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ANESTHESIA FOR CESAREAN SECTION: CURRENT TRENDS

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Cesarean section (C-S) is one of the most common operations in the world, with a current average rate of 21.1%, which means that one in 5 pregnant women delivers in this way. The percentage of C-S is different around the world and varies widely, from an average of 5% (sub-Saharan Africa) to 42.8% in Latin America and the Caribbean. At the global level, the trend of C-S is constantly increasing and it is estimated that by 2030, 28.5% of pregnant women in the world will be delivered with C-S. This means that even now, and even more in the future, a huge part of the population will be exposed to surgical termination of labor, which dictates that the risk of operative morbidity and mortality should be minimized, along with the possibility of other complications related to C-S. Furthermore, unlike spontaneous delivery, where there is no need for anesthesia and the presence of an anesthesiologist, the increasing number of C-Ss globally, implies that it will very likely have an impact on the workload of obstetric anesthesiologists in general, as well as their increased demand (1).

Although the choice of general, endotracheal anesthesia (GA) is a risky choice for C-S, it cannot be completely excluded from use, especially in emergency situations or the presence of contraindications for the performance of neuraxial anesthesia. The primary area of concern with the use of GA in pregnant women are the possible complications during the induction of endo-tracheal anesthesia as well as the risk of difficult or impossible intubation. It is generally accepted that pregnant women have a higher risk of difficult or unsuccessful intubation with rapid development of hypoxemia, as well as the risk of aspiration of gastric contents; the failed intubation in obstetrics is higher than in the nonpregnant, whereas the aspiration pneumonitis, although rare, is one of the most serious complications associated with GA for C-S (2,3,4). In a recent multicenter observational study in a series of over 2500 C-S deliveries, the incidence of failed intubation was reported to be 1:312 (5); in addition, specific changes in the respiratory system (reduced FRC, increased minute ventilation and metabolic index) put the pregnant women at risk of rapid onset of deep hypoxemia, incomparable to other surgical patients (6); from that aspect, the possibility of increasing oxygen reserves in pregnant women during the preoxygenation phase with the help of high-flow nasal oxygen (HFNC, with max. 60 L/min) is considered by some to be justified and necessary, but its definitive application in practice remains to be confirmed (7,8). Considering these facts, in less developed countries, exposure to GA for C-S triples the odds of maternal mortality and doubles the odds of perinatal mortality, so off-label general endotracheal anesthesia should be avoided whenever possible, because apart

from the association with higher mortality, it is also associated with a higher risk of morbidity as a result of numerous anesthetic complications, including surgical infections, venous-thromboembolic complications, etc. (9,10).

Indications where GA is considered "unavoidable and necessary", including obstetric indications (postpartum hemorrhage), certain contraindications to the performance of neuraxial analgesia (anticoagulation or coagulopathy) as well as the refusal of pregnant women for regional anesthesia, are still the most common indications for C-S and nowadays. Pregnant women with urgent obstetric indications for C-S, such as placental abruption, prolapsed umbilical cord, antenatal placental hemorrhage, fetal distress, fall under greatest risk for GA, where rates for GA (of this type of emergency) climb to 20%. However, several professional associations believe that the average rate of pregnant women delivering with GA for C-S should be less than 5% (SOAP), and others recommend that it should be lower than 1% for elective C-S and less than 5% for emergency deliveries (RCOA) (11,12,13).

In the last decade, the positive experiences with the application of supraglottic devices and especially video laryngoscopy in the field of obstetric anesthesia are becoming numerous and clear, and the benefits became evident. The invention of the GlideScope and its competitors, the C-MAC, King Vision, McGrath, and Airtraq video laryngoscopes, represented a major advance in the field of difficult airway treatment, whereas the popularity of fiberoptic intubation slowly declined, along with the availability of video laryngoscopy. Today, safety standards are at a higher level, and from that point of view, the Association of Obstetric Anesthesiologists and Difficult Airway (OAA,DAS) recommends that every physician performing laryngoscopy for endotracheal intubation should have immediate access to a video-laryngoscope as a backup option in case of difficult intubation. Moreover, the application of video laryngoscopy in obstetric anesthesia is already recommended by some centers as the first attempt at intubation with general anesthesia for C-S, instead of direct laryngoscopy (14).

