Obstetric Anesthesia Handbook

Fifth Edition

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Preface to the Fifth Edition

It is a great honor for us to join Dr. Sanjay Datta in presenting the fifth edition of *The Obstetric Anesthesia Handbook*. As former students and now colleagues of our mentor, we have attempted to update this classic and widely read book to reflect the constantly evolving face of obstetric anesthesiology. It is astounding to envision the initial writing of this text, nearly 20 years ago, in an era before the ubiquitous availability of online search tools, downloadable papers, and searchable textbooks. The early editions were formed predominantly out of Dr. Datta's personal command of the field, its literature, and his personal teaching files. Many benefited from the depth and breadth of his wisdom presented in the original *Handbook*, and it is now our privilege to help pass on this work to the next generation of residents, fellows, and obstetric anesthesia practitioners around the world. We have attempted to retain the compact style of the original single-author version, while adding some newer material, reorganizing some chapters to enhance their utility, updating references, and revising some figures and appendices. We hope you will find it as helpful in your practice as it is in ours.

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Preface to the First Edition

One of the major "perks" of an academic anesthesiologist is the opportunity to interact with residents and fellows. Most of them are bright, energetic, and hardworking individuals. During my professional life, I enjoyed my dealings with this special group, and their enthusiasm in obstetric anesthesia is the basis for the germination of this project.

Parturients are different from their nonpregnant counterparts in various ways. Their expectations, demands, and needs make obstetric anesthesia more challenging and also gratifying. This book basically deals with these aspects at a level that I found stimulating to the residents as well as fellows.

There are 19 chapters in this book that address the various aspects of maternal physiology, perinatal pharmacology, and, ultimately, anesthetic techniques for different procedures; my hope is that this is done in a concise manner. Every effort has been made to discuss the controversial issues of anesthetic techniques covering the majority of problems that might arise.

It is my deepest desire that this book be both helpful and stimulating to residents, fellows, and my contemporaries. To this end, periodic updates of this manual will be made to keep its contents current and to address topics of interest and controversy.

I want to express my gratitude to a few individuals without whom this project would remain incomplete. My thanks are directed to Dr. Knapp for his very eloquently expressed views regarding medicolegal aspects of obstetric anesthesia. My special thanks go to Ms. Vehring, whose editorial assistance was extremely necessary. Finally, I must also express my gratitude to Ms. Racke for her graphic illustrations and Ms. Russo and Ms. Spelling for secretarial help.

Sanjay Datta, MD, F.F.A.R.C.S. (Eng)

Contents

1
Maternal Physiological Changes During Pregnancy, Labor, and the Postpartum Period

Parturients undergo remarkable changes during pregnancy, labor, and the immediate postpartum period that can directly affect anesthetic techniques; hence a broad knowledge of these changes is essential for optimum management of these women.

Changes in the Hematological System

Maternal blood volume increases during pregnancy, and this involves an increase in plasma volume as well as in red cell and white cell volumes.[1] *The plasma volume increases by 40–50%, whereas the red cell volume increases by only 15–20%, which causes a "physiological anemia of pregnancy"* (normal hemoglobin 12 g/dL; hematocrit 35).[2] Because of this hemodilution, blood viscosity decreases by approximately 20%. The exact mechanism of this increase in plasma volume is unknown. However, several mediators such as

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renin–angiotensin–aldosterone, atrial natriuretic peptide, estrogen, progesterone, and nitric oxide may be involved. The most likely hypothesis attributes the increase to an "underfill" state caused by initial vasodilation, which stimulates hormones such as renin, angiotensin, and aldosterone to cause fluid retention.[3] Alternatively, some have proposed an "overfill" state characterized by an early increase in sodium retention (due to an increase in mineralcorticoids) that leads to fluid retention, causing an increase in blood volume, followed subsequently by vasodilation.

Blood volume increases further during labor, as uterine contractions squeeze blood out of the intervillious space and into the central circulation. After delivery, involution of the uterus and termination of placental circulation causes an autotransfusion of approximately 500 mL of blood.

Levels of clotting factors I, VII, VIII, IX, X, and XII and fibrinogen are elevated during pregnancy as well. Platelet production is increased, thrombopoietin levels are increased,[4] and platelet aggregation measured in vitro is likewise increased; indices of platelet destruction are also increased. The overall effect of these changes is variable, but prospective observations have reported a statistically significant fall in platelet count as pregnancy progresses, with 7.6% of women having a count less than 150,000 and 1% less than 100,000 at term.[5] Endogenous anticoagulants, such as protein S, are decreased in normal pregnancy and there is acquired resistance to activated protein C during pregnancy, adding to the prothrombotic state. Fibrinolysis is impaired in normal pregnancy due to placentally derived plasminogen activator inhibitor (PAI), but returns to normal following delivery of the placenta. Overall indices of coagulation indicate that normal pregnancy is a hypercoagulable state.[6]

Clinical Implications

Increased blood volume and enhanced coagulation serve several important functions: (1) the increased circulatory needs of the enlarging uterus and growing fetus and placenta are met and (2) the parturient is protected from bleeding at the

time of delivery. Anesthesiologists should consider the enlarged blood volume when making decisions on fluid and blood replacement in the peripartum period. Parturients become hypercoagulable as gestation progresses and are at increased risk of thromboembolism. After a rapid mobilization and diuresis of some fluid in the first few postpartum days, blood volume slowly returns to normal over 8 weeks.

