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O Tempo e a Anestesia Obstétrica: da Cosmologia Caótica à Cronobiologia *

*Time and Obstetric Anesthesia: from Chaotic Cosmology to Chronobiology**

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RESUMO

Vale NB, Vale LFB, Cruz JR - O Tempo e a Anestesia Obstétrica: da Cosmologia Caótica à Cronobiologia

JUSTIFICATIVA E OBJETIVOS*: Ciclos temporais (claro/escuro; nascer/morrer, etc.) ao lado de condições ambientais (sincronizadores) influenciam a fisiologia do parto em função da existência de relógios endógenos (osciladores) que interagem com pistas sociais diuturnas. Nesta revisão foram ordenados os parâmetros anestésico-obstétricos cíclicos mais importantes no atendimento à parturiente.*

CONTEÚDO*: Análise cronobiológica dos principais eventos da fisiopatologia obstétrica da* Mulier sapiens*: I) Período da embriogênese - risco de teratogênese; II) Da prematuridade ao pós-datismo: do parto eutócico à cerclagem uterina; III) A noite e o parto: maior incidência noturna do parto (facilitação fisiológica) e diurna da cesariana (opção do obstetra); IV) A lua e o parto - resultado não conclusivo; V) plantão noturno na Anestesia Obstétrica: contingência profissional de mais riscos; VI) Tempos da cesariana: retirada fetal: tempo UD (uterotomy – delivery) o mais curto possível; correção eficaz de hipotensão arterial e valorizar o tempo de jejum pré-anestésico; VII) Variação circadiana da distócia: dor; contração uterina; perda sanguínea; hipertensão arterial sistêmica (HAS); risco de alergia e asma brônquica. Na fase noturna há maior intensidade de contração e maiores riscos de hemorragia, de alergia e de asma. Em contraponto, há ausência de variação circadiana da HAS na eclâmpsia; VIII) Cronofarmacologia obstétrica: anestésicos locais, analgésicos, hipnóticos, anestésicos gerais e bloqueadores neuromusculares. A cronergia explica o pico analgésico matinal dos opioides, vespertino dos anestésicos locais e noturno dos anestésicos gerais inalatórios.*

CONCLUSÕES*: A abordagem cronobiológica do atendimento anestésico ao parto na maternidade enfatiza a importância obstétrica da ritmicidade circadiana na humanização e segurança do parto.*

Unitermos: ANESTESIA Obstétrica, CIRURGIA, Obstétrica: cesariana; CRONOBIOLOGIA: reprodução, parto.

SUMMARY

Vale NB, Vale LFB, Cruz JR – Time and Obstetric Anesthesia: From Chaotic Cosmology to Chronobiology.

BACKGROUND AND OBJECTIVES: *Temporal cycles (dark/light; birth/death; etc.), along with environmental conditions (synchronizers), influence labor physiology because of the presence of endogenous clocks (oscillators) that interact with social diuturnal clues. In this review, the most important cyclic anesthetic-obstetric parameters in parturient care are listed.*

CONTENTS: *Chronobiological analysis of the main events in the obstetric pathophysiology of Mulier sapiens: I) Embryogenesis – risk of teratogenesis; II) From prematurity to post-didacticism: from eutocic labor to cervical cerclage; III) Night and labor: higher incidence of nocturnal labor (physiological facilitation) and daylight cesarean section (choice of the obstetrician); IV) The moon and labor – non-conclusive results; V) The night shift in obstetric anesthesia: riskier professional contingency; VI) Phases of cesarean section: removal of the fetus: UD stage (uterotomy – delivery) as brief as possible; effective correction of hypotension and valorize pre-anesthetic fasting; VII) circadian variation of dystocia: pain; uterine contraction; blood loss; hypertension (HTN); risk of allergy and asthma. In the nocturnal phase, the intensity of contraction and risk of hemorrhage, allergy, and asthma are greater. On the other hand, HTN in eclampsia does not show circadian variation; VIII) Obstetric chronopharmacology: local anesthetics, analgesics, hypnotics, general anesthetics, and neuromuscular blockers. Chronoenergy explains the matinal peak of opioid analgesia, vespertine of local anesthetic, and nocturnal of inhalational anesthetics.*

CONCLUSIONS: *The chronobiological approach of labor anesthesia emphasizes the obstetric importance of circadian rhythmicity in labor humanization and safety.*

Keywords: ANESTHESIA, Obstetrics; CHRONOBIOLOGY: reproduction, labor; SURGERY, Obstetric: cesarean section.

