

Neuromuscular blocking agents and pregnancy

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Up to 2% of pregnant women have surgery during their pregnancy.¹ The anesthetic technique must take into account the physiological and anatomical changes associated with pregnancy and attempt to limit any disturbances in fetal-maternal homeostasis. When possible, loco-regional anesthesia will address these concerns, however, certain situations necessitate the use of a general anesthetic. Often forgotten in this context are the muscle relaxants, on which little has been published.

THE TOXICITY OF MUSCLE RELAXANTS

During pregnancy, the toxicity of a drug may manifest itself because it has teratogenic effects or because it contributes to late spontaneous miscarriage or the risk of premature delivery.

Teratogenic risk

The risk of teratogenic effects is much greater if drug exposure occurs between the 13th and 55th day of gestation. This is the embryogenic period, when individualization of the different organs begins. A study of the literature between 1983 and 2001 indicates that there were no articles published on the teratogenic effects of neuromuscular blocking agents in humans. While many animal studies are available,^{2,3} none has demonstrated the teratogenic effects of muscle relaxants *in vivo*. One *in vitro* study in rats described the appearance of many malformations; however, the embryos were exposed to muscle relaxant concentrations that were 30 times higher than those used in clinical practice.³

These data are reassuring, but do not allow us to formally conclude that neuromuscular blocking agents are safe in pregnant women. Given the rarity of events, follow-up studies on drug monitoring may provide some answers. Unfortunately, the case against neuromuscular blocking agents is weak because, in clinical practice, these agents are never used alone.

Late spontaneous miscarriage and the risk of premature delivery

Two large-scale studies^{1,4,5} examined fetal development in women who had undergone surgery during pregnancy. They did not reveal an increase in the number of fetal malformations or stillborn infants. On the other hand, the authors observed a higher risk of miscarriage, delayed development, or low birth weight (<2500 gr.). In women who underwent an appendectomy after the 23rd week of amenorrhea, the authors observed an increased risk of miscarriage in the first postoperative week; but thereafter, the risk of abortion was comparable to that in the pregnant population in general. No anesthetic agent was specifically implicated. The cause of these events was not identified, but was certainly multifactorial, including the pathology requiring the surgery, the mechanical impact of surgery, and associated medical therapy.

CHOOSING A NEUROMUSCULAR BLOCKING AGENT FOR INTUBATION

Hindrances to intubation in the pregnant woman

During the course of pregnancy, many physiological changes occur. These are due partly to hormonal modifications and partly to the increased size of the uterus, and make the patient particularly vulnerable during induction of anesthesia and control of airways (Table 1).

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TABLE 1: Principal physiological changes in pregnancy making anesthesia induction particularly risky

<p>Cardiovascular system:</p> <ul style="list-style-type: none">• Increase in cardiac output (especially the stroke volume and, to a lesser degree, the heart rate)• Increase in blood volume associated with dilution anemia (preponderant increase in plasma volume)• Aorto-caval compression by the gravid uterus. <p>Respiratory system:</p> <ul style="list-style-type: none">• Decrease in functional residual capacity• Increase in alveolar ventilation• Increase in oxygen uptake <p>Digestive system:</p> <ul style="list-style-type: none">• Decreased tonus of lower esophagus• Opening of angle of His• Increase in intragastric pressure

It is difficult to precisely date the moment when these physiological changes influence anesthesia management.⁶ Nevertheless, the constraints on intubation are well defined. During intubation, the anesthesiologist is confronted with a three-fold problem: a patient with limited oxygen reserves, a full stomach, and with changes in their airways.

The modifications in the airways may be rapid, even during labour itself.⁷ The incidence of difficult intubation was estimated to be 8 times higher in the pregnant woman than in the general population.⁸ In women in labour receiving a general anesthetic, Hawkins *et al* observed that the cause of death in 3 of 4 cases was related to the difficulty in providing oxygen to the patient.⁹ In this study, the difficulty was related to the inhalation syndrome in 33% of cases and a difficult intubation in 22% of cases. Using a neuromuscular blocking agent to intubate a pregnant woman should produce ideal conditions as quickly as possible, as well as allow a rapid return to spontaneous ventilation should the intubation be unsuccessful.

