solvent drag is the movement (bulk flow) of water in which drugs, solutes, gases and nutrients are dissolved. Bulk flow has been demonstrated in the perfused human placental cotyledon in response to hydrostatic pressure changes. With this mechanism the transfer of a drug would be passive, in the sense of flow with water into or out of placental tissue. This mechanism is unlikely to represent an efficient mechanism for drug access to the placenta or fetus.

#### Simple diffusion

Simple diffusion is the passive transfer of solutes driven by concentration and electrical gradients. All solutes are transferred by diffusion, but may also be transported by other transport mechanisms which enhance exchange between maternal and fetal circulations. As an example, respiratory gases are readily exchanged by simple diffusion.

Determinants of passive diffusion across the placenta include the physicochemical properties of the molecule, as well as protein binding in maternal and fetal circulations and metabolism in the

mother, placenta or fetus. One determinant of passive diffusion is the molecular weight of the chemical, with a decreasing transfer rate as the molecular weight increases. Hydrophobicity and ionizability also influence placental exchange, and may also influence the amount of the drug which remains sequestered, or bound within placental tissues. While differences in protein binding in fetal and maternal circulations influence total concentration differences between maternal and fetal circulations, the transfer across the placenta is a function of the free concentration difference. Consequently, total concentrations may be higher in maternal or fetal blood based on binding to albumin or alpha-1-acid glycoprotein, but the free concentrations would be similar.

#### Transcellular transfer

This type of transfer utilizes transport proteins in the microvillus, the basal membranes of the syncytiotrophoblast, or in the fetal capillary endothelium. Three types have been described:

**Channels:** These proteins form water-filled pores in the plasma membrane through which ions can diffuse down an electrochemical gradient. This allows transport of charged hydrophilic substances which otherwise would not cross the lipid barrier. Placental aquaporins and chloride channels are examples of channels that function in the transport of water and small molecules, and which are essential for fetal development.

**Facilitated diffusion:** These transporters are saturable carrier proteins, which function independently of metabolic energy so that transport occurs more rapidly than it would from simple diffusion, but it will not occur against a concentration or other driving gradient. As an example, glucose is transported by the facilitated GLUT transporters.

**Carrier-mediated active transport:** Primary active transport utilizes an energy source such as ATP to move solutes against a gradient; Na<sup>+</sup>K<sup>+</sup>ATPase and Ca<sup>2+</sup>ATPase are two examples. Secondary active transport utilizes concentration gradients across the cell that are set by the primary system such as Na<sup>+</sup> + amino-acid co-transport and Ca<sup>2+</sup> / Na<sup>+</sup> exchanger. Transport ATPases are known to be present in the human placenta. These include the Na<sup>+</sup>K<sup>+</sup>pump (Na<sup>+</sup>K<sup>+</sup>ATPase) which is localized on the microvillus and basal membrane, and a high-affinity Ca<sup>2+</sup>ATPase located on the basal membrane. These active transport proteins are dysregulated in fetal growth abnormalities.

**Endocytosis and exocytosis:** During endocytosis, material is engulfed in extracellular fluid during invagination of the cell surface to form a fluid-filled vesicle. Exocytosis is the reverse of this process, vesicles fuse with the cell membrane to release their contents. This

process can be receptor mediated i.e. triggered by a specific interaction between the solute and a receptor on the cell membrane.

Most drugs cross the human placenta by simple diffusion; however, any of the mechanisms described above may also be involved. Plasma membrane carriers, biotransforming enzymes, and efflux or influx pumps (transport proteins) may play a role in maternal-fetal exchange. Factors that affect the transfer rate include the molecular weight, the degree of ionization, lipid solubility, protein binding, and fetal and maternal-placental blood flow and pH. Non-ionized, non-protein-bound lipid soluble drugs with a molecular weight below 600 Da freely cross the placenta. High molecular weight drugs, such as insulin (6,000 Da), do not pass between maternal and fetal circulations in significant amounts. One important function of the placenta is transfer of antibodies (IgGs) from the mother to the fetus, which can occur when the mother is immunized during pregnancy. This passive immunization of the fetus requires the expression of placental FcRn receptor.