Changes in the Cardiovascular System

An increase in cardiac output is one of the most important changes of pregnancy. *Cardiac output increases by 30–40% during pregnancy, and the maximum increase is attained around 24 weeks' gestation.*[7] The increase in heart rate occurs first (by the end of the first month of pregnancy) and plateaus at an increase of 10–15 beats per minute by 28–32 weeks' gestation. Stroke volume increases by mid-first trimester and progressively increases through the second trimester. Echocardiography demonstrates increases in end-diastolic chamber size and total left ventricular wall thickness but no change in end-systolic volume, so ejection fraction is increased. Cardiac output can vary depending on the uterine size and maternal position at the time of measurement. The enlarged gravid uterus can cause aortocaval compression and reduced cardiac filling while the pregnant woman is in the supine position (Fig. 1-1), leading to an underestimation of cardiac function. Normal pregnant women exhibit a marked increase in femoral venous and inferior vena caval pressures. Collateral vessels maintain atrial filling but lead to engorgement of veins, including the epidural venous (Batson's) plexus.

Filling pressures (CVP, pulmonary capillary wedge pressure, LV end-diastolic pressure) do not change despite the increased cardiac dimensions, due to myocardial remodeling during gestation. Systemic vascular resistance is decreased approximately 20%. Blood pressure never increases in normal pregnancy, and systolic and diastolic blood pressures decrease by approximately 8 and 20%, respectively, on average.[9] Pregnancy hormones (estradiol and progesterone), prostacyclin, and nitric

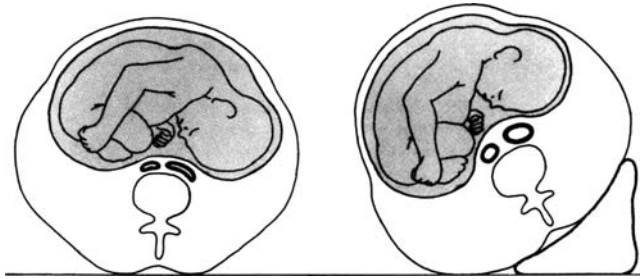

Figure 1–1. Aortocaval compression. (From Chestnut.[8] Used with permission from Elsevier.)

oxide all may play a role in the reduction in blood pressure observed despite an increase in cardiac output.

Cardiac output increases further during labor, up to 50% higher than pre-labor values, although effective analgesia can attenuate some of this increase. In the immediate postpartum period, cardiac output increases maximally and can rise 80% above pre-labor values and approximately 150% above nonpregnant measurements. An increase in stroke volume as well as in heart rate maintains the increased cardiac output.

The heart is displaced to the left and upward during pregnancy because of the progressive elevation of the diaphragm by the gravid uterus. The electrocardiogram of normal parturients may include (1) sinus tachycardia or benign dysrhythmias, (2) depressed ST segments and flattened T waves, (3) left axis deviation, and (4) left ventricular hypertrophy. Auscultation frequently reveals a systolic murmur of tricuspid or mitral regurgitation, and a third or fourth heart sound.

Cardiac output, heart rate, and stroke volume decrease to pre-labor values 24–72 h postpartum and return to nonpregnant levels within 6–8 weeks after delivery.[10]

Clinical Implications

An increased cardiac output might not be well tolerated by pregnant women with valvular heart disease (e.g., aortic or mitral stenosis) or coronary arterial disease. *Decompensation in*

myocardial function can develop at 24 weeks' gestation, during labor, and especially immediately after delivery.

Engorgement of the epidural venous plexus increases the risk of intravascular catheter placement in pregnant women; direct connection of the azygos system to the heart as well as brain also increases the risks of local anesthetic cardiovascular and central nervous system toxicity.

Changes in the Respiratory System

Changes in respiratory parameters start as early as the fourth week of gestation. Minute ventilation is increased at term by about 50% above nonpregnant values. The increase in minute ventilation is mainly due to an increase in tidal volume (40%) and, to a lesser extent, an increase in the respiratory rate (15%).[11] Alveolar ventilation is greatly increased as the tidal volume increases without any change in the ratio of dead space to tidal volume (V_D/V_T). At term PCO_2 is decreased to 32–35 mmHg, although renal excretion of bicarbonate keeps arterial pH normal. Increased progesterone concentrations during pregnancy likely stimulate increased respiration, even before an increase in metabolic rate.[12] Oxygen consumption and carbon dioxide production increase by approximately 60% over prepregnant values. PaO_2 is increased in early pregnancy due to a decrease in PCO_2.

Functional residual capacity, expiratory reserve volume, and residual volume are decreased at term (Fig. 1-2). These changes are related to the cephalad displacement of the diaphragm by the large gravid uterus. Inspiratory capacity increases somewhat because of increase in tidal volume and inspiratory reserve volume. Vital capacity is unchanged. Total lung capacity is only slightly reduced because chest circumference increases. Closing capacity (CC) does not change, but the reduction in FRC contributes to a tendency toward earlier desaturation, as lung volume more easily falls below CC.