GA at labor is associated with worse outcome in newborns compared with neuraxial anesthesia (15,16). Despite allowing the shortest period of time to surgical incision in emergency C-S deliveries, GA is not associated with better neonatal outcomes, as evidenced by several studies (17). More recently, questioners have arisen regarding maternal exposure to GA and the possibility of potential complications in the newborn in later development; the risk of fetal neurotoxicity with neurological consequences of short or long-term type is mentioned. However, these studies do not have evidentiary evidence for such accusations yet (18,19,20).

When applying GA for C-S, anesthesiologists should pay more attention to the depth of anesthesia, because the period until cord clamping and fetal extraction is vulnerable (opioid analgesics and other depressants are avoided) and may lead to a higher incidence of mother awareness, compared to other surgical procedures. Although rare, the consequences of intraoperative awareness after C-S can be serious, commonly including post-traumatic stress disorder and sleep-disturbances . Careful titration of doses and gas delivery, as well as the ability

to monitor the depth of anesthesia, help to prevent complications; there are views that an initial dose of propofol of 2.5 mg/kg is sufficient to prevent maternal awareness during C-S, although it causes worse fetal effects and a greater reduction in blood pressure compared to thiopental, e.g. (21,22).

For over 50 years the use of succinylcholine as an induction agent for C-S continues, primarily due to its rapid onset and ultra-short duration, but the severity of its side effects and the need for more advanced drugs, lead to searching for a new alternative of neuromuscular relaxant for rapid-sequence intubation (RSI) in C-S. In that context, parallel to the emergence of sugammadex, rocuronium starts to replace succinylcholine as the first choice in obstetric patients for C-S, whereas the exact dose for that purpose is still debatable. However, used under normal circumstances, it seems that a dose of 1,0 mg/kg is an appropriate intubation dose for C-S (23). Sugammadex, as a long-awaited agent for the reversal of neuromuscular paralysis, reached the market in 2016 and according to several analyses, the drug is well accepted; it reverses rocuronium paralysis in less than a minute, almost as quickly as succinylcholine does, and also eliminates complications caused by residual muscle paralysis. Time and experience show that its (combined) application for endo-tracheal intubation in C-S nowadays finds justification.

More recent research reports that maintenance of anesthesia, can also be achieved with total intravenous anesthesia (TIVA), which can replace inhalation anesthetics, among other, because of the lower degree of uterine relaxation enabled by propofol as the only hypnotic that should be used in TIVA for C-S. Dexmedetomidine has recently been reported to improve oxytocin-induced uterine contractility after delivery, and thus its positive effect on postpartum blood loss, so it is expected that its use in the maintenance of anesthesia after fetal extraction will become more frequent 24).

Neuroaxial anesthesia for C-S: The superiority of neuraxial anesthesia for elective C-S over GA has been proven and established, and it continues to be the main, gold approach for C-S delivery (25). Avoidance of the risks inherent in airway manipulation, and in particular the "can't intubate, can't ventilate, can't oxygenate" scenario, has contributed to the widespread use of neuraxial techniques in obstetric anesthesia. It is generally associated with better maternal and fetal outcomes, i.e.it is attributed to improved postoperative analgesia, less blood loss, and overall greater satisfaction among parturient compared to GA (1). It could be a more desirable choice than GA from both a social and emotional point of view, because the parturient is fully aware and experiences the newborn delivering(the partner should be encouraged to be present in the operating room), and the skin-to-skin contact is established quickly, i.e., immediately after delivery.

The choice of neuraxial anesthesia for elective C-S mainly lies in spinal, epidural or possibly combined spinal-epidural anesthesia, but spinal-intrathecal is the most commonly used technique for C-S, which provides a rapid onset of action and an efficient and reliable anesthetic block. The

duration of spinal anesthesia is variable and depends on the drugs used, but usually adequate surgical anesthesia is achieved in about 90 min., enough to perform C-S.

