

# Local anesthetic toxicity and lipid resuscitation in pregnancy

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## Purpose of review

Lipid emulsion has emerged as an effective treatment of local anesthetic-induced cardiac arrest, but its therapeutic application for the obstetric patient requires definition at present. This review discusses clinical reports, relevant laboratory studies, and future directions for the development of an optimal protocol for lipid resuscitation in pregnancy.

## Recent findings

Several mechanisms have been postulated to account for the apparent enhanced sensitivity to local anesthetic systemic toxicity during pregnancy. One case report of lipid resuscitation in the pregnant patient demonstrates favorable outcomes and supports the safety of lipid therapy. Current guidelines and case reports propose that a large bolus of lipid at the earliest signs of toxicity may prevent cardiovascular collapse.

## Summary

As the obstetric demographic becomes older and more obese, new technologies and strategies can assist in controlling maternal death and major morbidity secondary to anesthesia complications. Lipid resuscitation appears to be an effective treatment for toxicity induced by lipophilic medications and may be useful in treating systemic toxicity in the pregnant patient. Obstetric care providers should be aware of lipid resuscitation and consider its use as described by American Society of Regional Anesthesia and Pain Medicine guidelines.

## Keywords

intravenous lipid emulsion, lipid, local anesthetics, pregnancy, resuscitation

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## Introduction

Intravenous lipid emulsion (ILE) has emerged over the past decade as a promising antidote to local anesthetic systemic toxicity (LAST), a potentially fatal complication of regional anesthesia occurring in up to 1/500 peripheral nerve blocks [1–3]. A growing number of case reports have documented instances of severe LAST in which the use of ILE appeared to facilitate recovery. Infusion at the earliest signs of systemic toxicity is believed to have reduced fatalities associated with lipophilic local anesthetics, because several reports indicate that ILE resulted in return of spontaneous circulation after standard resuscitative measures had failed. The apparent efficacy of ILE is particularly encouraging in the context of LAST that is related to the lipophilic local anesthetics (e.g., bupivacaine, ropivacaine), which are known to produce intransigent cardiac toxicity [4–7]. Moreover, these successes have led the Association of Anaesthetists of Great Britain and Ireland (AAGBI), the American Society of Regional Anesthesia and Pain Medicine (ASRA) and other professional organizations to adopt recommendations for treatment of LAST that include ILE. Widespread acceptance of this technique has led

many facilities to store lipid emulsion in close proximity to operating rooms and labor suites.

Pregnancy represents one of several clinical settings in which LAST can be potentiated [8–10,11<sup>••</sup>,12]. LAST has been recognized for decades as an important potential cause of maternal mortality, and more so now that obstetric care providers face increasingly severe and complex cases due to rising maternal age, obesity, and other comorbidities [13]. Local anesthetic toxicity in pregnancy remains a critical issue, and the clinical success of ILE suggests that the parturient and anesthesiologist may both benefit from clinical translation of this new treatment modality. However, many questions remain unanswered in regards to the distinct considerations, risks, and optimal protocols for lipid resuscitation in the pregnant patient.

## Systemic toxicity in the parturient

LAST is caused by a high circulating plasma concentration of local anesthetic, generally occurring as a result of either intravenous entrainment of local anesthetic or delayed absorption from the anesthetic depot at the

injection site. A 1979 editorial by Albright [14] signaled the first alarm raising serious concern about the clinical dangers of toxicity secondary to long-acting, lipophilic local anesthetics (especially bupivacaine and etidocaine). This raised general awareness of the problem among the community of anesthesiologists and served as a stimulus for study of the underlying mechanisms and potential treatments for LAST. Notably, several of the original anecdotal reports of LAST-related fatal cardiac arrests involved pregnant women [15]. It has since been established that pregnancy increases the risk for LAST, and subsequent guidelines preclude use of 0.75% bupivacaine in late gestation because this concentration was involved in instances of fatal toxicity in parturients [8].