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Time and Obstetric Anesthesia: from Chaotic Cosmology to Chronobiology

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INTRODUCTION

Unlike oviparous animals whose offsprings are born in less than three hours, able to adapt to environmental conditions, the birth of mammals (viviparous) is more prolonged (more than six hours) and the newborns (NB) are unprotected and dependent on the permanent care of their parents. Seven million years of "humanoid" evolution provided australopithecines with a unique anatomic pattern: a large and triple (reptilian, limbic, and human) brain capable of developing instincts, emotions, imagination, and bipedalism. Encephalization stimulated the development of his/her own culture as a consequence of speech, vocalization, migration, life in groups, and the use of rocks as useful instruments[1-5]. Primordially, the biped female had a solitary painful labor dependent on the laws of survival, since she was not as influenced by instinctive forces as other mammals. A Jesuit reported (XVI Century) that native Brazilian females delivered alone, in the jungle, near a stream to wash themselves: *"their screams during labor echoed so strongly in the jungle that they sounded as if someone was being eaten by a beast"*[6]. Although labor is physiological, pain during vaginal delivery can be iatrogenic caused by hospital routines such as bed rest, induction or acceleration with oxytocin, Kristeller maneuver, and episiotomy. Currently, vaginal labor is considered as the "natural" method for the delivery of the offspring of *Homo*

sapiens and cesarean section is the surgical procedure to save the fetus, when the life of the mother and/or fetus is in danger[2,7,8].

Historical Aspects of Labor and Cesarean Section

The word obstetrician comes from *Obstetrix*, the Latin word for midwife (*obstare* = to stand by), due to the common position of obstetricians in front of the parturient to hold the NB in vaginal delivery. The word anesthesia (αν = no; αισθησίς = sensitivity) was used for the first time by Dioscorides, a surgeon and botanist, in I B.C. when he described in his book (*De Materia Medica*) the hypnotic-sedative actions of poppy, mandragora, and aconitum extract (atropinic action) [2,7,8].

Vaginal Delivery

The evolution of the African australopithecines to walking erect was the most important behavioral attitude that enabled man to leave the natural habitat of a quadruped primate (tree tops of African forests) looking for the independent life of a biped, hunting on the savanna and resting in caves, in two to three million years of survival. Although walking erect made man more visible to predators, the panoramic view of *Homo erectus* guaranteed more safety and the possibility of hunting, flight, or fighting. Walking on two feet guaranteed *Homo erectus* a panoramic view and free hands to start the epic trek from central Africa (80 thousand years after the ice age), looking for more caloric animal protein and fat. The exclusive use of the thumb allowed man to throw offensive objects during fights or hunting, making him the only creature capable of causing injury to another from afar. The exclusive imagination capacity along with an increase in the volume of gray matter by increasing the circumvolutions inside the skull was responsible for the definitive exit from historical obscurity[1,3]. Twelve thousand years ago (the last defrost) *Homo sapiens* crossed the Nile and the Red Sea in a victorious saga to conquer every continent through vales, mountains, deserts, lakes, seas, and oceans at 40 km a year[2-5]. To ensure this man with creativity and that he would ascend to the post of lord of the planet, the human brain (2% of the body mass) uses 100 billion neurons and one trillion synapses, consuming the energy (ATP) of just one fuel, i.e., 50% of the glucose available in the body, in aerobic mitochondrial reaction with the unstoppable expenditure of 20% of the plasma oxygen coming from the heart (20% of the cardiac output) after pulmonary hematosis. According to paleoanthropological studies, *Homo* was the first primate to hunt, create complex tools, speak, use fire, camp, care for the weak, and also the first one to believe that birth and death had a supernatural connection. Unfortunately, adaptation to being a biped demanded reformulation of the pelvis to make it an instrument capable of supporting loads. The female pelvis became adaptively narrower in the region of the vaginal canal, making labor anatomically more difficult[3-5]. The difficulty to dilate the uterine cervix (predominance of elastic fibers – 80%), the narrow birth canal, and the greater size of the head of the human fetus when compared to other mammals, made human labor the most painful among primates. Fortunately, a new anatomical adaptation compensated the narrowing of the pelvis in *Mulier sapiens* in relation to the greater relative size of the brain of NB: the greater immaturity of the central nervous system (CNS) among the offsprings of all primates, allowing the post-delivery compensation of structural head deformities of the NB secondary to the passage through the narrow birth canal or to the use of forceps. The human NB is the most defenseless offspring, since he communicates with the mother through high intensity crying (70 to 90 db), but this does not guarantee survival for more than 24 hours in case of maternal absence. This implies the need of a short- and medium-term solid union between male and female, since the immaturity of the CNS demands special parental care for a long time[3-5].

The secular belief that the macro cosmos (i.e., the sun, planets, and stars) interferes with the organic micro cosmos (cells and atoms) is still part of medical thinking, with eventual repercussions on human behavior and physiological functions. Chronobiology from the (Greek: κρονος = time; βιος = life; λογος = study) studies the day-night (light-dark) circadian cycle that leads to adaptive changes in pathophysiological parameters to guarantee anticipative homeostasis of birth, growth, aging, and death of *Homo sapiens*. Since the early days, survival on Earth of the beings best temporally adapted was based on the evolutionist knowledge of chaotic environmental and organic modifications regarding days (ultradian and circadian), seasons, and year (infradian). Thus, hunting, feeding, flight, and the struggle of daytime animals (genre *Homo*) are potentiated by the increased intensity of the autonomous function of the sympathetic nervous system and adrenal gland under the sunlight. In the darkness of night, parasympathetic hyperactivity and hypophyseal melanin facilitate digestion, fertility, sleep, birth, and death[7,10]. Although labor is more painful in the dark phase, nocturnal labor is more frequent due to geophysical factors, such as phases of the moon and nocturnal neurohumoral changes in the last days of gestation (increase in histamine, oxytocin, prostaglandins, serotonin, and melatonin), ensuring shorter labor under the moon light, a nocturnal protection against night dwelling predators[7-11].