Hyperbaric spinal anesthesia with 0.5% bupivacaine (10-15 mg) in a combination with opioids remains the gold standard for elective C-S, although some clinical effects cannot be fully predicted. The challenge of spinal anesthesia lies in the balance between the lowest possible dose that produces adequate surgical anesthesia and minimal side effects, especially spinal hypotension and the risk of inadequate anesthesia. A meta-analytic study evaluated that hyperbaric 0.5% bupivacaine at low doses (≤8 mg) led to a significant reduction in intraoperative hypotension and nausea and vomiting, but this advantage was negated by a significantly increased need for additional analgesia and the need for conversion to GA (26); therefore, if a low dosage, ≤ 8mg, is chosen, it mandates the use of a combined spinal-epidural technique (CSE), in order to allow prolongation or deepening of anesthesia, if necessary. The difference in the therapeutic profile between the opioids allows the option of an intrathecal combination of fentanyl and morphine as an adjunct to the local anesthetic. A dose of fentanyl (15-20 μg) would supplement local anesthetic effects and analgesia during the operative procedure, while morphine (50-150 μg) would provide long-lasting postoperative analgesia (13-33 h). The addition of long-acting opioids is the basis of postoperative analgesia in C-S and is recommended from the international guidelines (SOAP, ERAS, PROSPECT); The American Society of Obstetric Anesthesiology and Perinatology (SOAP) recommends that at low doses of intrathecal morphine in healthy pregnant women (0.05-0.15 mg; ED 1-3 mg), respiratory monitoring (O2 saturation) is not required, but only monitoring the respiratory rate and the level of sedation, the first 12 h; more frequent and prolonged monitoring (O2 saturation) is recommended only in those at high risk of respiratory depression, such as the obese, parturient with obstructive sleep apnea, preeclampsia or those who receive additional sedatives, opioids, Mg, GA, etc. (27,28).

More recent studies show that compared with fentanyl (meta-analysis, 639 patients), dexmedetomidine as an adjuvant to spinal anesthesia in surgical patients prolongs the duration of spinal anesthesia, improves postoperative analgesia, reduces the occurrence of pruritus, and does not increase the frequency of hypotension and bradycardia (29); another meta-analytical study (278 pregnant women), which refers to obstetrical patients exposed to C-Sin bupivacaine spinal anesthesia, shows that dexmedetomidine as a spinal adjuvant at local anesthetic, can effectively reduce the occurrence of shivering without causing nausea and vomiting; in addition, bradycardia and hypotension are not incease indicating that its spinal administration during pregnancy has a stable effect on hemodynamics, with fewer side effects (30).Additionally, more recent clinical studies of obstetric spinal anesthesia with prilocaine report that hyperbaric (2%) prilocaine, compared with bupivacaine, induce more reliable but shorter motor block, faster recovery, and more stable hemodynamics in healthy pregnant women (31,32).

The performance of spinal anesthesia is technically easier than the epidural one and, in most cases, the help of additional technology is not required. However, in the last decade, the use of ultrasound (US) in regional anesthesia is becoming a widespread practice, and the analysis of the

economic and overall benefits is going in a positive direction. US is also widely used in obstetrical anesthesia, both for identification of the lumbar space (especially for pregnant women with problematic anatomy, obesity, scoliosis, etc.), and for scanning the fascial blocks (TAP and QLB) in accordance with multimodal treatment protocols for postoperative pain in C-S. The first-attempt success rate of ultrasound-guided obstetric epidurals has been reported to be 30-60% higher compared to the traditional method, and the inclusion of US in lumbar scanning in daily clinical practice in pregnant women is thought to be beneficial and could significantly improve the success of epidurals and thus the safety and comfort of parturient undergoing C-S (33,34).