Anatomic changes also accompany pregnancy. The respiratory mucous membranes become vascular, edematous, and friable. The voice may deepen and there is a progressive increase in the Mallampati score during gestation and labor.[13]

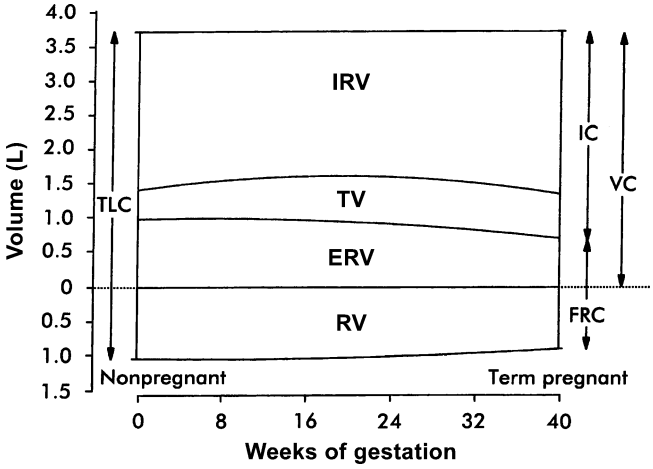

Figure 1–2. Pulmonary volume and capacity changes in pregnancy. (From Chestnut.[8] Used with permission from Elsevier.)

In labor, minute volume further increases in the absence of pain relief, and PCO_2 may decrease to 17 mmHg. Opioids somewhat attenuate this change, but epidural analgesia does so more completely. In the second stage, maternal expulsive efforts increase ventilation, even in the presence of effective regional analgesia.[14,15]

FRC changes return to normal 1–2 weeks postpartum, accompanying the reduction in uterine size. All other respiratory parameters return to nonpregnant values within 6–12 weeks postpartum.

Clinical Implications

Decreased FRC as well as increased oxygen consumption can cause a rapid development of maternal hypoxemia during apnea. Decreased FRC decreases the time for denitrogenation and speeds the uptake of inhaled anesthetics.

Because of the increased edema, vascularity, and friability of the mucous membrane, one should try to avoid nasal

intubation in pregnant women, and smaller endotracheal tubes should be used for oral intubation.

Maternal alkalosis associated with decreased $PaCO_2$ values due to hyperventilation as a result of labor pain can cause fetal acidosis because of (1) decreased uteroplacental perfusion due to uterine vasoconstriction and (2) shifting of the maternal oxygen dissociation curve to the left.

Changes in the Gastrointestinal System

The enlarging uterus displaces and disrupts the lower esophageal sphincter, and progesterone relaxes this high-pressure zone, causing a progressive increase in the incidence of heartburn (up to 80% at term). An increase in gastric pressure due to mechanical compression also contributes to heartburn. Despite the prevalence of this symptom, total acid production is decreased (although placental production of gastrin increases the total concentration of this hormone).

Gastric emptying is normal throughout pregnancy, as measured by acetaminophen absorption, ultrasound, dye-dilution, and radiographic techniques. Intestinal transit time is increased, leading to frequent complaints of constipation in pregnant women. Studies of gastric pH and volume in pregnant and nonpregnant women show no differences in the proportion of women meeting "at risk" criteria (pH <2.5, volume >25 ml[16]) for pulmonary aspiration of gastric contents.[8]

Labor fundamentally alters this pattern. Gastric emptying time is significantly slower during labor and hence gastric volume is increased. Opioids administered by any route will further increase the gastric emptying time. Studies demonstrate solid food in the stomachs of laboring women even after 18 h of fasting.[17] Gastric emptying remains abnormal on the first postpartum day but returns to normal on the second day.

Hepatic transaminases, bilirubin, and LDH are increased slightly in pregnancy. Alkaline phosphatase is markedly increased (2–4 fold), but due to placental production, not hepatic changes. *Serum cholinesterase activity is reduced 24% before delivery and reaches a nadir (33% reduction) on the third postpartum day*[14] (Fig. 1-3). Approximately 11% of post-

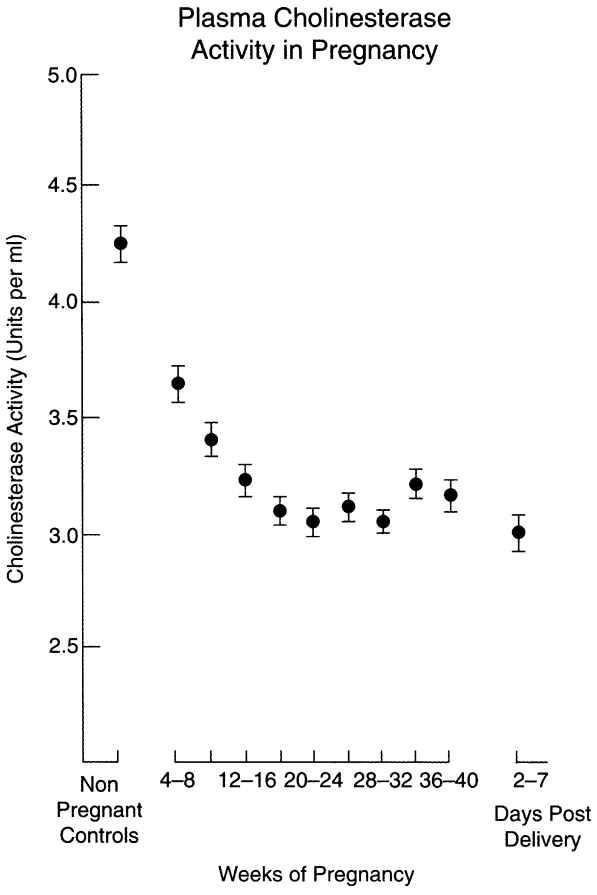

Figure 1–3. Plasma cholinesterase activity in pregnancy. (From Cohen.[18] Used with permission from Elsevier.)

partum women exhibit clinically deficient activity, manifest as an exaggerated response to normal doses of succinylcholine. *Even with this lower activity, normal dosing of succinylcholine for intubation is recommended when general anesthesia is required, though use of a peripheral nerve stimulator seems prudent.*

Gallbladder function and emptying are impaired during pregnancy, and there is evidence that pregnant women may be more prone to gallstones.