Although Jehovah was the first to use general inhalational anesthesia for the birth of Eve from a rib from Adam (*Genesis, 2:21*), there are biblical Judaic-Christian reports on the glory and damnation of labor in the life of a woman. According to the creationism point of view, labor, after expulsion from the Garden of Eden, would be characterized by punishment and pain (*Genesis, 3:16*), *"with pain you shall give birth"*, i.e., similar to Rachel (*Genesis, 35:*16), whose son was called "*son of my trouble*", it would be forever associated with pain[13]. The New Testament ratifies labor pain, according to Saint Paul (*1 Thessalonians 5:3*) "*as labor pains in a pregnant woman, and they will not escape*", and Saint John's Revelations (*Revela-*

tions 12:2): "*she was pregnant and cried out in pain as she was about to give birth*" [12]. For centuries Christianity accepted pain as just punishment from God, which should be accepted with submission to purify ones soul. In 1591 E. MacAyane, a young Scottish mother, was buried alive for requesting relief of labor pain! In Occidental history, the biblical damnation of painful labor continued until 1847, when James Simpson used inhalation of ether, and later chloroform, to abolish or minimize labor pain. Tracy was responsible for the first general anesthesia (01/25/1847) for cesarean section, executed by Skey at the Saint Bartholomew's Hospital (London) (Lancet, 1847;1:139-140). In 1853, John Snow, physician of the English royal court, made Queen Victoria inhale chloroform to help the delivery of her eighth son (Leopold), who was hemophiliac (birth a la reine). Analgesia by the oral administration of opium (Gilette, 1877) or with the vaginal administration of cocaine (Schleich, 1894) was not successful in achieving obstetric anesthesia. In 1900, Kreis used spinal block for the first time in six Swiss parturients (five primiparas) as an option for the preferential inhalational anesthesia: three of them complained of headache, four developed vomiting, and the obstetrician had to use forceps in four out of six deliveries. In 1933, Cleland published the scientific basis for the effective anesthetic control o labor pain by describing the thoracolumbar (T_{10}-T_{12}-L_2), during the phase of cervical dilation, and sacral (S_2-S_4), during expulsion, pain pathways. Narco-acceleration of labor (Irving, 1945) with thiopental and oxygen was the dominant method in the 1950s and 1960s. From 1942 on, Hingson, Edwards, and Tuohy introduced continuous epidural analgesia and saddle block anesthesia. In 1981, Brownridge disseminated the promising method of combined spinal-epidural block. The association of local anesthetics (LA) with other spinal analgesics in the end of last century began the boom in the search of labor humanization, making it less painful and safer. Adequate pain control guaranteed labor with the use of the abdominal press during expulsion of the fetus and positive first intimate maternal-fetal contact (imprinting), which is a requirement for the future harmony of familiar relationship (Chart I). According to the Brazilian Health Ministry (2002), the maternal mortality rate during labor is still high: 74.5 deaths in 100,000 live born[13-17].

There is a worldwide movement to recover and motivate vaginal labor. The availability of non-pharmacological methods that facilitate adequate pain management (acupuncture, hypnosis, chromotherapy, massage, etc.), through complementary alternative toco analgesia, is capable of minimizing labor pain in modern maternity hospitals[7,8,16-19]. Free of pain, future mothers can stay awake and participate in labor, interacting with alternative analgesia methods associated or not with analgesic drugs with the eutocic follow-up of the mother-fetus binomium. Delivery methods that prioritize both mother and fetus (Dick, Lamaze, and LeBoyer) represent valid attempts to minimize and humanize the impact of birth within the family. It is always gratifying for the anesthesiologist to obtain effective relief of labor pain without great motor involvement. Spontaneous maternal bliss under spinal block is evident on her expression, handshake, or on the emotional verbalization of her gratitude… it is, without a doubt, an unforgettable professional experience[2,7,19-22]!

