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# Placental transfer of anaesthetic drugs

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In an attempt to define the risk to the fetus associated with anesthesia during pregnancy, this essay was performed. It includes an anatomical and physiological description of the maternal-placental-fetal unit with description of the placental functions: 1- Nutritional function. 2- Hormonal enzyme production. 3- Blood placental barrier function. 4- Placental transfer of respiratory gases. 5- Immunological. Placental transfer of the drugs was found to depend upon: 1- Lipid solubility of the drug. 2- Degree of ionization of the drug. 3- Protein binding. 4- Molecular weight to the drug. 5- Maternal-fetal concentration gradient. 6- Placental factors as area and thickness of the membrane, maternal and fetal blood flow, and placental enzymes. Also, fetal uptake of the drugs depends on: 1) Alteration in fetal circulation. 2) Fetal pH. 3) Plasma protein binding. 4) Fetal metabolism. 5) Tissue binding.

Effects of anesthetic drugs on the fetus. It includes the effects of: 1- Intravenous anesthetic agents e.g. thiopentone, methohexitone, barbiturates, ketamine, etomidate, althesin, propanidid, propofol, benzodiazepines, narcotic analgesic and narcotic antagonists. 2- Neuromuscular blocking agents e.g. -suxamethonium, tetrahydroamine, decamethonium, alcuronium, pancuronium, D Tubocurarine, gallamine, rapacuronium, rocuronium, fazadinium, vecuronium and atracurium. 3- The volatile and gaseous anesthetics e.g. nitrous oxide, halothane, methoxyflurane, fluroxene, trichloroethylene, ether, cyclopropone, enflurane isoflurane, and sevoflurane. 4- Local anesthetics placental transfer of local anesthetic drugs depends upon: a. Maternal factors 1- Total dose of drug. 2- Protein binding. 3- The ionization constant. 4- Metabolism and excretion. 5- Injection site. 6- Addition of adrenaline. 7- Placental blood flow. b. Fetal factors as protein binding, hepatic uptake and fetal pH. The local anesthetic drugs include lignocaine, prilocaïne, mepivacaine, bupivacaine, ropivacaine, procaine. All commonly used anesthetic agents and drugs undergo placental transfer. Understanding the placental transfer of anesthetic drugs and their effects on the neonate is essential for optimal administration of both regional and general anesthesia. Drug exposure before organogenesis usually causes all or no effect, i.e. the embryo either doesn't survive or develops without abnormalities, while use of drugs in late pregnancy may lead to multiple organ involvement, developmental syndrome or intrauterine growth retardation. There is no overall increase in congenital abnormalities and no obvious relationship, between outcome and type of anesthesia. Elective surgery should not be performed in parturient as it can have both immediate and long term undesirable effects on the fetus, hypertension, hypovolemia, hypoxemia and marked increase in sympathetic tone can seriously

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compromise the transfer of oxygen and other nutrients across the uteroplacental circulation and promote intrauterine fetal asphyxia. The stress of surgery may also precipitate preterm labor which often follows intra abdominal surgery. Second trimester procedures and those do not involve uterine manipulation carry the lowest risk of preterm labor. Volatile anesthetics depress myometrial irritability and theoretically are advantageous for abdominal procedures, however there is no evidence that any specific technique influences the risk of preterm labor. In any serious maternal condition the remote fetal risk of anesthesia and operation are secondary to preserving the life of the mother. The choice of anesthesia for cesarean section is determined by multiple factors, including obstetric indication, its urgency, patient and obstetrician preferences and the skills of the anesthetist.

**Summary** There is a world wide shift in obstetric practice in favor of regional anesthesia. Both epidural and spinal anesthesia have advantages and disadvantages for cesarean section compared to general anesthesia. Regional anesthesia offers reduced maternal mortality as it minimizes the problem of maternal aspiration, the ability to use fewer drugs, more direct experience of child birth and the capability to decrease blood loss, besides it provides excellent postoperative pain control and avoid neonatal depression associated with general anesthesia, recently the regional anesthesia provides fewer modification of neonatal immune function. The disadvantage of the regional anesthesia include, hypotension, nausea, vomiting, intra operative discomfort, post lumbar headache and potential for neurologic and cardiac toxicity from local anesthetics.