Clinical Implications

Pregnant women *in labor* should always be considered to have a full stomach irrespective of the time of their last meal. General anesthesia should be avoided when possible, and routine precautions (rapid sequence induction and endotracheal intubation) should be employed when general anesthesia is unavoidable. The routine use of nonparticulate antacid is important before cesarean section and before induction of regional anesthesia, and one should allow for proper mixing of the antacid and stomach contents. Pregnant women who are not in labor and who do not have other risk factors for aspiration may not require such treatment.

Changes in the Renal System

The glomerular filtration rate is increased during pregnancy because of increased renal plasma flow.[19] A rise in the filtration rate decreases plasma blood urea nitrogen (BUN) and creatinine concentrations by about 40–50%, to approximately 8–9 mg/dL and 0.5–0.6 mg/dL, respectively. Tubular reabsorption of sodium is increased. However, glucose and amino acids might not be absorbed as efficiently; hence glycosuria (up to 300 mg/day) and aminoaciduria may develop in normal gestation. The renal pelvis and ureters are dilated, and peristalsis is decreased. Physiological diuresis during the postpartum period occurs between the second and fifth days. The glomerular filtration rate and BUN concentration slowly return to nonpregnant values by the sixth postpartum week.

Clinical Implications

Normal nonpregnant values of BUN and Cr in parturients suggest abnormal kidney function.

Changes in the Central and Peripheral Nervous Systems

The central and peripheral nervous systems undergo significant changes during pregnancy. MAC is decreased by 25–40% during pregnancy.[20] Increased progesterone and endorphin concentrations during pregnancy have been implicated as a cause of this change. However, a few studies have shown that endorphin concentrations do not increase until the onset of active labor,[21] so this cannot explain early decreases in MAC. By injecting exogenous progesterone in oophorectomized rabbits, a decrease in MAC was observed when compared with control animals.[22]

A wider dermatomal spread of sensory anesthesia was observed in parturients following the use of epidural anesthesia as compared with nonpregnant age-matched controls.[23] The difference was explained by a reduction in epidural space volume caused by an engorged epidural venous plexus due to aortocaval compression. However, a subsequent report showed that this difference exists even during early pregnancy (8–12 weeks) when one might not expect any mechanical obstruction by the small gravid uterus,[24] and epidural venous engorgement later in pregnancy appears to reduce CSF volume, not epidural extravascular volume. The factors suggested were (1) compensated respiratory alkalosis of pregnancy, (2) reduced plasma and cerebrospinal fluid (CSF) protein levels during pregnancy, leading to increased free local anesthetic, and (3) pregnancy hormones. The latter is the most likely explanation, based on animal studies. An increased sensitivity to bupivacaine in isolated nerve fibers has been demonstrated (Fig. 1-4).[25]

It is possible that progesterone or one of its active metabolites is responsible for the observed increased sensitivity of the peripheral nervous system to anesthetics in parturients. This increased sensitivity was also observed in nerves from oophorectomized rabbits treated chronically with exogenous progesterone.[26] Interestingly, this phenomenon was not observed following acute exposure to progesterone.[27] In humans, enhanced sensitivity of peripheral nerves to local anesthetic has also been documented.[28]

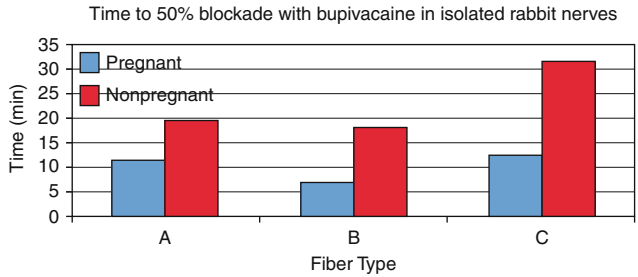

Figure 1–4. Increased sensitivity in nerves in pregnant vs. nonpregnant rabbits. (Data from Datta et al.[25])

Clinical Implications

Even though the exact mechanism of the increased sensitivity of the central nervous system and peripheral nervous system to general and local anesthetics is not known, in general, it is prudent to reduce the dose of anesthetics in pregnant women, at least on initial dosing.

Because of a paucity of data and uncertainty regarding the actual mechanisms underlying enhanced local anesthetic sensitivity in pregnancy, it is not known when these changes revert to their nonpregnant state. Spinal anesthetic sensitivity appears normal 24–48 h postpartum.

Changes in the Endocrine System

Thyroid-binding globulin is increased in pregnancy, but free T_3 and T_4 are normal. Adrenal cortical hyperplasia leads to increases in both free and total cortisol in pregnancy. Fasting blood sugar is lower in pregnant than nonpregnant women, but tolerance to a glucose load may be somewhat impaired due to the actions of placental lactogen, producing a mild diabetogenic state. Occasionally, this progresses to gestational diabetes. Glucose responses return to normal promptly after delivery of the placenta.