Neuraxial anesthesia for emergency C-S: recently it has been reported that in emergency C-S, in the lack of time, standard spinal anesthesia can be transformed into the so-called rapid sequence spinal technique (RSS), which is actually a simplified and accelerated spinal procedure, with the goal of avoiding the risk of GA (35). Rapid sequence induction for GA is the fastest technique for anesthesia in C-S for fetal distress (category 1), but the goal of RSS is also to quickly and safely achieve anesthesia for C-S cat.1, without further compromising of fetal oxygenation and be prepared for eventual GAin case of failure. Training of junior anesthetists and obstetric ward staff in the implementation of RSS is crucial in order to ensure rapid and safe practice, avoid any unnecessary delay and safely avoid the risks associated with GA in C-S cat.1. It involves training and performing a series of rapid planned procedures that include, among others: no-touch technique, rapid and shortened field disinfection, omission of spinal opioid (higher dose of anesthetic), limitation of spinal attempts, allowing surgery to begin before full recovery and checking the block, simultaneous preparation for conversion to GA if there is a need, etc. Performing RSS anesthesia safely and promptly is a cooperative team action that requires adequate plan of action, with proper training preparation and practice.

C-S in pregnant women with a previous labor epidural: It is a common practice to "top up" the epidural to convert labor analgesia to surgical anesthesia for C-S (about 18% of emergency C-Ss in U.K. are undertaken using this technique, 36). Key considerations in ensuring an effective and safe management of epidural conversion for C-S revolve around the questions: which epidurals to top up, what drugs to use, and where to initiate the conversion (see in: Neuraxial technique for labor analgesia: current approach).

Management of spinal hypotension in C-S: hypotension following spinal (or combined spinal epidural) anesthesia in normal labor or C-S is common and, if prolonged and uncorrected, can cause adverse maternal and fetal effects. Dealing with it, the most important thing is to use prophylactic measures,correlated withthe professional guidelines regarding this problem (37). State-of-the-art protocols mandate usage of preventive infusion of alpha 1 vasopressor, instead of the current mixed agonists (ephedrine). Phenylephrine is the vasopressor of choice, although norepinephrine is also mentioned, along with measures of pre- or co-hydration and relief of aorto-caval obstruction in the pregnant woman (using the left lateral tilt).

Prevention and management of pain during C-S under neuraxial anesthesia: Although well performed neuraxial anesthesia is in general painless and safe procedure, it may sometimes be associated with the occurrence of intraoperative pain. In such cases, the only remaining option is the supplementation of IV fast acting agents: fentanyl 25–50 μg, alfentanil 250–500 μg or ketamine 10 mg bolus doses or conversion to general endotracheal anesthesia, with all associated risks from it. From that aspect, it is necessary to ensure an adequate neuraxial blockade before starting the surgical incision.

Postoperative pain after C-S: Although latest and modern analgesic modalities and drugs for postoperative analgesia treatment for C-S have been introduced in the recent years, a review of the literature suggests that we are far from achieving the goals of optimal postoperative analgesia. The administration of IV opioids after C-S is still widely used and their side effects have made the incorporation of non-opioid analgesic regimen to be mandatory. Fascial blocks and especially the TAP block have been the most researched modalities in the last decade, but also QLB block has gained popularity. The analgesic efficacy of fascial blocks as part of a multimodal analgesia approach has been established as an integral part of analgesic regimes after C-S, but only where neuraxial morphine was not used or parturient had received GA. Nonsteroidal anti-inflammatory drugs (including COX-1 inhibitors) in combination with IV paracetamol have been found to be beneficial in the postoperative analgesic regimens, whereas perioperative use of ketamine may be beneficial if C-S was performed under neuraxial anesthesia. It is evident that the guidelines of the multimodal type of analgesia including paracetamol, NSAIDs and spinal morphine (ITM) as adjuvant to bupivacaine, are the most effective regimen for postoperative analgesia in C-S; recent research suggests that a dose of 50-75 μgr ITM balances the desired analgesia with fewer side effects compared to higher morphine doses (100-150 μgr). Further studies are needed to define the role of: gabapentinoids, dexamethasone, ketamine, wound infiltration (infusion), and ilio-iliac and ilio-hypogastric block (II or IN NB) for regular post-analgesic regimens in C-S (38,39).