Chart I – Pharmacological and Alternative Methods of Labor Analgesia

Regional Block	Labor	Cesarean Section
Infiltration of the Perineum	++	0
Pudendal nerve block	++	0
Paracervical block	++	0
Simple epidural	+++	+++
Continuous epidural	++++	+++
Simple spinal block	+++	++++
Combined spinal/epidural	+++	+++
Systemic analgesia (+ O_2 + curare)		
General inhalational	++	++++
General parenteral	++	+++
Complementary Alternative Toco analgesia (CAT)		
Invasive: Acupuncture, TENS, sacral injection of distilled water (sc)	+	0
Non invasive: half-light, air conditioner, massage, exercises, soft music, meditation, hypnosis, presence of doulas, adequate breathing	+	0

Obs.: (+) used; (++) frequent; (+++) very frequent; (++++) most frequent

Cesarian or Cesarean Section

From the XX Century on, hospital toco-analgesic safety transformed parturients in the only primate to need assistance during vaginal delivery or cesarean section. Giving birth in the "modernity" of the delivery room or operating room was no longer a high risk, solitary, and painful act as it was among primitive people. The denomination of cesarian or cesarean section (opening of the uterus to remove the fetus) has been associated with the name of the emperor Julius Cesar, who was born by this method (caesus = cut). This version is questionable, since the abdomen was opened for removal of a live fetus only after the death of the mother, and the mother of the emperor lived for many years after the birth of her son… The version that Nero had his mother Agrippina killed and opened her abdomen to see where he was generated is also inconsistent. During the reigning of Numa Pompilius (715-673 BC), the Roman law (*Lex Regis de Inferendo Mortis*) forbade the burial of a parturient before removing of the fetus: *Si mater pregnans mortua sit, fructus quam primum caute extrahatur…* The word cesarean is linked to the Latin verb *caedere* (to cut): *qui caeso matris utero nascitur* = that who is removed from the mother's womb. In reality, the word cesarean comes from the French *césarienne*, which comes from the Latin *caedere* (to cut). Due to medieval theocracy, the church, based on the *Lex Romana*, reestablished *post-morten* cesarean section allowing removal of the fetus from a dying mother to fulfill the religious principle of baptism since only by water the soul of the NB could enter heaven free of the original sin[9,13,21-32]. Although Jehovah used "anesthesia" for the painless delivery of Eve from Adam's rib (*Genesis, 2:21*), the first report of cesarean section on a live parturient refers to the successful procedure performed by Jacob Nüfer (1500), a swine gelder, in Switzerland, on his wife with the support of the people of the village he lived in. In Brazil, José Maria Picanço (Baron of Goiânia) was supposedly the first person to perform a cesarean section on a live slave in Recife in 1817. In almost all cesarean sections performed by physicians under general anesthesia, the fetus and/or the mother died from hemorrhage or infection *a posteriori*. Only after the cesarean section performed by the Italian surgeon Porro (1877), with removal of the fetus after subtotal hysterectomy, it became feasible that not all parturients undergoing cesarean section died of hemorrhagic or infectious shock! The great surgical change started in Germany (1881), when Ferdinand Kehrer stitched successfully the uterus without the need of a hysterectomy. In the XX Century, new basic and clinical knowledge were added: anatomy, autonomous and cardiovascular physiology, physiopathology of pain, and new local anesthetics and adjuvant drugs. Clinical-surgical improvement, blood transfusion, and pharmacological improvement with uterotonics, antiseptics, chemotherapeutics, and antibiotics also contributed to make cesarean sections safer. Cesarean sections are routinely done all over the world saving thousands of lives every year. Modern analgesic therapy, the improvement in anesthetic-surgical technique, and advanced monitoring ensure the tripod of defensive obstetric strategy. Besides pain relief, anesthesia for cesarean section should preserve maternal consciousness without negative effects on her contact with the fetus after birth and during breast feeding[2,15-17,31-34]. If balanced general inhalational anesthesia for cesarean section was dominant in the 1960s, spinal block has been the choice of method for surgical toco-anesthesia since the 1990s[21-23]. Simple spinal or epidural block, or combined spinal/epidural block represents the preferred method of Brazilian obstetricians, especially simple spinal block with 0.5% hyperbaric bupivacaine associated with new adjuvant drugs (opioids and clonidine) with little negative fetal repercussion[35-44]. However, balanced general anesthesia can be used, especially when spinal block is contraindicated, such as in patients with hypovolemia, sepsis, decompensated cardiopathy, coma, dyscrasia, and deformities of the spine, among others. An additional factor has increase the need of special NB care: increased prematurity associated with immediate respiratory problems and reserved intellectual perspectives *a posteriori*[4-8]. The challenges of toco-anesthesia in high risk pregnancies and the safety of the maternal-fetal binomium in premature labor are faced by conventional regional and systemic pharmacological methods. In spinal blocks, some items are mandatory: six- to eight-hour fasting to prevent chemical pneumonitis due to aspiration of gastric contents; control of maternal hypotension and fetal hypoxia (acidosis) by moving the uterus to the left, volume expansion, administration of vasopressors (ephedrine, phenylephrine, metaraminol), and rapid fetal extraction after uterotomy (UD interval, uterotomy-delivery, lower than three minutes) [24,45-54].