Changes in the Musculoskeletal System

The hormone relaxin is responsible for both the generalized ligamentous relaxation and the softening of collagenous tissues. The lumbar spine demonstrates exaggerated lordosis, possibly complicating regional anesthesia. Stretching of the lateral femoral cutaneous nerve can occur, leading to sensory loss in the lateral thigh (meralgia paresthetica). This must be differentiated from neural injury due to childbirth or anesthesia. In addition, back pain frequently accompanies late pregnancy, and pregnant women must be counseled against relating this to regional anesthesia.

Changes in the Dermatological System

Hyperpigmentation of certain parts of the body such as the face, neck, and midline of the abdomen is not uncommon during pregnancy. Melanocyte-stimulating hormone is responsible for this change.

Changes in Mammary Tissue

Enlargement of the breasts is typical and may complicate use of a conventional laryngoscope during induction of general anesthesia. A short-handled laryngoscope may facilitate easier instrumentation of the airway.[29]

Changes in the Ocular System

Intraocular pressure has been shown to decrease during pregnancy; this is related to (1) increased progesterone levels, (2) the presence of relaxin, and (3) decreased production of aqueous humor due to increased secretion of human chorionic gonadotropin. Changes in intraocular pressure in parturients may produce visual disturbances as well as contact lens intolerance.

References

1. Lund CJ, Donovan JC. Blood volume during pregnancy. Significance of plasma and red cell volumes. *Am J Obstet Gynecol*. 1967;98(3):394–403.
2. Ueland K. Maternal cardiovascular dynamics. VII. Intrapartum blood volume changes. *Am J Obstet Gynecol*. 1976;126(6): 671–677.
3. Barron WM, Mujais SK, Zinaman M, Bravo EL, Lindheimer MD. Plasma catecholamine responses to physiologic stimuli in normal human pregnancy. *Am J Obstet Gynecol*. 1986;154(1):80–84.
4. Frolich MA, Datta S, Corn SB. Thrombopoietin in normal pregnancy and preeclampsia. *Am J Obstet Gynecol*. 1998;179(1): 100–104.
5. Burrows RF, Kelton JG. Thrombocytopenia at delivery: a prospective survey of 6715 deliveries. *Am J Obstet Gynecol*. 1990;162(3):731–734.
6. Sharma SK, Philip J, Wiley J. Thromboelastographic changes in healthy parturients and postpartum women. *Anesth Analg*. 1997;85(1):94–98.
7. Mashini IS, Albazzaz SJ, Fadel HE, et al. Serial noninvasive evaluation of cardiovascular hemodynamics during pregnancy. *Am J Obstet Gynecol*. 1987;156(5):1208–1213.
8. Chang AB. Physiologic changes of pregnancy. In: Chestnut DH, ed. *Obstetric Anesthesia: Principles and Practice*. Philadelphia: Elsevier-Mosby; 2004:15–36.
9. Clark SL, Cotton DB, Lee W, et al. Central hemodynamic assessment of normal term pregnancy. *Am J Obstet Gynecol*. 1989;161 (6 Pt 1):1439–1442.
10. Robson SC, Hunter S, Moore M, Dunlop W. Haemodynamic changes during the puerperium: a Doppler and M-mode echocardiographic study. *Br J Obstet Gynaecol*. 1987;94(11):1028–1039.
11. Prowse CM, Gaensler EA. Respiratory and acid-base changes during pregnancy. *Anesthesiology*. 1965;26:381–392.
12. Bayliss DA, Millhorn DE. Central neural mechanisms of progesterone action: application to the respiratory system. *J Appl Physiol*. 1992;73(2):393–404.
13. Kodali BS, Chandrasekhar S, Bulich LN, Topulos GP, Datta S. Airway changes during labor and delivery. *Anesthesiology*. 2008;108(3):357–362.
14. Pearson JF, Davies P. The effect of continuous lumbar epidural analgesia on the acid-base status of maternal arterial blood