### Transport Proteins

Within the placenta there are specific proteins, likely developed for endogenous substrates, which transport them with high efficiency from the maternal to the fetal circulations (influx transporters) or in the opposite direction (efflux transporters). Transport proteins may be expressed in the microvillous brush border or basal membrane of the syncytiotrophoblast or the endothelium of the fetal capillaries found in the villi. Many of these transport proteins are found in other organs including gut, liver, brain and kidney where they perform similar functions. Recognizing the presence and substrate specificity of these transport proteins provides opportunity in drug development to target or exclude drug access to fetal or placental tissues. Examples of efflux transporters in the placenta include ATP binding cassette proteins (ABC), breast cancer resistant proteins (BCRP) and the multiple drug resistance associated proteins (MDRP). Examples of influx transporters include organic cation transporters, dicarboxylate transporters, and the sodium/multivitamin transporters.

The expression of Permeability-glycoprotein (P-gp) on the maternal side of the placenta (eg in the placental brush border of the syncytiotrophoblast facing the intervillous space) is encoded within the syncytiotrophoblast by the multidrug resistance gene. The function of this protein is to mediate active efflux of substrates from the cell with the driving force coming from ATP hydrolysis. P-gp-mediated active transport is unidirectional, facilitating efflux of substrates due to the asymmetrical membrane topology of the protein. It appears that this efflux transporter may have evolved as a protective mechanism.

### Transport of Opiates under *Ex vivo* Placental Perfusion Conditions

The following information is derived from Malek and Mattison [76]. Although placental drug permeability and pharmacokinetics are important factors in determining fetal exposure to drugs, placental inaccessibility *in vivo* and concern for maternal and fetal safety have limited direct human investigation (although nonhuman primates can be utilized [77-79]). While useful data on the mechanism and time course of transport and placental metabolism, and fetal exposure to drugs can be derived from single-point determinations of maternal, umbilical cord, and neonatal blood concentrations sampled at or shortly after birth [80-82], as briefly discussed above there are data gaps from such studies (Table 3). The isolated, *ex vivo* dual perfused human placental model enables evaluation of placental transfer and metabolism of substances at, or close to, term, without raising methodological or

ethical problems [83]. Additionally, this approach allows integration of placenta and fetus into physiologically based pharmacokinetic models of pregnancy [84,85].

The study by Kopecky and colleagues [86] investigated the transfer of morphine across the perfused human placenta and its interaction with naloxone under *ex vivo* conditions. This study found that morphine readily crosses the term human placenta. Naloxone does not alter placental transfer or clearance of morphine, suggesting that transfer across the placenta is not altered by changes in vascular resistance. Placental retention of morphine may prolong or moderate fetal exposure to morphine (see discussion of placental retention of buprenorphine below).

The placental transfer of three opioids used in peridural analgesia, fentanyl, alfentanil and sufentanil, and two reference compounds, antipyrine and tritiated water ( $^3\text{H}_2\text{O}$ ), was determined with placental perfusion [87]. Antipyrine and  $^3\text{H}_2\text{O}$ , which are neither metabolized nor bound to placental tissues, were used to validate the procedure and compare the rates of transfer of the three opioids. Experiments were carried out at fixed, physiological flow and at various maternal blood flow rates. Under these conditions, the magnitude of the materno-fetal transfer was in the following order:  $^3\text{H}_2\text{O}$ =antipyrine=fentanyl>alfentanil>sufentanil. The study also showed that a marked fall in maternal flow rate, as may be observed in pathological situations, may lead to a reduction in placental transfer of water-soluble substances. On the other hand, materno-fetal transfer is more rapid and complete for opioids and the lipid-soluble local anesthetics used in obstetrics than for water-soluble substances. These findings emphasize the importance of the lipophilic and hydrophilic characteristics of drugs on placental transfer, especially in the event of fluctuations in maternal flow [88].

In several studies the transfer of methadone was investigated using concentrations in the maternal perfusate which were similar to those measured in serum of pregnant women under treatment with the drug. The transfer of methadone and its clearance index was significantly higher in the fetal to maternal than in the maternal to fetal direction with no adverse effects on placental viability and functional parameters, although a substantial fraction of this opiate is retained by the placental tissue [89]. The observed asymmetry in methadone transfer could be explained by the unidirectional activity of the efflux transporter P-glycoprotein (P-gp) that is highly expressed in variable amounts in trophoblast tissue [90,91]. This study suggested that placental disposition of methadone might be an important contributor to the regulation of its concentration in the fetal circulation and consequently may affect the incidence and intensity of NAS in offspring of women treated with the drug during pregnancy. Recently, the same study group showed that the fetal transfer rate of methadone in preterm placentae was significantly lower than in term placentae and placental expression of P-gp was higher in preterm than term placentae [92].