Recovery from anesthesia after C-S: regardless of the method of anesthesia, all patients must receive the same standard of care for recovery as after recovery from anesthesia in any other surgical specialty, i.e. with staff trained in post-anesthetic care and an environment containing adequate space and equipment to provide safe and effective care for both beings. The basic equipment should include blood pressure measurement, ECG, oxygen saturation and, if necessary, capnography monitoring.

Spinal anesthesia for C-S after failed epidural conversion: some anesthesiologists decide to give spinal anesthesia after failed ED conversion, which mainly has the potential for at least two risk conditions: the risk of failure and the risk of high neuraxial block. The epidural space can be filled with local anesthetic from the previous dose and its compression of the dural compartment can lead to difficulties in obtaining CSL; the epidural local anesthetic can flow back through the spinal needle and be misidentified as CSL. On the other hand, if the dural puncture is successfully done, the injected anesthetic can cause a high spinal block, as a result of

compression of the dural sac or partial passage of the anesthetic through the dural hole into the spinal space; the risk of such a block is avoided by injecting a reduced dose of anesthetic, at least 30 minutes after the last epidural bolus and by delaying the supine position. However, the optimal dose of spinal anesthetic is not known, and delaying the supine positionmay be impractical. Cases of high spinal block have also been reported 40 minutes to 1 hour after the last epidural bolus (40).

ERAC protocol in obstetric anesthesia: operative delivery with C-S is a common surgical procedure, which means that a large part of the (pregnant) population is exposed to potential operative risk and complications, which should be minimized. The postoperative period is unique and specific because new mothers have to balance from recovering of surgery (often unplanned) and also taking care of the newborn and breastfeeding. ERAC (Enhanced Recovery After Cesarean) is a term that denotes a multidisciplinary, evidence-based approach that implies a strategy, i.e. a set of evidence-based on practical measures and recommendations, with a focus on the components related to anesthesia and the perioperative period, and refer to optimizing and accelerating recovery of the mother (and the newborn) from C-S. Its purpose is to minimize the physiological response from the operation and to optimize the final outcome of the patients, by reducing the risk of postoperative complications. ERAC extends the principles of ERAS (Enhanced Recovery After Surgery) in obstetric problems; the guidelines were introduced in 2018, much later than the ERAS protocols that apply to other surgical specialties. ERAC incorporates recommendations from existing guidelines issued by professional associations, such as American College of Obstetricians and Gynecologists (ACOG), American Society of Anesthesiologists (ASA), SOAP, etc. (41).

The preoperative recommendations and instructions for the ERAC protocol refer to pregnant women who will be scheduled as elective C-S; the obstetrician starts educating program from early 10-20GW of pregnancy and explains the goals of the protocol in relation to the upcoming period (42). It mainly refers to comorbid conditions that should be optimized before delivery, including possible anemia and iron deficiency, as well as glycemic function for pregnant women with diabetes (43). The period of starvation before C-S is also emphasized; the last light meal is allowed up to 6 hours before surgery (up to 8 hours for a solid meal) and (clear) liquids up to 2 hours before anesthesia; for unplanned or emergency delivery with C-S, the preoperative pathway is narrowed to a 30- to 60-minute interval (44).

Intraoperative recommendations are focused to minimize the surgical complications and to preparethe pregnant for a safe perioperative course and a successful discharge from the hospital stay. Prophylactic IV antibiotic should be administered in the first 60 min., preferably before the surgical incision and before clamping the umbilical cord; in doing so, the effectiveness of the drug is improved which poses no risk for the fetus; cephalosporins of the first generation (cefazolin) are recommended for all pregnant women without allergies or for those at risk (ruptured amnion) the addition of azithromycin is suggested (45); disinfection but also adequate drying of the skin before the surgical incision is mandatory; preoperatively, pregnant women

should receive at least two IV antiemetics with a different mechanism of action, from the group of ondansetron, dexasone and/or metoclopramide.