during the first stage of labour. *J Obstet Gynaecol Br Commonw*. 1973;80(3):218–224.
15. Pearson JF, Davies P. The effect on continuous lumbar epidural analgesia on maternal acid–base balance and arterial lactate concentration during the second stage of labour. *J Obstet Gynaecol Br Commonw*. 1973;80(3):225–229.
16. Roberts RB, Shirley MA. Reducing the risk of acid aspiration during cesarean section. *Anesth Analg*. 1974;53(6):859–868.
17. Carp H, Jayaram A, Stoll M. Ultrasound examination of the stomach contents of parturients. *Anesth Analg*. 1992;74(5):683–687.
18. Cohen SE. Why is the pregnant patient different? *Semin Anesthesia*. 1982;1:73.
19. Jeyabalan A, Conrad KP. Renal function during normal pregnancy and preeclampsia. *Front Biosci*. 2007;12:2425–2437.
20. Palahniuk RJ, Shnider SM, Eger EI, 2nd. Pregnancy decreases the requirement for inhaled anesthetic agents. *Anesthesiology*. 1974;41(1):82–83.
21. Steinbrook RA, Carr DB, Datta S, Naulty JS, Lee C, Fisher J. Dissociation of plasma and cerebrospinal fluid beta-endorphin-like immunoactivity levels during pregnancy and parturition. *Anesth Analg*. 1982;61(11):893–897.
22. Datta S, Migliozzi RP, Flanagan HL, Krieger NR. Chronically administered progesterone decreases halothane requirements in rabbits. *Anesth Analg*. 1989;68(1):46–50.
23. Bromage PR. Continuous lumbar epidural analgesia for obstetrics. *Can Med Assoc J*. 1961;85:1136–1140.
24. Fagraeus L, Urban BJ, Bromage PR. Spread of epidural analgesia in early pregnancy. *Anesthesiology*. 1983;58(2):184–187.
25. Datta S, Lambert DH, Gregus J, Gissen AJ, Covino BG. Differential sensitivities of mammalian nerve fibers during pregnancy. *Anesth Analg*. 1983;62(12):1070–1072.
26. Flanagan HL, Datta S, Lambert DH, Gissen AJ, Covino BG. Effect of pregnancy on bupivacaine-induced conduction blockade in the isolated rabbit vagus nerve. *Anesth Analg*. 1987;66(2):123–126.
27. Bader AM, Datta S, Moller RA, Covino BG. Acute progesterone treatment has no effect on bupivacaine-induced conduction blockade in the isolated rabbit vagus nerve. *Anesth Analg*. 1990;71(5):545–548.
28. Butterworth JFT, Walker FO, Lysak SZ. Pregnancy increases median nerve susceptibility to lidocaine. *Anesthesiology*. 1990;72(6):962–965.
29. Datta S, Briwa J. Modified laryngoscope for endotracheal intubation of obese patients. *Anesth Analg*. 1981;60:120–121.

2
Local Anesthetic Pharmacology

Local anesthetics are the most common and important drugs in obstetric anesthesia; hence an adequate knowledge of these chemical agents is absolutely essential.

Chemistry

Chemically, local anesthetics are classied as amino-esters or amino-amides (Fig. 2-1). All clinically used local anesthetics (except cocaine) link a substituted aromatic ring via an ester or amide bridge and an intermediate alkyl chain to a tertiary amine. Commercially, most are packaged as hydrochloride salt, protonating the amino group to improve aqueous solubility.

Amino-esters undergo hydrolysis by plasma cholinesterase (pseudo-cholinesterase) to derivatives of para-aminobenzoic

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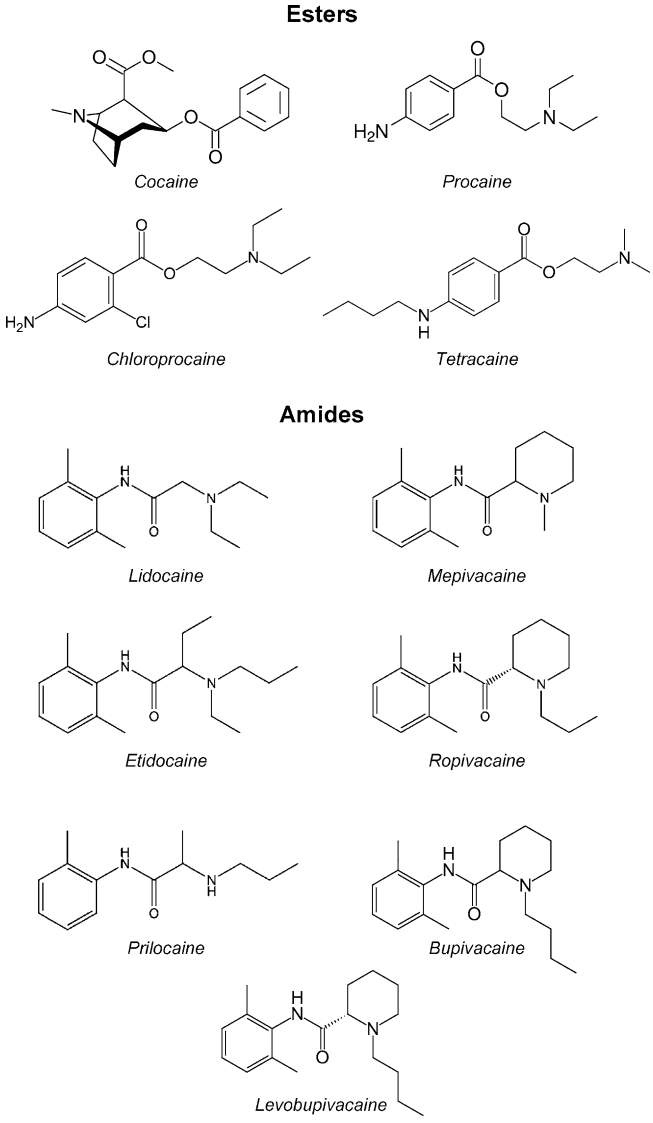

Figure 2–1. Local anesthetics, esters and amides with chemical structures.

acid, which is a known allergen. Hence allergic reactions to amino-esters are not unusual. Conversely, amino-amides are metabolized by the liver to a variety of products with very low potential of triggering allergic reactions.

All local anesthetics except lidocaine contain a chiral carbon atom and thus exist as two enantiomers. Conventional preparations are racemic mixtures, but the development of techniques for bulk separation of optical isomers has led to the development of levobupivacaine and ropivacaine, which are marketed as pure left-handed ("L" or "S") forms.