Choosing a neuromuscular blocking agent to facilitate intubation

No nondepolarizing neuromuscular blocking agent can meet all the criteria previously described. Hawkins *et al* studied the onset of action of vecuronium in 21 patients having a cesarean section.¹⁰ Two doses were studied: 100 µg/kg preceded by a low dose of 10 µg/kg versus 200 µg/kg. In both groups, the onset of action, defined by the 100% disappearance of a single twitch was on average <3 minutes. Patients were intubated under conditions deemed to be excellent in 19 of 21

cases. The duration of action for both doses of vecuronium (return to 25% of the initial twitch height) were 73 and 115 minutes, respectively.

In another obstetrical study, Abouleish *et al*¹¹ demonstrated that a dose of 0.6 mg/kg (ED₉₅ x 2) of rocuronium permitted optimal intubation in 36 of 40 patients in <90 seconds (82.6 ± 4.3 seconds). In this study, the action duration of rocuronium (reappearance of the second twitch on the train-of-four response) was 32.7 ± 1.8 minutes.

Finally, Pan *et al*¹² demonstrated that for an immediate postpartum laparoscopy, a dose of 0.2 mg/kg (ED₉₅ x 4) of cisatracurium provided intubation conditions deemed acceptable at 90 seconds. The action duration of cisatracurium (return of the initial value of single twitch height to 25%) was 60 ± 6.3 minutes.

Therefore, none of the nondepolarizing neuromuscular blocking agents described above allows rapid intubation while maintaining a limited duration of action. They are not ideal when one considers the constraints on intubating the pregnant women.

On the other hand, succinylcholine, at a dose of 1 mg/kg, provides good conditions for intubation in 60 to 90 seconds and has an average duration of action of 470 seconds.¹³ It appears that succinylcholine is the only agent that is able to provide quality intubation conditions in < 90 seconds and a limited duration of action.

THE USES AND LIMITATIONS OF SUCCINYLCHOLINE

Dosing and practical use

Succinylcholine is hydrolyzed by plasma cholinesterase. During the first trimester of pregnancy, cholinesterase diminishes by about 30%, reaching its lowest level in the second trimester. Paradoxically, the onset and duration of action of succinylcholine remain unchanged. This may be explained by an increase in distribution volume. However, values of the distribution volume, distribution at equilibrium, and succinylcholine's central compartment volume remain unknown.

The decrease in cholinesterase, on the other hand, suggests a decrease in dosing during induction. Doses should not exceed 1 mg/kg, or even 0.7 mg/kg. With higher doses, there is the risk of prolonged apnea and a Phase II block.¹⁴

The injection of succinylcholine is followed by involuntary contractions that may cause pain. In the general population, a prior injection of a low dose of a nondepolarizing neuromuscular blocking agent will help decrease this side effect. However, a comparative study reported no benefit from this practice in preventing pain in pregnant women;¹⁵ therefore, it cannot be recommended. Furthermore, the injection of a low dose of nondepolarizing neuromuscular blocking agent may lead to early muscular relaxation and alter the quality of preoxygenation.¹⁶

Although its action is limited to striated muscles, the possibility that succinylcholine affects the uterine muscle has been reported. However, an increase in intrauterine pressure (with risk of fetal distress) following an injection of succinylcholine has not been proven.¹⁷

Contraindications to succinylcholine

Succinylcholine is formally contraindicated in patients susceptible to malignant hyperthermia. Likewise, given the risk of severe hyperkalemia, it should not be administered to patients suffering from a disorder involving membrane fragility as it may predispose them to rhabdomyolysis (muscular dystrophies, severe trauma). Succinylcholine should not be given to patients who have been receiving neuromuscular blocking agents for several days. The onset of hyperkalemia has been reported in pregnant women who were bed-ridden for several days and receiving tocolytic treatment with magnesium sulphate and ritodrine.¹⁸ In these situations, the agent of choice for induction is rocuronium since it is the only nondepolarizing agent that allows rapid intubation.

Traditionally, succinylcholine is contraindicated in subjects with a qualitative or quantitative deficit in plasma cholinesterase because of the risk of prolonged paralysis. Prolonged muscular relaxation may then necessitate ventilation of the mother and/or child for a number of hours. The administration of succinylcholine in these patients is unjustified since the benefit of a short-action duration is lost.

In general, airway management during pregnancy is difficult. To date, succinylcholine is the only agent that satisfies the requirements imposed by the constraints on intubation in pregnant women. In cases where there are formal contraindications to succinylcholine use, rocuronium is the best alternative.