The incidence of cesarean section at the Maternidade-Escola J Cicco (UFRN-SUS) is higher than 40%, i.e., lower than the 70% incidence in private hospitals (Natal, RN, Brazil). The World Health Organization (WHO-1985) recommends that, based on the mean rate observed in European countries, the rate of cesarean sections should be 15%, but no more than 20%. In the USA 15 to 25% of NB are delivered by cesarean section, but there is a generalized attempt to reduce this incidence. In England and the Netherlands the current rate of cesarean sections (10 to 15%) is lower of that observed in the 1930s. Until the 1970s, general anesthesia was the predominant British obstetric option. From the 1990s on, general anesthesia (22%) was gradually substituted by regional block in cesarean sections: 47% under spinal block, 22% epidural block, and 9% under combined spinal-epidural block. In fact, parturients undergoing spinal block have better perception of labor than those who underwent general anesthesia (emotional involvement, contact with the NB, more inclined to breast feed). However, general anesthesia is still necessary in specific obstetric emergencies and when spinal block is contraindicated. Although a good proportion of the Brazilian fertile population live in tropical regions (North-

Northeast) and present a smaller skeleton than those living in temperate areas, the Health Ministry (MS, from the Portuguese) recommends that the incidence of cesarean sections should represent no more than 15% to 30% of all live births (decree number 2.816 of 29/05/1998-MS), since they can reflect negatively on women's health. For several reasons, this decree represents an evolutional contradiction, such as: North-South ethnic differences; nutritional deficiencies in tropical areas (periodical droughts or low tides with a reduction in the amount of fish available); excess heat with a reduction in total sleeping time and paradoxal sleep (REM); and greater Earth gravity on the inhabitants of areas close to the Equator. According to MS sources, with institutional stimulus for vaginal deliveries, the rates of cesarean sections of the SUS (Brazilian public health service) fell from 32%, in 1997, to 28%, in 1998, 25%, in 1999, and 24%, in 2000[33-34].

Time and Obstetrics

On Hellenic mythology, Zeus was the higher god of the Olympus because he was the only son of Hera (Earth) who was not devoured by his father, Chronos (Time). In Judaic-Christian tradition, time (from the Latin, *tempus*) appeared after the creation of day light: *And God said: "Let there be light. And there was light... and God called the light Day..." (Genesis, 1:3-5)*. Creation was done by separating opposites: light-darkness[3,4-13]. The day/night cycle (light/dark) became the most primitive influence of time in human survival. Adaptive human knowledge is conditioned to the ability of measuring movements (time) and perceive dualistic conformity according to reason: "*A time to be born and a time to die; a time for war and a time for peace; a time to be silent and a time to speak; a time to love and a time to hate"... (Ecclesiastes 3, 1-8)*. In Saint Agostine Theology, "*time would be the path to non-existence, since the present only appears to become the past...*". For Newton (1642-1727), "*The duration of absolute time flows uniformly without relating to anything external*". Time would be eternal and nothing could change its constant "tic-tac". In reality, living changes temporal perception after a certain age but never time itself since, in childhood, we had the perception that time progressed slowly and, as we grow older, it seems to accelerate. According to Einstein's theory of general relativity (1879-1955), events are indissolubly intertwined in space and time since the Big Bang. In speeds close to the speed of light (300,000 $km.s^{-1}$), the mass of a body increases imperceptibly, space contracts, and time moves more slowly. Since time is part of space, it can present in a tridimensional form called space-time. This space-time is the binomium given to each creature for its development on Earth because its distortion results in gravity, which is essential to life on the planet in its intragalactic rotation. Opposite to what is commonly said: "time passed", we are the ones moving in the space-time of each plane of existence. The hands of a clock only register numerically our passage through time. Although it is the mean, and not the end to be achieved, time is the only variable that is equal for everyone. Its control and knowledge are indispensable for an eutocic labor[3-5,57].

Chronobiology is the science that investigates biological rhythms, with time as their main determinant of evolutive events responsible for the anticipative homeostasis of living beings. Several human biological mechanisms, such as reproduction, are chaotic. The variable ô makes the clinical variability of labor predictable in time, which has allowed the reevaluation of current anesthetic and obstetric practices and to study circadian, infradian, and ultradian rhythms, with their mechanisms that generate oscillations sustained in all biological levels. Circadian periodicity is determined genetically in complex life forms for their phylogenetic adaptation to the environment, since it measures the interdependency of human physiology and environmental cycles. Human rhythms are periodic, persisting even under continuous light or dark conditions. Hypothalamic suprachiasmatic nuclei (SCN) along with the pineal gland are considered the neural pacemakers that maintain the inner temporal synchronization between physiological and behavioral rhythms. Exogenous synchronizers participate in the temporal organization of the organism, such as light/dark, rest/activity, and fasting/feeding cycles, besides social factors (on-call and vacation schedules; intercontinental flight – jet lag). According to evolution, only beings fittest to perceive beforehand environmental geophysical changes and able to modify their physiology in order to adapt were capable of surviving and to evolve in ontogenic and phylogenic scales. The frequency that an event follows another can be measured. The separation of two events (interval) can be measured (duration periods) by clocks (day, hour, minute, and second) and calendars (week, month, year, decade, century, and millennium) that record our passage in time. Several organic events connected to reproduction of the species have a well-determined chronobiological pattern – ultradian (< day), circadian (= day), infradian (weekly, monthly, seasonal, annual) – whose knowledge will contribute for good medical, obstetric, and anesthesiologic care. Chronopharmacology studies the influence of the moment a drug is administered (chronopharmacokinetics) to maximize its therapeutic effects and reduce its systemic toxicity (chronopharmacodynamics). Effective obstetric control of eutocic birth depends, partially, on the knowledge of the variable time – fertility, menstruation, gestation, labor, cesarean section – as well as the chronopharmacoeconomics of drugs used in the control of obstetric analgesia-hypnosis-amnesia and uterine contraction (oxytocin, uterine retractors, and tocolytics) [9-12,31-35].