Physicochemical Properties

The physicochemical properties of local anesthetics correlate with some of their clinical properties (Table 2-1). *Lipid solubility* correlates with the potency of the local anesthetic. This effect is also seen with general anesthetics (the Meyer–Overton observation) and is sometimes attributed to easier passage through the lipid membranes of nerve cells by more lipophilic local anesthetics. More modern views of this observation suggest that it is the perineural lipid-rich tissues which actually form a depot of drug, enhancing continued blockade and thus clinical potency.

Protein binding correlates with the duration of action of local anesthetics. Local anesthetic is bound to two principal sites in plasma: (1) the high-affinity but low-capacity α_1-acid glycoprotein and (2) low-affinity, high-capacity albumin. Although classically taught, this association is not thought to be causal. Plasma protein binding is closely related to lipophilicity, which actually is more responsible for long duration of action.

The p*K*a of local anesthetics correlates to some degree with the speed of onset of neural blockade. p*K*a is defined as the pH where 50% of the local anesthetic will remain in uncharged form and 50% will exist in charged form. Agents with p*K*a closer to the body's pH will be less likely to be protonated and therefore exist more prevalently in the uncharged form (Table 2-1). This form is less polar and more easily able to diffuse across the nerve membrane, perhaps explaining a

Table 2–1. Properties of Local Anesthetics

Anesthetic	Lipid Solubility	Protein Binding (%)	p*Ka* (Unionized Fraction pH 7.4)	Molecular Weight	Potency	Speed of Onset	Duration of Action	UV/MV ratio
Chloroprocaine	0.14	~0	8.7 (5%)	271	Low	Very rapid	Short	~0
Procaine	0.02	6	8.9 (3%)	236	Low	Rapid	Short	N/A
Lidocaine	2.9	64	7.7 (35%)	234	Medium	Rapid	Medium	0.5–0.7
Mepivacaine	0.8	78	7.6 (39%)	246	Medium	Medium	Medium	0.7–0.8
Bupivacaine	8.2	96	8.1 (15%)	288	High	Slow	Long	0.2–0.4
Ropivacaine	8.0	92–94	8.1 (15%)	274	High	Slow	Long	0.2

Lipid solubility: Heptanol or octanol/buffer partition ratio; UV/MV ratio=ratio of concentration in umbilical vein to maternal vein; total concentration, not free drug concentration, is shown in the table (see text for details); N/A = not available.

more rapid onset of blockade. However, the astute reader will note that this mechanism is essentially the same as that asserted for lipid solubility, so the in vivo importance of this action is unclear. Indeed, chloroprocaine, with a p*K*a of 8.7, has the fastest onset of action in clinical practice among all local anesthetics for epidural blockade. Moreover, although the uncharged form is important for diffusion across the nerve membrane, it is believed that the charged form ultimately binds with the sodium channels intracellularly. Hence both forms of the local anesthetic are important for neural blockade.

Some local anesthetics possess *intrinsic vasoactive properties*. Lidocaine produces modest vasodilation in low concentrations, possibly reducing its potency in vivo by increasing vascular uptake. Conversely, ropivacaine has been found to have dose-dependent vasoconstrictive activity,[1] which might increase its duration of action, especially after local infiltration.

Passage of local anesthetics across the placenta is influenced by the physicochemical properties of the drugs. All local anesthetics are relatively small molecules, and therefore molecular weight does not affect their transport. Lipid solubility and degree of nonionization will affect the proportion of maternal venous concentration that exists in the fetal blood, because both enhance passage across the lipid membranes in the placenta (Table 2-1). However, more recent evidence suggests that free drug concentrations for all local anesthetics are in equilibrium across the placenta and in maternal and fetal blood, so the greater protein binding in maternal blood does not necessarily confer a safety advantage to the fetus.

Other Factors Affecting Local Anesthetic Activity

Besides intrinsic physicochemical properties, a number of clinically modifiable factors have a major effect on the degree of neural blockade achieved with local anesthetics.

Volume and Concentration

The total dose (mass or mg) of local anesthetic will ultimately dictate the onset, quality, and duration of the block. In

general, increased doses of the agents speed onset and lengthen duration of the block. For example, increasing the concentration of bupivacaine from 0.125% to 0.5% while maintaining constant volume improved the onset, quality, and duration (but not dermatomal spread) of the block.[2] Volume, concentration, and dose, however, are intimately related, because dose = volume × concentration. Therefore, changing one parameter necessarily changes the others, complicating the study of one feature in isolation. Clinically, volume of drug has a profound effect on the spread and quality of epidurally administered local anesthetics, whereas total dose seems most important in spinal anesthesia.

Addition of Vasoconstrictor Agents

Epinephrine is frequently used with local anesthetics to improve the quality and duration of analgesia. Because of the vasoconstriction produced by epinephrine more local anesthetic will be available for neural blockade because of less absorption through vascular beds. Norepinephrine and phenylephrine have also been used for prolonging blockade, though they are much less popular. Addition of epinephrine will also decrease the peak plasma concentrations of certain local anesthetics, including mepivacaine and lidocaine. Epinephrine is usually added to epidural lidocaine or bupivacaine at concentrations of 1.7–5 μg/ml, or 1:600,000 to 1:200,000 (the latter is also the commercially available concentration). This lowers the median effective concentration of local anesthetic by 30%.[3] In addition, the duration of epidural lidocaine and, to a lesser extent, bupivacaine is significantly prolonged by the addition of epinephrine. In spinal anesthesia, by contrast, epinephrine has minimal effects, increasing the duration of motor but not sensory block with lidocaine, and extending sensory block with bupivacaine by just 4–19 min.[4]

Site of Injection

The onset of action of a local anesthetic varies depending on the site of administration. Spinal and subcutaneous routes

are associated with a more rapid onset, whereas epidural and brachial plexus blocks are associated with a slower onset of action.