A third study was performed to characterize the transfer of methadone and its effect on placental tissue in the presence of heroin [26]. This study was conducted because during treatment with methadone, around 80% of women continued to use other drugs (including opioids like heroin) during pregnancy [93]. The perfusion study demonstrated that methadone has a significant influence on placental permeability. In perfusion experiments with methadone alone, antipyrine (a reference marker for placental permeability) transfer decreased. This alteration in placental function could lead to a dysfunction in the supply of the fetus with oxygen and nutrients from the maternal circulation. Intrauterine growth restriction observed during treatment with methadone [94] could be based on

this mechanism. In contrast to the effect of methadone, antipyrine transfer increased significantly in the experiments where heroin was added to the perfusate. Even though the supply of the fetus with oxygen and nutrients may be better, the amelioration of the placental permeability could affect the barrier function of the placenta adversely. Consequently, more toxic substances or bacteria and viruses may cross the placenta and harm the fetus. Previous studies reported increased prevalence of infectious diseases in infants exposed to illegal drugs during pregnancy [95]. Furthermore, the presence of heroin increased the number/concentration of microparticles (MPs) produced by the placenta and found in the maternal circulation [26]. It was also shown that, this *ex vivo* method is a good model to investigate the shedding of MPs from syncytiotrophoblast as a sign for oxidative stress seen in preeclampsia [96]. This study suggests that methadone alone does not influence the tissue structure whereas the combination with heroin may induce oxidative stress [26].

Other opiates like the agonists buprenorphine (BUP) and L- $\alpha$ -acetylmethadol (LAAM), which were introduced as alternatives to methadone for treatment of the pregnant opiate addict, have also been evaluated using the *ex vivo* placental perfusion model [97-99]. The perfusion study with BUP using similar plasma peak concentration known from patients under treatment, showed that within 60 min of perfusion most of BUP was sequestered in the placental tissue, while the transplacental transfer of the drug to the fetal circulation was less than the BUP added to the maternal circulation. Although there was no adverse effect on placental tissue viability, less than 5% of the perfused BUP was metabolized to norbuprenorphine [98]. *In vivo* however most of the BUP is metabolized in the liver to norbuprenorphine. In the perfusion study with LAAM with a concentration comparable to its peak plasma levels, following administration of a therapeutic dose does not seem to adversely affect placental tissue viability and functional parameters [99]. Placental tissue retains most (80%) of the administered LAAM, and only a fraction (20%) is transferred to the fetal circulation. Conversely, LAAM is biotransformed *in vivo* by the liver to norLAAM by first-pass metabolism, leading to higher serum levels of the latter than the parent compound. Therefore, it is likely that placental tissue would be exposed to increasing concentrations of norLAAM following the administration of a therapeutic dose of LAAM. Data obtained in this investigation indicate that the fetal transfer rate of norLAAM is almost twice that of LAAM, and the former can have adverse effects on the placental viability and functional parameters as determined in the *ex vivo* system used. The authors suggested that administration of LAAM to a pregnant woman would result in higher concentrations of norLAAM than LAAM in placental tissue and in the fetal circulation [99]. It is unclear whether the observed adverse effects for norLAAM on placental tissue would also occur *in vivo*.

### Effect of Opiates on Breastfeeding

The efficacy of intravenous patient-controlled analgesia (PCA) has been well documented with a variety of opioid analgesics in post-caesarean delivery patients [100-102]. Although morphine is the standard analgesic used in this setting, a recent blinded comparison noted a more rapid onset of pain relief and less sedation with meperidine [102]. Morphine and meperidine, as well as their major metabolites morphine-3-glucuronide and normeperidine, are secreted into colostrum and breast milk [103,104]. Morphine and meperidine have very similar pharmacokinetics [105,106], although they differ in onset, duration of action, and metabolism. As a result, concentrations of parent opioids, measured alone, in tissue compartments show inconsistent correlation with concurrent clinical effects. Notably, meperidine is metabolized via