Neuraxial technique is the gold standard for anesthesia with C-S; spinal anesthesia results in a faster and shorter onset of action compared to epidural; neuraxial morphine (intrathecal or epidural) should be given for better postoperative pain control (46); truncal interfascial block (TAP or QLB) is used in those parturients who do not receive neuraxial morphine. Administration of non-steroidal anti-inflammatory analgesics (NSAIDs) should begin immediately after closure of the peritoneum and begin with early non-opioid analgesia (acetaminophen). Such a multimodal approach to pain control aims to reduce IV opioid use and it side effects they cause (ORADEs), especially undesirable in pregnant and newborns; the use of non-opioid analgesics prevents gastrointestinal and other side effects associated with opioids (nausea, vomiting, constipation, reduced intestinal motility, sedation of newborns, etc.); less sedating analgesics may also improve early maternal mobility as well as breastfeeding.

A preventive infusion of vasopressors (phenylephrine, possibly noradrenaline) is recommended immediately after spinal puncture, in order to prevent spinal hypotension and maintain normal blood pressure in pregnant women (47). For adequate euvolemia IV fluids should be limited to less than 3 liters; it is recommended that oxytocin be limited to the minimum dose necessary to achieve and maintain adequate uterotone, but also to avoid side effects (tachycardia, hypotension, ischemia, hyponatremia), bronchospasm (prostaglandins) or hypertension (ergot alkaloids), and. C. bolus dose of 1 - 3 i.e. (intrapartum C-S), continued with an infusion dose (48). Intraoperative hypothermia can have adverse effects for both mothers and newborns (including coagulopathy, possibility of infection, arrhythmia, etc.), therefore, forced warming of the mother, warm IV fluids and increasing the temperature in the operating room (23 degrees), as well as adequate drying of newborns are necessary (49).

The ERAC guidelines also address immediate care of newborns after delivery-clamping of the umbilical cord for full-term newborns should be delayed for at least 1 min, while for preterm infants it should be delayed for 30 seconds (50); the routine use of oxygen and suctioning of the newborn's airway is avoided, except in cases of obstructed airway; skin-to-skin contact is encouraged immediately after delivery, as well as promoting early breastfeeding during the first hour of life (51).

Postoperative guidelines refer to the postoperative outcome, which depends on the steps taken during the preoperative and intraoperative period. The primary goal is to ensure that pregnant women return to preoperative baseline functions and to ensure an early and successful hospital discharge. Early mobility after neuraxial anesthesia is considered to reduce the risk of thromboembolic events and is one of the initial steps to return the pregnant woman to preoperative functional status; in addition, prophylaxis with mechanical pneumatic compression is beneficial for women not receiving pharmacologic thromboprophylaxis. Maintaining euvolemic status and preventive treatment of spinal hypotension reduces the risk of emetic

complaints in the postoperative period; early oral fluid intake should begin within 60 min. after admission to the recovery unit; women in labor are encouraged to resume a light diet within 4 hours after surgery, if there are no contraindications. Published guidelines recommend early removal of Foley catheters, if there is no need to monitor diuresis; it is believed to be beneficial for early mobility of the women and leadsto reduction of the risk of symptomatic urinary tract infections (52).

Ideally, a multimodal analgesia regimen that begins in the operating room with neuraxial anesthesia, continues postoperatively; the prolonged effect of morphine, added with IV acetaminophen and non-steroidal anti-inflammatory drug has an advantage over others regimens. Before discharging the patients, it is recommended to monitor the anemic patients, i.e. hemoglobin level on the 1st and 2nd postoperative day, but only in those with more extensive blood volume lossesand those with anemia. Mothers should receive appropriate measures to support breastfeeding during the hospital stay and finally, to get information regarding outpatient help for the period that follows.

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