Bicarbonate

Local anesthetic solutions, particularly those containing epinephrine, are packaged at low pH to increase the shelf life of the agents. Addition of sodium bicarbonate (1 ml of a 1 M solution to 10 ml local anesthetic) will increase the pH of these solutions and thus the percentage of the nonionized or uncharged form, which is important for diffusion through the nerve membrane. Speed of onset and quality of the block are both improved with this maneuver. Addition of bicarbonate to bupivacaine is not recommended because of the chance of precipitation when the pH rises above 7.7. Laboratory evidence suggests that bicarbonate also enhances local anesthetic activity by other mechanisms distinct from its effect on pH, because its effect is more profound than that induced by equivalent alkalinization with other buffers.[5]

Mixtures of Local Anesthetics: Chloroprocaine and Other Drugs

Historically, combinations of local anesthetics have been used both to shorten the onset of action as well as to improve the quality of the block. A combination of spinal 1% tetracaine and 10% procaine in equal volumes was associated with superior sensory anesthesia when compared with hyperbaric tetracaine (5% dextrose) alone.[6] For epidural administration, it was once hoped that the rapid onset of 2-chloroprocaine and long duration of bupivacaine would produce a desirable combination. However, the use of 2-chloroprocaine shortened the duration of bupivacaine's action.[7] The mechanism of this interaction is unknown but may be related to inhibition of the binding of bupivacaine to membrane receptor sites in the presence of 2-chloroprocaine or its metabolite chloraminobenzoic acid.[8]

The eutectic mixture of local anesthetics (EMLA) is a 1:1 mixture of prilocaine and lidocaine that induces cutaneous

anesthesia through intact skin. Applied in doses of 0.5–1 g under an occlusive dressing, it induces anesthesia for subsequent needle stick in 30–60 min.

Pregnancy

Pregnancy reduces the amounts of local anesthetic needed for both spinal and epidural anesthesia in parturients as compared with age-matched nonpregnant women.[9] The onset of blockade is also faster with the use of spinal, epidural, and peripheral nerve blocks. Although various mechanisms for these observations have been proposed (including influence of mechanical factors in the epidural space and alterations in the central nervous system[10]), the most likely explanation is an effect of progesterone on the sensitivity of nerve fibers themselves.[11]

Temperature

Warming the local anesthetic to a temperature of 100°F has been shown to reduce the onset of epidural anesthesia blockade. A decreased p*K*a due to increased temperature is probably the mechanism.[12]

Toxicity of Local Anesthetics

Local anesthetics can result in systemic toxicity manifest in the CNS or the cardiovascular system, as well as peripheral toxicity manifest as irreversible conduction blockade or other neurological symptoms. Local anesthetics may also cause untoward effects on the fetus.

Systemic Toxicity: CNS

The clinical features of systemic toxicity depend on the blood concentrations of the local anesthetics. In most cases, CNS symptoms will precede cardiovascular derangements. In lower concentrations, the patient may complain of (1) tinnitus, (2) light-headedness, (3) metallic taste, and (4) perioral numbness. With higher concentrations, convulsions and

unconsciousness, followed by respiratory arrest, may ensue. If a large bolus dose of local anesthetic is accidentally injected intravenously the parturient may manifest convulsions as the first sign. This may also occur if the pregnant woman receives large doses of diazepam or midazolam as premedication, because these drugs may mask the subjective symptoms associated with lower blood levels. Respiratory acidosis (increased $PaCO_2$ and low pH) decreases the convulsive threshold and may also increase drug delivery to the brain by increasing cerebral blood flow. Acidosis may also decrease the free plasma concentrations by reducing protein binding. The potency of local anesthetics closely parallels their relative toxic potential: bupivacaine > lidocaine > > chloroprocaine.

Systemic Toxicity: Cardiovascular System

Local anesthetics inhibit cardiac sodium channels and in some cases potassium and calcium channels. However, the heart is highly resistant to toxicity from lidocaine, and indeed seven times the convulsive dose is required to produce cardiovascular collapse with this drug (at plasma concentrations of approximately 25 μg/ml vs. 7–12 μg/ml). Cardiovascular toxicity may result indirectly from respiratory depression, however (at approximately 20 μg/ml). In contrast, high systemic levels of more potent local anesthetics (bupivacaine, etidocaine) produce cardiovascular toxicity at much lower multiples of the convulsive dose. This is due to their pro-arrhythmic effects on the pacemaker and conduction cells in the heart, decreasing the duration of the action potential and the effective refractory period. Thus reentrant-type ventricular dysrhythmias (ventricular tachycardia or fibrillation) may result.

Cardiovascular toxicity of local anesthetics appears significantly more likely with right-handed (R- or D-) isomers of potent lipophilic local anesthetics. This observation led to the development of levobupivacaine and ropivacaine, which are both packaged as pure L- or S-isomers. Levobupivacaine has essentially identical clinical properties as racemic bupivacaine, but is less toxic in both isolated cardiac and intact animal preparations. In human studies, racemic bupivacaine produces more signs of impending cardiovascular toxicity (changes in