Several mechanisms have been postulated to account for the apparent enhanced sensitivity to LAST during pregnancy. Epidural vein distention makes entrainment of local anesthetic and catheter migration more likely. Increased cardiac output can presumably alter uptake of local anesthetic from the epidural space and distribution to potential target sites. Pregnancy-related decreases in protein binding may also alter local anesthetic dynamics by increasing the availability of free drug in the vascular compartment [16,17], although this effect has been challenged to some extent [18]. The hormonal effects of estradiol [10] and progesterone [9] appear to alter cardiomyocyte electrophysiology sufficiently to increase the risk of arrhythmias specifically and cardiotoxicity in general. Increased neuronal susceptibility to anesthetics may also occur during pregnancy [8], reducing the threshold to local anesthetic induced seizure.

A Mayo clinic report estimates that 54% of cardiac arrests during spinal anesthesia are directly attributable to an anesthesia complication [19]. Cardiac arrest secondary to LAST remains a serious potential problem during delivery, despite the use of low concentration anesthetics and increased awareness of toxicity [20,21]. Today, with modern neuraxial labor analgesia (which uses very low concentration of local anesthetic solutions) the 'therapeutic dose' corresponds to the 'test dose' and the accidental intravenous or intrathecal injection will not cause harmful signs of systemic toxicity but may produce respectively the absence of analgesic effects or a faster onset of analgesia or even anesthesia and some motor block, depending on the dose given. Specifically, a recent British survey by Regan and O'Sullivan [22] suggests that the conversion of epidural analgesia during labor to surgical anesthesia for Caesarean section can have important medical implications and that the incidence of life-threatening complications due to local anesthetic toxicity were strongly associated with the epidural extension. The pregnant woman in cardiac arrest, although younger than the average out-of-hospital cardiac arrest

### Key points

- ILE has emerged over the past decade as a promising antidote to LAST.
- Pregnancy represents one of several clinical settings in which LAST can be potentiated.
- At present, the 'lipid sink' effect remains the dominant mechanistic theory for the efficacy of ILE in LAST.
- Lipid resuscitation should represent a step forward in parturient safety by facilitating a reduction in morbidity and mortality associated with LAST in pregnancy.
- We emphasize the need for effective airway management, controlling for lean body mass in lipid dosing, and urgent cesarean delivery without compromised maternal resuscitation.

patient, might actually have a poorer survival rate, currently estimated at 6.9% [23<sup>•</sup>]. Attempted resuscitation of the pregnant woman is complicated by physiological changes during pregnancy, including aortocaval compression by the gravid uterus that reduces venous return and cardiac output, causing hypotension and aggravating the pathophysiology of the arrest state [12]. A logical plan for the prevention and treatment of maternal anesthesia-related complications is crucial for the safety of both mother and fetus. Lipid resuscitation should represent a step forward in parturient safety by facilitating a reduction in morbidity and mortality associated with LAST in pregnancy.

### Lipid resuscitation: mechanism of action

Despite laboratory and clinical efficacy of lipid resuscitation, the exact mechanism has not been established. At present, the 'lipid sink' effect remains the dominant mechanistic theory for the efficacy of ILE in LAST. It is thought that the rapid addition of exogenous lipid into the vascular compartment can create a concentration gradient between tissue and blood that draws the anesthetic from the heart or brain (and other target areas of high concentration) into the aqueous plasma phase, where the bulk lipid phase provides an adequate reservoir (or sink) to harbor the offending drug from plasma and target tissues. We predict that lipid emulsion would operate in a similar manner in the parturient, providing a safe and effective alternate binding source for lipophilic local anesthetics. However, this has not been studied and it is possible that the lipid sink could demonstrate different characteristics due to pregnancy-related changes in blood volume, cardiac output, protein composition, or overall metabolism. Moreover, the possible effects of rapid lipid infusion on uteroplacental circulation and drug exchange are unknown. This is certainly an area ripe for basic laboratory investigation.