NEUROMUSCULAR BLOCKING AGENTS FOR MAINTAINING ANESTHESIA

During pregnancy, just like in the general population, the choice of a muscle relaxant depends on the type of surgery. When anesthesia is required, the choice of a muscle relaxant depends on its duration of action in relation to the surgery and patient characteristics. Pregnancy causes metabolic changes likely to influence the pharmacokinetics and pharmacodynamics of muscle relaxants. Obstetrical surgery (cesarean section) requires special consideration because, in addition to the usual criteria for choosing a neuromuscular blocking agent, the possible effects on the neonate must be recognized.

Anesthesia in nonobstetrical surgery

Studies have been conducted primarily during the third trimester (cesarean) and in the immediate postpartum period. This latter period represents an ideal window

of study because many of the changes caused by pregnancy are still present, but there is no longer a fetal risk.

The pharmacokinetics of atracurium do not change in pregnant women because of its metabolism (hydrolyzed by nonspecific esterases and degradation by Hoffman's elimination). Pharmacodynamically, the duration of action of this agent in the pregnant woman does not appear to be increased (postpartum 37 ± 4 minutes versus nonpregnant 36 ± 6 minutes) when used at a dose of 0.5 mg/kg.¹⁹ Cisatracurium (0.2 mg/kg), also degraded via Hoffman elimination, has a shorter duration of action in postpartum women than in the general population (60.0 ± 12.3 min vs 69.1 ± 6.3 min).¹² The authors offer several explanations for this observation (eg, partial clearance of cisatracurium may be via the kidneys, while respiratory alkalosis in the pregnant woman may favour Hoffman elimination). Mivacurium, with a short duration of action, is metabolized by plasma cholinesterase and, in the postpartum period, its duration of action is lengthened.²⁰ Vecuronium and, more recently, rocuronium, have been the subject of numerous studies in pregnant women. During a cesarean section, the duration of action of vecuronium ranges from 31.4 ± 1.5 minutes to 115 ± 19.0 minutes after 1 to 4 ED₉₅ bolus doses.^{10,21} During pregnancy, the elimination half-life of vecuronium is decreased and its clearance increased.²² There is no unequivocal explanation for this paradox in the literature. Rocuronium has been studied in pregnant women, but only at a dose of 0.6 mg/kg (ED₉₅ x 2). The duration of action of rocuronium (evaluated by the return of a T2 in the train-of-four) was 32.7 ± 1.8 minutes, comparable to observations in the nonobstetrical population.¹¹

Generally, the pharmacodynamics of most muscle relaxants are modified during pregnancy. However, these changes, considered independently, would not lead to favouring one molecule over another. On the other hand, strict monitoring of muscle paralysis is imperative to guide for an eventual reinjection or the use of an antagonist. Given the circumstances (full stomach, airway modifications), a complete return of the protective oropharyngeal reflex on recovery is indispensable. All patients paralyzed with a nondepolarizing neuromuscular blocking agent should receive an anticholinesterase preparation, accompanied by an anticholinergic, glycopyrrolate or atropine.

Anesthesia for cesarean sections

The choices of general anesthesia for cesarean sections have been established to allow for extraction of the fetus as quickly as possible, while minimizing the effects of the agent on the neonate. After induction, anesthesia is usually maintained by a halogenated agent, with or without nitrous oxide. This type of anesthesia causes only mild muscle relaxation and the use of

TABLE 2: Advantages and disadvantages of nondepolarizing neuromuscular blocking agents during pregnancy

	Alternative to succinylcholine	Lengthening of action duration in full-term parturient	Residual paralysis of neonate: Observations published	Placental transfer	EC ₅₀ Ratio Mother/neonate
Atracurium	NO	NO	YES	3-33%	6.5±0.7
Cisatracurium	NO	NA	NA	NA	5.8±0.5
Mivacurium	NO	NO	NO	NA	NA
Vecuronium	NO	YES	YES	11-14%	9.3±1.6
Rocuronium	±	±	NO	16%	12.5±1.4

NA: Data not available

a neuromuscular blocking agent may make the hysterotomy easier. The total duration of the surgery is about 1 hour. Based only on duration of action, all of the neuromuscular blocking agents of intermediate duration may be used for a cesarean, with the exception of vecuronium. This agent, particularly in high doses (ED₉₅ x 4), is not appropriate given the usual duration of the surgery.

Because they cross the placental barrier, neuromuscular blocking agents used during a cesarean expose the neonate to possible paralysis. The first studies conducted during cesareans concluded that neuromuscular blocking agents were safe for neonates. The authors used the Apgar score as a measurement tool for the neonate. Methodologically, this approach might be criticized because the Apgar score allows a determination whether resuscitation is necessary or not. The introduction of the Neurologic Adaptive Capacity Score (NACS),²³ created to determine the effects of anesthesia on neonates, made it possible to better assess the effects of neuromuscular blocking agents.