hepatic n-demethylation to normeperidine, which is approximately one half as potent as meperidine with respect to analgesia, but more potent as a central nervous system (CNS) stimulant and convulsant. In contrast, morphine undergoes hepatic conjugation to form, predominantly, inactive morphine-3-glucuronide. (Approximately 10% of morphine conjugates are recovered as the active, morphine-6-glucuronide [107,108]. Opioid secretion into colostrum was documented after administration of single doses by oral, intramuscular, and epidural routes [103,104]. By these routes, meperidine and normeperidine appear to accrue in equal concentrations in breast milk, whereas morphine accumulates to a lesser degree than does morphine-3-glucuronide. In addition, evidence that morphine, meperidine, and normeperidine all have prolonged plasma elimination half-lives in neonates, compared to adults [109,110], does suggest that neonates are at increased risk for opioid toxicity. In a prospective single-blinded manner comparing two groups (morphine vs. meperidine), the examination of post-caesarean delivery patients using PCA and also the examination of their nursing infants were studied [111]. Breast milk specimens, obtained at 12, 24, 36, 48, 72, and 96 h postpartum and analyzed for opioids and metabolites, showed persistently elevated normeperidine concentrations in the meperidine group. A blinded psychologist evaluated each infant once on the 3rd day of life with the Braselton Neonatal Behavioral Assessment Scale (NBAS). A priori, the "alertness" and three "human orientation" outcomes of the NBAS were chosen for analysis as best measures of opioid-induced effects. The neonates in the morphine group scored significantly higher ( $P < 0.05$ ) than neonates in the meperidine group. This study concludes that post-caesarean delivery PCA with morphine provides equivalent maternal analgesia and overall satisfaction as that provided by PCA with meperidine, but with significantly less neurobehavioral depression among breast-fed neonates on the 3rd day of life [111].

Pethidine is a  $\mu$ -opioid receptor agonist with potent spinal and supraspinal effects [112]. Its moderate lipophilicity makes it attractive for epidural administration, after which it provides rapid onset of analgesia and a very low risk of respiratory depression. The estimation of infant dose and exposure to pethidine and norpethidine via breast milk following patient-controlled epidural pethidine for analgesia post caesarean delivery was investigated [113]. The combined absolute infant dose of pethidine and norpethidine received via milk was 1.8% of the neonatal therapeutic dose and the combined relative infant dose was below the 10% recommended safety level. Breastfed infants are at low risk of drug exposure when mothers self-administer epidural pethidine after caesarean delivery. In additional studies the pethidine excretion in breast milk following i.m. or i.v. administration postpartum was investigated. The infant exposure to pethidine (relative infant dose) ranged from 0.6 to 6% of the weight-adjusted maternal dose [104,114,115].

With respect to the therapeutic levels, most prescribed opioids are safe to take during breastfeeding, because only small amounts are excreted into the breast milk [116,117]. However, it is still recommended, that babies be carefully monitored for signs of excessive drowsiness. Breastfeeding is not recommended when non-prescribed opioids are being used, because of the risks associated with a baby being exposed to fluctuating and higher than therapeutic levels of opioids. Methadone maintenance treatment is compatible with breastfeeding regardless of the methadone dose prescribed to the mother [118]. Use of Suboxone during breastfeeding is not recommended. Women with some blood-borne infections, such as HIV/AIDS and tuberculosis,

should not breastfeed, because there is a risk of the infections being transmitted to the baby.

## Conclusions

The naturally opiates and the opioids including semi-synthetic and synthetic drugs which are used as analgesics for pain therapy; and prescription use of this class of drugs increases during pregnancy. Researches of these drugs suggest that the opiates and opioids are transported to the fetus with an impact on human placental function. Consequently we need to understand placental disposition and fetal exposure of these opiates and opioids. Approaches using maternal and fetal blood and placental tissues obtained at or before delivery will allow a static view of placental disposition and fetal exposure. Experiments using the *ex vivo* placental perfusion model will allow analysis of placental retention and disposition of the opioids. Ultimately it will be necessary to combine *in vivo* with *ex vivo* approaches to develop a complete understanding of the exposure to and impact of opiates and opioids on placental function, maternal adaptation to pregnancy and fetal/neonatal growth and development.

The therapeutic levels of the most prescribed opiates and opioids are safe to take during breastfeeding, because only small amounts are detected in the breast milk. Methadone maintenance treatment is compatible with breastfeeding regardless of the methadone dose prescribed to the mother.

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