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### **Dosing and resuscitation guidelines**

The 2010 ASRA practice advisory on the management of local anesthetic systemic toxicity suggests the following infusion of 20% lipid emulsion (values in parenthesis are for a 70-kg patient) as a therapeutic antidote [11<sup>••</sup>]:

- (1) Bolus 1.5 ml/kg (lean body mass) intravenously over 1 min (~100 ml).
- (2) Continuous infusion at 0.25 ml/kg per min (–18 ml/min, adjust by roller clamp).
- (3) Repeat bolus once or twice for persistent cardiovascular collapse.
- (4) Double the infusion rate to 0.5 ml/kg per min if blood pressure remains low.
- (5) Continue infusion for at least 10 min after attaining circulatory stability.
- (6) Recommended upper limit: approximately 10 ml/kg lipid emulsion over the first 30 min.

An initial intravenous bolus of 1.5 ml/kg (lean body mass) should be administered over 1–2 min and repeated after 5 min if there is no clinical improvement after the first bolus. The first bolus is generally followed by a continuous infusion at a rate of approximately 0.25 ml/kg per min (lean body mass) for 10 min after establishing stable vital signs. The current recommendations give a total dose limit recommendation of 10 ml/kg over the first 30 min. It is not known how this dose limit would be affected in pregnancy. Age of the patient, pre-existing conditions, site of the injection, and presence or absence of epinephrine are also variables that may influence the maximum total dose of lipid, as well as local anesthetic pharmacokinetics [24]. The goal in setting a dose limit is to provide sufficient lipid for resuscitation but avoid any adverse reactions due to patient overload of either volume or lipid.

Lipid therapy is not a substitute for Advanced Cardiac Life Support (ACLS) or standard resuscitation techniques. Early recognition of the problem, in addition to prompt and effective airway management, is the most important step in treating severe LAST. Successful ILE in the pulseless patient also requires high-quality Basic Life Support (BLS) to assure circulation of the lipid bulk to the coronary circulation. Inadequate resuscitation can result from poor airway management and secondary inadequate oxygenation and ventilation. The parturient may be especially vulnerable to hypoxia in the latter half of pregnancy, as a gravid uterus pushes the diaphragm more cephalic, reducing maternal functional residual capacity.

The specific exigencies of resuscitation during pregnancy are addressed at length in the American Heart Association/Advanced Cardiac Life Support (AHA/ACLS)

guidelines for resuscitation in special situations (part 12.3) [25<sup>••</sup>]. Patient positioning for left uterine displacement is one important BLS modification that can reduce aortocaval compression syndrome, resulting in improved maternal hemodynamics and cardiopulmonary resuscitation quality. The recommended left-lateral tilt position may be accomplished manually or by placement of wedge support. As a result of the mother's elevated diaphragm, chest compressions should be performed higher on the parturient sternum and a reduction in ventilation volumes may be necessary. Bag-mask ventilation with 100% oxygen before intubation is emphasized because airway management of the parturient may be difficult due to pregnancy-related changes in airway mucosa, size, and significantly faster desaturation [26–29]. Resuscitation team leaders are encouraged to activate the protocol for emergency cesarean delivery as soon as cardiovascular instability is identified to ensure that delivery occurs within a 4–5-min window after the mother's heart stops. Expedient perimortem cesarean delivery not only improves infant survival rate, but may also prove life-saving to the mother – a benefit unappreciated by many clinicians [30]. Several cases [23<sup>•</sup>,31,32,33<sup>•</sup>,34] have reported spontaneous circulation and improved maternal hemodynamic status only after emptying the uterus, and there are no reports of worsened maternal status after cesarean section [34].