Time (τ) in the Chronology of Obstetric Anesthesia

Birth is a unique moment in familial, social, affective, and even the religious life of the NB. According to Gaia, "*Conditions necessary for life are maintained and created by life itself, in a self-supporting process of dynamic retro-feeding*" [35]. Almost always, nature gives visible and perceptible signs of impending labor, but its date continues to be random. In

reality, labor is in itself a dynamic chaotic system and, due to the complexity of factors involved, it does not obey the laws of linear mathematics[2,4,16,31-34]. It is up to the couple and the medical team (obstetrician, anesthesiologist, nurses) to follow-up pre-natal trimesters in the probability of delivering a more eutocic labor. Obeying the principles of a normal curve (Gauss) related with the random nature of birth, maternal neurohumoral cascade, and placenta that determine birth at term occur around the ninth month of gestation (36th to 37th week). However, birth can be premature (between the 22nd and 35th weeks) or late term (between the 40th and 42nd weeks), with evident loss of fetal vitality indices in both cases. Cesarean section is an important component of obstetric practice, since it constitutes the surgical procedure that protects maternal and fetal lives, with an incidence of 10% to 50% of deliveries in public hospitals. However, the surgical intervention can also be unnecessary and contribute to the increase in maternal-fetal morbimortality and delay in hospital discharge if it is used only at the convenience of the obstetrician or the mother-to-be in the absence of signs of labor. Thus, the knowledge by the obstetric team of the phases of labor, and the option to use them as a guide for eutocic labor can be indispensable for the final success of the birth of another offspring of *Homo sapiens sapiens*[1,4,35].

I. Embryogenesis

Self-medication during pregnancy is condemned, especially up to the 12th week of gestation due to the lack of efficiency of the placental barrier to protect fetal embryogenesis. All liposoluble drugs are more potent when distributed in a compartment with a small volume, since the fetus and premature NB have a small amount of fat and a high proportion of water (90%). Most organs are formed (embryogenesis) in the first trimester (from the 1st to the 12th weeks), and some drugs can be teratogenic by interfering with proper organ formation, such as thalidomide (1961), responsible for the birth of children without limbs (focomelia), and alcohol (1989), responsible for fetal alcohol syndrome. All drugs are potentially teratogenic, including drugs routinely used in anesthesia. Depending on its chemical composition and maternal gestational, nutritional, and genetic status, the drug can only be used by the mother during embryogenesis (up to the third month) when indicated by the physician as a function of the fetal risk/benefit binomium. Some drugs can cause fetal injury in later stages of pregnancy: acetaminophen (liver), cytostatics (abortion), calcium inhibitors (renal agenesia), and antithryroid drugs (fetal goiter), among others (lithium, furosemide, tretinoin, diazepam, etc.). Thus, regional blocks, especially spinal block, with a preference for saddle block, is the anesthesia of choice in the first trimester of pregnancy due to the lower systemic load of the analgesics used. Pneumoperitoneum greater than 10 mmHg should be avoided in emergency surgeries in the first trimester[16,36].

II. From Prematurity to Late Term

1) Eutocic Labor: Vaginal or Cesarean Section

Although the onset and evolution of labor are secondary to changes in myometrial sensitivity to different autocrine or paracrine uterotonics, a consensus on which molecular and biochemical events related to the fetus, placenta, and systemic determine labor is lacking[16]. Birth is safer for the maternal-fetal binomium in the ninth month of pregnancy (37th to 38th weeks). Prematurity (from the 22nd to 24th weeks) and late term (40th to 42nd weeks) can affect the health of the NB. Induction of labor, especially in high risk pregnancies, represents an important strategy to reduce the rate of cesarean sections. However, even using adequate corticotherapy (betamethasone) premature fetuses are at a higher risk of developing acute respiratory distress syndrome (ARDS), due to immaturity of the lungs. In the absence of surfactant, the lungs are forced to work in an aerial environment when they should be developing in a liquid medium. It is the decision of the obstetrician whether the pregnancy should be interrupted based on gestational age, weight of the fetus (> 500 g), fetal maturity (> 22nd week), cervical dilation, and the presence of contractions. The risk/benefit binomium is always evaluated in a maternity hospital with neonatal ICU that has an incubator and adequate drugs and respirators. Continuous epidural block with ropivacaine, bupivacaine, or low concentration (%) enantiomeric mixture associated with fentanyl, or sufentanil, or clonidine, is the anesthetic technique of choice for vaginal delivery. For cesarean sections, simple spinal block with hyperbaric bupivacaine (10 to 12 mg) associated with morphine (0.1 mg) and/or fentanyl, due to the good analgesic quality and minimal anesthetic mass associated with the absence of seizures, is currently the technique of choice despite the risk of post-spinal block headache[17,18,23-28].

