# The Use of Dexmedetomidine as an Adjuvant for Pre-eclamptic Patients Undergoing Cesarean Section Under General Anesthesia

*Thesis*

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# Abstract

The introduction of parenterally administered drugs in the obstetric population encounters many challenges. Such obstacles are imperative, as careless systemic administration of any medication may have a profound effect on both mother and fetus.

Dexmedetomidine use in obstetric analgesia is being explored in view of its high lipophilicity. It is retained in the placental tissue, thereby resulting in less fetal transfer and a decreased incidence of fetal bradycardia.

Premedication with dexmedetomidine not only offers anxiolysis, sedation and analgesia, but also helps in attenuating the stress responses to tracheal intubation in pre-eclamptic parturients.

Dexmedetomidine is also associated with a decreased hemodynamic response to extubation and recovery time after surgery, cause minimal respiratory depression and posses hemodynamic stabilizing effects.

**Key words:**

Dexmedetomidine
Analgesia
Hemodynamic
Pre-eclampsia

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# List of Abbreviations

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| **AFOI** | Awake Fibrooptic Intubation |
| **AR** | Adrenergic Receptor |
| **IVPCA** | Intra Venous Patient Controlled Analgesia |
| **ABP** | Arterial Blood Pressure |
| **ATN** | Acute Tubercular Necrosis |
| **CSF** | Cerebro Spinal Fluid |
| **DAMP** | Deoxy Adenosine Mono Phosphate |
| **DIC** | Disseminated Intravascular Coagulapathy |
| **$ETCO_2$** | End Tidal Carbon Dioxide |
| **HIF1 Alpha** | Hypoxia Inducible Factor 1 Alpha Subunit |
| **HLA** | Human Leukocyte antigen |
| **L.A** | Local Anesthesia |
| **MAC** | Minimum Alveolar Concentration |
| **$PaCO_2$** | Partial Pressure of Carbon Dioxide |
| **$PaO_2$** | Partial Pressure of Oxygen |
| **PLGF** | Phospholipid Growth Factor |
| **ROS** | Reactive Oxygen Species |
| **ALT** | Alanine Amino Transferase |
| **AST** | Aspartate Amino Transferase |
| **TNF** | Tissue Necrosis Factor |
| **PO** | Per Oral |

# Introduction

Alpha (α)-2-adrenergic receptor (AR) agonists have been the focus of interest for their sedative, analgesic, perioperative sympatholytic, anesthetic-sparing, and hemodynamic-stabilizing properties.[1] Dexmedetomidine, a highly selective α2-AR agonist with a relatively high ratio of α2/ α1activity (1620:1 as compared to 220:1 for clonidine), possesses all these properties but lacks respiratory depression [2,3] making it a useful and safe adjunct in diverse clinical applications[4].

Intravenous patient-controlled analgesia (IVPCA) with opioid remains an acceptable option for establishing labor analgesia, especially when neuraxial techniques are contraindicated[5]. Although relatively safe, opioid-based IVPCA is not uncommonly associated with incomplete analgesia and respiratory depression in the mother and neonate[6]. The α2 agonist clonidine is used occasionally for neuoraxial labor analgesia, but rarely by the intravenous route in the obstetric setting due to detrimental effects on uterine tone and fetal heart rate with high plasma concentrations [7].

Dexmedetomidine, an agent with greater α2 selectivity and significantly less placental transfer, may serve as a valuable alternative, particularly when responding to inadequate labor analgesia with systemic opioids.

Perioperative applications of dexmedetomidine include premedic-ation, as part of multimodal anesthetic regimen, prevention of emergence delirium, and management of postoperative pain [2,8].

Premedication with dexmedetomidine not only offers anxiolysis, sedation and analgesia, but also helps in attenuating the stress responses to tracheal intubation/extubation and emergence from anesthesia[9]. As an adjunct to general anesthesia it decreases minimum alveolar concentration (MAC) and opiate sparing properties, which helps in decreasing the inhalational anesthetic

and opioid requirements,which can be used to advantage in situations where high anesthetic concentration is either undesirable or not tolerated [2,10,11].

An emerging application, dexmedetomidine has role in facilitating awake fibro optic intubation (AFOI) in difficult airway situations[12,13].