Concern over the difficulties and delays associated with parturient transport to the operating room for emergency cesarean delivery has sparked discussion as to whether maternal resuscitation should ever be intentionally delayed to expedite fetal delivery [35]. One letter in particular [36] addressed the merits of urgent cesarean delivery in nonoperating room locations. Although some obstetricians believe that perimortem delivery always merits transfer to the operating room, a crash cesarean delivery in the labor room may optimize maternal survival by allowing maternal resuscitation and fetal delivery to be accomplished simultaneously. Given the narrow 5-min window between maternal arrest and infant delivery, urgent cesarean delivery in nonoperating room locations is an alternative that must be re-emphasized.

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### **Intravenous lipid emulsion safety**

A literature search revealed one documented instance of lipid resuscitation during pregnancy [37]. An 18-year-old primigravida presented at 38 weeks gestation for induction of labor when an inadvertent intravenous bupivacaine injection led to central nervous system toxicity. The patient became hypertensive, tachycardic, agitated, and subsequently unresponsive. Although the crash cart was being brought into the labor ward, the anesthesiologist elected to begin ILE therapy. Within 30s the patient regained full consciousness and was transported

to the operating room. This case supports the merits of lipid resuscitation in the pregnant patient, but additional cases will be necessary to fully determine its effects.

The upper limit for lipid administration is unknown, but there has been concern that pulmonary or neurological complications could result from high volume infusions. A recent study by Hiller *et al.* [38] has preliminarily addressed the question of maximum dose in a rat model of lipid infusion. Results demonstrated normal tissue histology after administration of 20% lipid emulsion at volumes nearly one order of magnitude above typical doses reported in the literature ( $\sim 4$  ml/kg). The LD50 for a 30-min infusion was 67 ml/kg. It is not clear how to translate this value to a well tolerated maximum human dose, but these data suggest that there is a substantial margin of safety in ILE, particularly considering that it is generally used in settings where life (here, of both mother and child) are at stake. [11\*\*].

Another key issue is whether adverse reactions may develop from the coadministration of lipid and other medications. A recent study addressed the effects of an epinephrine injection during concomitant lipid resuscitation in a rat model of bupivacaine overdose [39]. Interestingly, a threshold effect was observed. Doses of epinephrine above 10  $\mu$ g/kg were found to impair lipid resuscitation from bupivacaine overdose, possibly by inducing acidosis and hyperlactatemia. There is a possibility that other medications could impair lipid resuscitation, but it should be noted that ILE does not produce adverse effects when administered with sodium bicarbonate, atropine, or calcium [40,41]. Nonetheless, drug interactions remain a consideration when administering lipid.

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### Potential complications during pregnancy

It is important to consider the possible complications due to lipid administration for both mother and fetus. The only case of lipid resuscitation in the parturient supports its efficacious role and does not discuss any adverse effects from its use [37]. As randomized controlled trials are not feasible, we are forced to speculate about potential complications in light of previous studies. Pregnancy outcomes after administration of total parenteral nutrition to pregnant women may provide some insight into the effects of lipid infusion for the purpose of toxicity reversal. One study used ultrasonography to track fetal growth during a course of total parenteral nutrition in malnourished women [42]. Results indicate that total parenteral nutrition promoted fetal growth, in addition to reversing maternal malnourishment.

Another study looked at the effects of parenteral nutrition on the placenta [43]. Twenty cases of maternal hyperalimentation with lipid emulsions were described, with

each woman having a normal placenta. However, in the case of a 31-year-old pregnant woman who had received total parenteral nutrition with daily lipid emulsions for 8 weeks, placental fat deposits were noted before intra-uterine fetal death was diagnosed at 22 weeks gestation. This is the only reported case of placental fat deposition. Certainly, future laboratory studies are needed to gain insight into the potential impact of lipid administration on uteroplacental circulation.