2) Time for Cervical Cerclage

Cervical cerclage is the procedure of choice for closure of the internal cervical orifice in cervical incontinence with an 85% expectative of fetal survival. Since any drugs should only be used during gestation if prescribed by a physician, due to the risk of teratogenesis, cervical cerclage should be performed electively between the 13th and 18th weeks and occasionally between the 22nd and 24th weeks. Spinal block, especially saddle block with bupivacaine (5 to 10 mg) associated with morphine (0.1 mg) is the technique of choice for this procedure. The use of uterolytics and bed rest are recommended in the first 24 hours, as well as strict follow-up until the 37th or 38th week, when the suture is removed, if cesarean section is not indicated[16,37].

III. Night Time and Labor

Pre-historic hunters and their pregnant mates spent days and nights crowded in cold caves knowing that at any time they could be caught and slaughtered. Despite the chaotic occurrence, the rhythmicity of biological parameters as a function of the time of the day (temperature, secretions, excre-

tions, fatigue, etc.) always accompanied birth: temporal variability ensured greater protection of the defenseless infant, especially in non-experienced nulliparas, whose labor was more prolonged[57,58]. In the view point of evolution, the low luminosity of the night increased labor safety both for mother and the fragile offspring in face of natural predators during the variable period of labor, from six to 15 hours. With the discovery of T. Edison (1869), electric light became more universal, changing the pattern of human behavior, especially in large urban centers, where socialization under nocturnal artificial light is a constant in industries, commerce, tourism, and home. Considering the multiplicity of facilitators of uterine contraction and rupture of the amniotic sac, nocturnal labor continues to be frequent, being faster (by one to two hours) and more painful (30% more) than during the day, especially in nulliparas[38]. Most spontaneous vaginal deliveries, without pharmacological induction, commonly begin at the end of the morning or beginning of the night, especially in nulliparas. Obstetric studies with large populations indicate that labor begins, most often, at the end of the afternoon and the duration of nocturnal labor is shorter[38,39]. In private hospitals, cesarean sections are more common between 9 a.m. and 3 p.m., demonstrating the direct intervention of the obstetrician. Nocturnal deliveries increase the risk of neonatal mortality (12%), especially after midnight: 2.3/1,000, at dawn, *versus* 1.8/1,000, during the day; rate of cesarean sections: 4.7/1,000[9,13]. It has been observed that oxyhemoglobin desaturation (< 90%), according to pulse oximetry, is more common at night[39]. Pharmacological induction of labor at the end of the afternoon or beginning of the night most likely requires lower dose of oxytocin or prostaglandin E (vaginal), which might contribute for a more eutocic labor.

IV. The Moon and Labor

For Brazilian tupi-guaranis, the moon (Jaci), the younger brother of the sun (Tupã), managed maritime life by changing the tides. Elevation of the tides is always influenced by the phases of the moon: during full moon and new moon, the star (sun) is aligned with the planet (Earth) and its natural satellite, interfering with the expansion of the crust of the Earth, especially the liquid surface (seas and oceans). In those phases of the moon, tides and waves at the beach are more potent and more elevated in relation to first quarter and last quarter moon. Although the gravitational forces of the moon are discrete, they are capable of influencing the 12,800 km of the earth, moving oceans, seas, and lakes, especially when moon-earth-sun are aligned. Greater peak tides are seen in the full moon, especially in August and January, due to the geophysical interactions of the inclination of the axis of the Earth in relation to the sun and the orbit of the moon in its 29.53-day trajectory. In tropical regions, the height of the tides is four to six times smaller than that of temperate and cold regions. The greater turbulence of the waves in cold regions justifies the abundance of fish as a function of the increase in phytoplankton and maritime currents. However, the influence of the luminosity reflected by the moon is more perceptible in regions closer to the Equator, since the magnitude of the tides is smaller in the tropics. During the full moon, some parturients can develop “false” contractions (Braxton Hicks) without cervical dilation. Trap et al. observed more frequent and earlier rupture of the amniotic sac in an 8-hour period (22 p.m.to 6 a.m.) during the full moon[39]. Some authors have detected a significant influence of the phases of the moon in the frequency of deliveries in different months in the modern world: the full moon is more important than the new moon in the induction of nocturnal labor. However, most investigators do not ratify this positive relationship between the full moon and labor induction[39-41]. Although the fetus is immersed in a warm liquid medium, the small volume of amniotic fluid receives little “lunar push” for the rupture of the amniotic sac and onset of labor. Besides the biopsychosocial changes of women in the XX Century, research methods used are not uniform. Until the discovery of fire 500 thousand years ago, the precarious luminosity (0.1 to 0.5 lux) of the full moon (which is lower in the new moon: 1^{-4} lux) made delivery safer for both the mother and defenseless infant. However, it is curious that psychoprophylactic methods of humanized labor (Lamaze and LeBoyer) preconize low luminosity in the delivery room, since high intensity electrical light bulbs make light an stressful factor for women in labor. Low luminosity is also beneficial for the fetus who for nine months lived in a dark environment without the night-time reduction of the antalgic activity of melatonin. Although individual variability is important in studies on behavioral circadian variation, patients with sleep disorders are more susceptible to clinical improvement when exposed to low intensity light[20]. With the increment of nocturnal urban and rural illumination in the last century, the importance of the light of the full moon in labor, as well as the evaluation of comparative clinical studies, became increasingly more subtle.