For acute and chronic pain ; the greater α2-AR selectivity of dexmedetomidine enhances the therapeutic window of dexmedetomidine in the treatment of pain[14].

Pre- and intra-operative intravenous dexmedetomidine prolongs the duration of sensory block of local anesthetics during spinal anesthesia[15] and peripheral nerve block[16].

Postoperatively, intravenous dexmedetomidine infusion is associated with a reduction in nausea and vomiting, reducing postoperative morbidity[14].

Is there a role for intravenous dexmedetomidine in obstetrics? the introduction of parenterally administered drugs in the obstetric population encounters many regulatory and other challenges. Such obstacles are imperative, as careless systemic administration of any medication may have a profound effect on both mother and fetus[17].

Dexmedetomidine use in obstetric analgesia is being explored in view of the high lipophilicity. It is retained in the placental tissue, thereby resulting in less fetal transfer and a decreased incidence of fetal bradycardia. Continuous intravenous dexmedetomidine infusion has been successfully used as an adjunct to systemic opioids in laboring parturients who could not benefit from epidural analgesia[18,19].

Dexmedetomidine has some potentially useful features. A recent study demonstrated the value of a dexmedetomidine infusion to prevent post-anaesthetic shivering after gynaecological surgery [20].

Dexmedetomidine, if used appropriately, maintains psychomotor function, which could help participation in the labouring process[21]. It has also been shown to enhance spontaneous contractions in rat and human myometrium, which may have relevance to its use before and during labour[22,23]. In isolated, perfused human placenta, dexmedetomidine passes less readily than clonidine into the fetal circulation, as its high lipophilicity results in its retention by placental tissue[24].

Dexmedetomidine is also associated with a decreased hemodynamic response to extubation and recovery time after surgery [25]. Intravenous dexmedetomidine has been shown to reduce opioid induced muscle rigidity, lessen postoperative shivering, cause minimal respiratory depression and possess hemodynamic stabilizing effects [26].

# Maternal physiological and anesthetic consideration

Normal pregnancy involves major physiological and anatomical adaptation by maternal organs. It is important that anesthetists involved in the care of the pregnant woman understand these changes, to provide safe maternal anesthetic care which is compatible with safe delivery of the baby[27].

Pregnancy affects virtually every organ system. Many of these physiological changes appear to be adaptive and useful to the mother in tolerating the stresses of pregnancy, labor and delivery [28].

The maternal physiologic changes during pregnancy contribute to increased anesthetic risk for both the mother and fetus.

## ***Cardiovascular changes:***

### Changes in blood volume

Expansion of the plasma volume and an increase in red blood cell mass begin as early as the fourth week of pregnancy, peak at 28 to 34 weeks of gestation, and then plateau until parturition.

Plasma volume expansion is accompanied by a lesser increase in red cell volume. As a result, there is a mild reduction in hematocrit, with peak hemodilution occurring at 24 to26 weeks .Blood volume in pregnant women at term is about 100 mL/kg [29].

### Changes in vascular resistance and blood pressure

Blood pressure (BP) typically falls early in gestation and is usually 10 mmHg below baseline in the second trimester, declining to a mean of 105/60

mmHg. In the third trimester, the diastolic blood pressure gradually increases and may normalize to non-pregnant values by term [30].

The factors responsible for the vasodilatation are incompletely understood, but one of the major findings is decreased vascular responsiveness to the pressor effects of angiotensin II and norepinephrine. Several additional mechanisms for the fall in vascular resistance have been proposed:

1-Increased endothelial prostacyclin.

2-Enhanced nitric oxide production.

3-Reduced aortic stiffness[31].

**Changes in Cardiac Output**

The cardiac output rises 30 to 50 % (1.8 L/min) above baseline during normal pregnancy; one-half of this increase occurs by 8 weeks of gestation.

The elevation in cardiac performance results from changes in three important factors that determine cardiac output:

1-Preload is increased due to the associated rise in blood volume.

2-Afterload is reduced due to the decline in systemic vascular resistance.

3-Maternal heart rate rises by 15 to 20 beats/min[32].

The stress induced by the increase in cardiac output can cause women with underlying and, in some cases, asymptomatic heart disease to decompensate during the latter half of pregnancy [32].