Perreault *et al*²⁴ demonstrated in 25 neonates that there was residual anesthesia after administration of atracurium, 0.3 mg/kg (ED₉₅ x 1.3) that was not detected by the Apgar score. At 15 minutes, the newborns had an altered NACS due to a decrease in the active tone of the flexor muscles in the neck (the muscle group classically tested with the head-lift test). Similarly, Hawkins *et al*¹⁰ reported that after administration of vecuronium (used for intubation), only 50% of neonates had a normal NACS at 1 hour. Again, the active muscle tone of the infants was altered. These effects, however, were not encountered after administration of 0.6 mg/kg of rocuronium.¹¹ In all the studies reporting the presence of residual paralysis, no specific resuscitation technique was needed for the neonate. Still, these effects should not be disregarded. In fact, all the patients in these studies had a scheduled cesarean

at full-term and the presence of fetal distress was a criterion for exclusion.

In determining which neuromuscular blocking agent has the least impact on the neonate, several parameters must be considered: the rate of placental transfer, the action of the agent on the endplate of the newborn, and the pharmacokinetics of the agent in the newborn. Fick's law governs the placental transfer of neuromuscular blocking agents by passive diffusion. Above a molecular weight of 500 daltons, transfer is incomplete and the maternal concentrations of the molecule are higher than those in the fetus. This difference in concentration is traditionally measured by the ratio between concentrations found in the uterine and the maternal veins. This ratio is not known for all the neuromuscular blocking agents, however, for atracurium, it is 3% - 33%,²⁵ vecuronium, 11% - 14%,^{10, 26} and for rocuronium, it is 16%.¹¹ This ratio may be influenced by many factors: free circulating fraction of the molecule, initial bolus dose, time of exposure of the placenta to the neuromuscular blocking agent (interval between the bolus and fetal extraction). The effect of the agent is thus influenced by the pharmacokinetics and pharmacodynamics relating to the fetus, which is particularly sensitive to the neuromuscular blocking agent.

An experimental study²⁷ conducted on rats demonstrated that the concentrations associated with a 50% block (EC₅₀) were lower in neonates than in adults. The EC₅₀ ratios (adult/neonate) were:

- 6.5 ± 0.7 for atracurium
- 5.8 ± 0.5 for cisatracurium
- 9.3 ± 1.6 for vecuronium
- 12.5 ± 1.4 for rocuronium.

For succinylcholine, the ratio was lower (2.9 ± 0.4), since the neonate is more difficult to paralyze with this product. Furthermore, the newborn can metabolize succinylcholine with its plasma cholinesterase, which is another advantage of

succinylcholine. There is no “ideal” neuromuscular blocking agent for maintaining anesthesia during a cesarean section; the advantages and disadvantages of each agent are listed in Table 2.

NEUROMUSCULAR BLOCKING AGENTS AND PATHOLOGIES DURING PREGNANCY

Many clinical situations are likely to interfere with and/or change how neuromuscular blocking agents act during pregnancy. When there is a risk of premature delivery, special attention must be given to the duration of bed-rest and tocolytic treatments. An enhancement of the effects of vecuronium has been described in the presence of salbutamol.²⁸ Also, an unpredictable increase in the duration of action for nondepolarizing neuromuscular blocking agents has been observed in the presence of magnesium sulphate.²⁹ In cases of pregnancy-related toxemia, the possibility of increased toxicity with laudanosine, a metabolite of atracurium, has been described.³⁰ However, the use of atracurium does not seem to be contraindicated in this situation.

IMMEDIATE POSTPARTUM ANESTHESIA

At induction of anesthesia during the postpartum period, the risk of inhalation appears to be theoretically lower since gastric emptying returns to normal 24 hours after delivery. Therefore, the systematic use of a rapid sequence induction beyond this period is not indicated. Also, during this period, a 1 mg/kg dose of succinylcholine has a slightly lengthened duration of action.¹³ Most of the pregnancy-induced changes take 6 to 8 weeks to completely regress.

With respect to maintaining anesthesia, the pharmacodynamic changes during the postpartum phase are more or less the same as during pregnancy, ie, for vecuronium and rocuronium, the duration of action is lengthened; it does not change for atracurium; and for cisatracurium, it is decreased. To our knowledge, there are no particular precautions associated with neuromuscular blocking agents with respect to breast-feeding.