**Direct effects of local anesthetics:** Although a diminution of variability of FHR has been reported after the beginning of an epidural anesthesia using lidocaine, no significant modification of FHR after epidural anesthesia using lidocaine or bupivacaine with epinephrine has been shown. Fetal neurologic toxicity is rare and there are very little alterations of neurobehavioral scores, however the addition of opioids to the epidural infusions may reintroduce the problem of neonatal respiratory depression with systemic opioids. Although the addition of opioids allow the reduction in the dose of local anesthetics without compromising analgesia, lesser motor blockade, greater maternal mobility and satisfaction. Sufentanil in doses up to 30 µg in association with bupivacaine seems to be devoid of depressive effects on neonate.

**Indirect effects of local anesthetics:** In high concentrations, local anesthetics entail a vasoconstriction of uterine vessels but the main feared effect is maternal hypotension that impedes directly the uteroplacental blood flow (best prevented by 20-25 mL/kg crystalloid preload and prompt treatment with ephedrine) fetal consequences depend on the importance and the duration of uteroplacental blood flow (UBF) decrease, the preliminary, state of uteroplacental circulation and hemodynamic adaptive capacities of the fetus when the former are exceeded, fetal hypoxia occurs and both myocardial and brain oxygenation can be rapidly impaired if the hemodynamics is not corrected.

Ropivacaine (0.08%) in labor epidural analgesia produces good labor pain relief with no detectable adverse effects on the mother and the neonate and without causing significant increase in cesarean section rate, also epidural 0.5% ropivacaine for CS do not compromise the uteroplacental circulation in healthy parturient and provides surgical anesthesia as effective as 0.5% bupivacaine. In contrast to regional anesthesia for CS, general

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anesthesia has the following advantages, less hypotension better control of airway and ventilation. Pre-oxygenation is followed by rapid sequence induction, muscle relaxation and endotracheal intubation accompanied by cricoid pressure. Hyperventilation should be avoided, maintaining end-tidal CO<sub>2</sub> in the normal range for pregnancy (32- 34 mmHg). Respiratory alkalosis can compromise maternal-fetal oxygen transfer by causing umbilical artery constriction and shifting the maternal hemoglobin dissociation curve to the left. In addition positive pressure ventilation may reduce uterine blood flow and cause fetal acidosis as a consequence of increased intra-thoracic pressure decreasing venous return and cardiac output. A technique employing a high concentration of oxygen, an opioid and moderate concentration of volatile agent with a muscle relaxant is often used. In halothane anesthesia diffuse readily but provided that the induction-delivery is short. Neuromuscular blocking compounds and fully ionized cross the placenta very slowly, fetal/maternal ratio at delivery very low also bolus doses of succinylcholine are safe. Doses of thiopental greater than 8 mg/kg- maternal weight produce neonatal depression. A dose of 4-7 mg/kg- maternal weight is commonly advocated for induction of general anesthesia as it ensures unconsciousness beside wide clinical use testifies to the safety of thiopental. On the other hand there is conflicting evidence concerning the effect of propofol on the neonate, induction doses as 5 mg/kg/h have shown to cause significant neonatal depression. Neonatal elimination of propofol is slower than in adults unless thiopental is contraindicated. There seems little advantage in using propofol in cesarean section. The use of Benzodiazepines should be avoided if possible as the neonate may suffer from respiratory depression, hypotonia, poor thermoregulation and raised bilirubin concentrations. Opioids are mainly weak bases bound to albumin, glycoprotein, pethidine and its metabolite normeperidine depress all neurobehavioral aspects of the neonate. Neonatal elimination is slower, resulting in prolongation of its effect. Neonatal elimination is slower, resulting in prolongation of its effect. Transfer of pethidine is increased in the presence of fetal acidosis, depressant effect are maximum when administration to delivery time is 2-3 hours (Elton and MacDonald, 2001). On the other hand Apgar and neurobehavioral scores are less affected after maternal IV administration of fentanyl and alfentanil, while remifentanyl is useful in obstetric situation in which opioid based general anesthesia is desirable with excellent fetal outcome. Maternal monitoring should include blood pressure measurement, ECG, pulse oximetry, capnography, temperature monitoring and use of nerve stimulator. FHR and uterine contractions should be monitored intra and post operatively when possible. Neonatal resuscitation is not without risk, iatrogenic laryngospasm, trauma to upper airway, pneumothorax and tracheal perforation are all recognized hazards. The administration of drug as oxygen, naloxone, adrenaline and sodium bicarbonate are potentially dangerous particularly if clinician is inexperienced. In addition, an infant who is depressed secondary to anesthetic agents, will develop biochemical changes of asphyxia if apnea persists for more than a few minutes or resuscitation is ineffective. Finally, the skill and knowledge of the anesthesiologist are more important than the type of the anesthesia administered, therefore when properly performed, both regional and general anesthesia are quite safe in terms of neonatal outcome.