During labor**:** Cardiac output increases by 15 % above pre labor levels in early labor and by approximately 25 % during the active phase. Immediately postpartum **:** Cardiac output increases to 80 % above pre labor values due to significant autotransfusion associated with uterine involution that is more pronounced than the normal blood loss of delivery [32].

The cardiac output and systemic vascular resistance gradually return to nonpregnant levels over a period of three months or more[34].

**Maternal supine hypotension syndrome**

Results when the gravida assumes a supine position, leading to uterine compression of the inferior vena cava. Venous blood return to the heart is decreased. The decreased preload reduces stroke volume and may result in a 25%to 30% decrease in cardiac output. Maternal symptoms include pallor, sweating, nausea, vomiting, hypotension, tachycardia, and mental status changes. Symptoms are more pronounced in the third trimester because of the expanding uterus and are alleviated by maintaining a left lateral decubitus position and displacing the uterus laterally [33].

## ***Respiratory Changes:***

Difficult endotracheal intubation is a leading cause of maternal morbidity and mortality. Airway edema, breast engorgement, and the generalized weight gain of pregnancy may contribute to airway obstruction and reduced glottis opening [34].

Laryngoscopy and intubation should be accomplished with care. Sufficient smaller endotracheal tubes may be required for successful intubation and also lubricants to minimize trauma[35].Oxygen consumption increases to meet the increased demands of both the mother and the fetus. These factors increase the risk of hypoxia during a rapid sequence induction[36].

Maternal oxygen saturation should be maintained at 95% to maintain a PaO2 greater than 70mmHg, thereby optimizing oxygen diffusion across the placenta [37].

## *Central Nervous Changes:*

Generally, maternal sensitivity to anesthetic agents is increased. Minimum alveolar concentration (MAC) for all general anesthetic agents is lower in pregnancy due to sedation effect of progesterone and increased endorphin during labor. Pregnancy also increases sensitivity to non-depolarizing muscle relaxants.

In pregnancy, decreased volume of spaces (epidural , subdural and subarachnoid spaces) and venous engorgement leading to increase pressure of spaces of CSF and decrease escape of Local anaesthetics. along epidural sleeves so low volume of local anesthetic are used [38].

## *The Gastrointestinal System:*

The pregnant patient is at risk for aspiration of gastric contents increasing risk for aspiration pneumonitis due to:

1.Upward displacement of stomach by the uterus.

2.Progestrone decreases gastric motility and tone of gastro-intestinal sphincter

3.Placental gastrin increases gastric acidity[38].

Thus, a rapid sequence induction is always performed for endotracheal intubation

## *Hematologic Changes:*

Increase in blood volume is mainly in plasma that lead to dilutional anemia. Plasma protein concentrations, particularly albumin, are relatively decreased during pregnancy. This change may alter the peak plasma concentrations of drugs that are highly protein bound. Prothrombin, factor V, protein C, and antithrombin III levels remain unchanged.[39]

The incidence of venous thromboembolic complications is five timesgreater during pregnancy, due to:

1-Increase in procoagulants.

2-Decreased fibrinolysis.

.3-Increased venous stasis, particularly in lower extremities.

So, there is a need for adequate hydration and early postoperative ambulation[39].

## ***Utero placental blood flow changes:***

Placental circulation is important for development and maintenance of a healthy fetus. The integrity of this circulation is dependent on both adequate uterine blood flow and normal placental function [40].

Utero placental blood flow is characterized by:

1) It is 10% of the cardiac output i.e. 600-700 ml/min compared to 50 ml/min in non pregnant uterus.

2) 80% of the uterine blood flow supplies the placenta while the remainder goes to the myometrium.

3) Pregnancy maximally dilates the uterine vasculature. So that autoregulation is absent but it is sensitive to alpha -adrenergic agonists.

4) Uterine blood flow is not significantly affected by respiratory gas tensions but extreme hypocapnia ($PaCO_2$<20mmHg) can reduce uterine blood flow and causes fetal hypoxemia and acidosis.

5) Uterine blood flow is directly proportional to the difference between uterine arterial and venous pressures but inversely proportional to the uterine vascular resistance [40].