PRENATAL FETAL SURGERY

Prenatal diagnostic techniques make it possible to recognize and precisely assess lesions that may be treated surgically. Generally, malformations are corrected after birth or, if the situation calls for it, following induced pre-term delivery. There is a small group of pathologies, however, where it is preferable to act prenatally (eg, obstructive bilateral hydronephrosis, diaphragmatic hernia, cystic adenoid malformations, large sacrococcygeal teratoma).

In the majority of techniques, fetal movement is an obstacle that can lead to complications. To eliminate this risk, fetal anesthesia is used. In a study by De Crespigny *et al*,³¹ a single intravenous dose of 0.1 mg/kg of pancuronium was administered; the average duration of the neuromuscular block was 210 minutes. Doses of 0.3 mg/kg lengthened the block up to 5, even 8 hours. However, the undesirable side effects of pancuronium (change in fetal heart rate and variability) have led to the use of other agents.

Another pharmacodynamic study³² suggests the administration of vecuronium, since it produces fewer hemodynamic side effects. It is likely that atracurium and rocuronium represent appropriate choices for these surgical techniques.^{33,34}

CONCLUSION

Loco-regional anesthesia is unquestionably the recommended anesthetic technique during pregnancy. In fact, there are few studies on muscle relaxants during pregnancy. To date, there are no studies on the fetal toxicity of neuromuscular blocking agents. Succinylcholine remains the agent of choice to assist in intubation during pregnancy. The use of a nondepolarizing neuromuscular blocking agent for anesthesia maintenance requires strict monitoring. In obstetrics, the use of a neuromuscular blocking agent exposes the neonate to partial paralysis that may be detected by a thorough clinical examination. Postpartum data obtained on cisatracurium makes it an interesting therapeutic choice; however, additional work is necessary before recommending its use during pregnancy.

Dr. Emmanuel Nouvellon was once a Fellow in the Department of Anesthesiology at the University of Montreal. He is now working at the Nîmes University Hospital, Nîmes, France.

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Abstract of Interest

Comparison of cisatracurium-induced neuromuscular blockade between immediate postpartum and nonpregnant patients

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STUDY OBJECTIVES: To evaluate and compare cisatracurium-induced neuromuscular blockade and intubating conditions between immediate postpartum (PP) and nonpregnant (NP) patients.
DESIGN: Prospective control study.

SETTINGS: University Hospital Center.

PATIENTS: 44 ASA physical status I and II patients: 22 immediate postpartum (PP) patients (<48 hours after delivery) scheduled for elective postpartum tubal ligation and 22 nonpregnant (NP) patients (>40 weeks from prior pregnancy) scheduled for elective gynecological procedures.

INTERVENTIONS: General anesthesia was induced intravenously (IV) with thiopental sodium 5 mg/kg, fentanyl 2.0 to 3.0 ug/kg, midazolam 0.015 to 0.025 mg/kg, and cisatracurium 0.2 mg/kg. Evoked electromyographic responses of the adductor pollicis muscle were obtained by supra-maximal train-of-four stimulation of the ulnar nerve every ten seconds via surface electrodes at the wrist. Intubation was attempted at 90 seconds after completion of cisatracurium administration and again at 120 seconds if the first attempt was unsuccessful. The intubating anesthesiologist assessed the intubating conditions with four variables: jaw relaxation, vocal cord immobility and exposure, patient/diaphragmatic movement, and overall intubating impression. Intraoperative anesthetic was maintained with 30% oxygen, 70% nitrous oxide, and 1% end-tidal isoflurane, as tolerated. Patient temperature was maintained at 35.5 degrees to 37.5 degrees Celsius (C), and end-tidal carbon dioxide at 30 to 36 mmHg.

MEASUREMENTS AND MAIN RESULTS: The mean onset times to 50%, 90%, and maximal T(1) depression and mean time to 25% T(1) recovery in the PP group (68 +/- 19 sec, 110 +/- 26 sec, 147 +/- 32 sec, 60 +/- 6 min) were significantly less than those in the NP group (80 +/- 17 sec, 131 +/- 28 sec, 181 +/- 44 sec, 69 +/- 12 min), respectively (p < 0.05). All patients were successfully intubated on the first attempt at 90 seconds. 91% of the NP group and 81% of the PP group had excellent overall intubating conditions.

CONCLUSIONS: This is the first published control study to compare the effects of cisatracurium between NP and PP patients. The results suggest that the mean onset time and clinical duration of cisatracurium are significantly shorter in immediate postpartum patients than those in nonpregnant female patients.

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