The potential association between neonatal lipid infusion and the presence of pulmonary lipid emboli has been observed. Using a lung-staining technique on post-mortem neonatal necropsy specimens, one study found lipid occlusion of small pulmonary capillaries in 15 of 30 infants who had received parenteral feeding, including intravenous lipid [44]. Another study assessed pulmonary lesions and parenteral nutrition in children admitted to the pediatric intensive care unit. These results indicated that lung injuries were significantly more frequent in children who had received total parenteral nutrition [45]. However, the authors state that it was impossible to conclude that the lipid infusion had a direct relationship with these injuries because there were many other significant cofactors.

These potential complications raise questions about the timing of lipid resuscitation in the parturient and whether the infant should be delivered, if possible, before administering lipid. Notably, AHA/ACLS guidelines support expeditious perimortem cesarean delivery to promote both fetal and maternal survival [25\*\*,30]. Maternal resuscitation and cesarean delivery should occur simultaneously, so total fetal exposure to lipid would likely be very short, if at all. Anxiety over possible lipid deposits therefore seems unreasonable and should not preclude the use of lipid resuscitation as a means of treating LAST during pregnancy. In successful resuscitation of the parturient, it is important to remember that the best hope of fetal survival is maternal survival.

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### Implementation and training

The first step to reducing the LAST-associated morbidity and mortality in the parturient is the education of obstetric care providers. Recent studies indicate that providers are unaware of the special considerations for resuscitation of the parturient [30,46]. Educational programming provides a valuable tool that may profit in improved patient safety. Advanced scenario simulation training may also facilitate prevention, detection, and management of LAST, according to a recent case report by Smith *et al.* [47]. Their description of the sequence of events following local anesthetic injection details events in a real patient shortly after the team had simulator training on LAST. The patient lost consciousness then

developed a generalized tonic-clonic seizure and asystolic cardiac arrest. The team quickly began cardiopulmonary resuscitation and ILE administration, with the patient soon converting to normal sinus rhythm and regaining consciousness. The authors attribute their early, successful management to the previous simulation training focused on preparing clinicians to recognize and treat potentially fatal toxicities with innovative treatments in the setting of supportive ACLS measures and coordinated team efforts.

## Conclusion

Lipid resuscitation has emerged as a promising solution to local anesthetic toxicity refractory to conventional modes of resuscitation. The 2010 ASRA practice advisory on the management of LAST [11\*\*] endorses the therapeutic use of ILE and provides recommended dosing guidelines. The clinical success of ILE suggests that this treatment modality can assist in reducing the likelihood of maternal death and major morbidity secondary to LAST. Obstetric care providers should be aware of lipid resuscitation and consider its use in conjunction with current AHA/ACLS guidelines for resuscitation of the pregnant patient [25\*\*]. We emphasize the need for effective airway management, controlling for lean body mass in lipid dosing, and urgent cesarean delivery without compromised maternal resuscitation.

Case reports and bench research together have guided our current treatment of local anesthetic toxicity and will continue to provide insights into the scope of its use. Physicians have the responsibility to document all cases of lipid resuscitation at the educational sites [www.lipidrescue.org](http://www.lipidrescue.org) and [www.lipidregistry.org](http://www.lipidregistry.org) so that retrospective and prospective data analyses may be possible. Future laboratory studies and the development of more comprehensive registries are also crucial for evaluating the efficacy and potential side-effects of lipid resuscitation in pregnancy. Specifically, the effects of ILE on uteroplacental circulation should be studied, as well as the mechanisms, dosing, and timing of ILE in the parturient.

Many operating rooms and labor suites have made lipid kits available. This case of rapid adoption and implementation of ILE suggests that national guidelines, editorials, and scientific articles may motivate its introduction [48]. We anticipate that future reports will shape the evolving recommendations for local anesthetic toxicity and support the development of clinical guidelines specific for lipid resuscitation during pregnancy to help reduce confusion among obstetric care providers, as well as provide a motivating force to make lipid kits available. Enhanced parturient sensitivity to LAST is a long-recognized and deadly challenge,

but lipid resuscitation may be a life-saving tool to control anesthesia-related morbidity and mortality during pregnancy.

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## References and recommended reading

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- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 355).

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