V. The Nightshift of Obstetric Anesthesia

Labor is a diuturnal occurrence. Nocturnal work under artificial light affects negatively the health of health professionals who work in maternities and hospitals. Fatigue, sleep deprivation, and desynchronization of biological rhythms interfere directly with the levels of melatonin and cortisol, as well as the psychomotor development especially the level of alertness and attention the following day. Since sleep is a circadian activity, recovery of the level of alertness and reduction of somnolence especially due to deprivation of paradoxal sleep only occurs in the following night[10,42,43]. Working on nightshifts will, on the long run, hinder cognitive and motor performance, but it can also cause neurophysiological, psychological, and immunologic changes: insomnia, autonomic dysfunction (gastrointestinal and cardiovascular), increased aggressivity, depression, increased divorce rate, drug abuse, abortion, and even breast cancer. The availability of continuous electric light and modern social pressure on

service providers in maternity hospitals have resulted in diuturnal shifts, affecting negatively their health and increasing the incidence of work-related accidents secondary to the reduction in vigilance and alertness. Although intense artificial illumination (2,500 lux) during nightshifts reduces the production of melatonin and its protective action (induction of sleep, antalgic action, immunologic protection), other chronobiological factors related to neurotransmission must be involved in the failure of anticipative homeostasis. Intense artificial illumination especially blue (fluorescent) light suppresses melatonin leading to changes in sleep, a new hypothesis on the increased incidence of breast cancer. The nightshift reduces the technical performance and vigilance of the anesthesiologist, which is reflected in the higher frequency of accidental dura mater puncture in epidural blocks, accidental auto-puncture with injection needles, as well as unnecessary change in medication[43]. The greater incidence of nocturnal neonatal mortality can be correlated with worse intellectual and psychomotor performance of the physician on-call, along with endogenous factors related with the internal temporal disorder provoked by successive nights on-call.

VI. Phases of Cesarean Sections

1) Fetal Extraction: UD

Cesarean sections have two important surgical phases: ID (incision-delivery = time between skin incision and fetal extraction) and UD (uterotomy-delivery = time between uterotomy and fetal extraction) [44]. UD time (uterotomy-fetal extraction) is more important because if it is longer than 180 seconds it leads to fetal asphyxiation for several reasons: 1. uterine manipulation reduces umbilical blood flow and placental perfusion, with an increase in anaerobic metabolism and fetal acidosis; 2. Uterine manipulation with an increase in aortocaval compression, and reduction of maternal cardiac output and placental perfusion; 3. Aspiration of amniotic fluid or meconium, with potential respiratory damage in the NB; and 4. Compression of the head of the fetus, threatening neurological integrity and postnatal neurobehavioral changes. ID time is less important, but for when the time of fetal extraction is above 30 minutes. Crawford detected, in general anesthesia, an inverse relationship between the duration of the UD interval and neonatal acidosis[44]. Datta et al. observed, in general anesthesia for cesarean section, that UD time above 3 minutes or ID time above 8 minutes was reflected on low Apgar scores and fetal acidosis[16]. In general anesthesia with 100% oxygen, when the UD interval was lower than 90 minutes the NB was less acidotic than a NB under epidural block. An ID interval below 30 minutes does not cause fetal acidosis, since more than 65% O_2 is administered. In breech presentation, longer UD interval leads to depression and fetal asphyxiation in cesarean section under general anesthesia[94,95]. In prolonged UD time (> 180 seconds), administration of 100% O_2 does not correct acidosis properly. Maternal hyperventilation with 100% O_2 also does not correct fetal hypoxia properly because maternal respiratory alkalosis causes the compensatory loss of bicarbonate by the fetus and possible rebound acidosis[16]. Twin gestation can by itself be an indication for cesarean section, especially in primiparas in cases of abnormal presentation, fetal weight below two kilos, and anomalies in the second fetus.

2) Correction of Hypotension in Cesarean Section

In regional block, if hypotension is not corrected within three minutes, it reduces fetal pH and increases the level of norepinephrine in the uterine artery[45]. In prophylaxis of hypotension during general anesthesia for cesarean section, it is important to move the uterus to the left side of the patient and maintain normal ventilation with 100% O_2 for five to eight minutes during induction (denitrogenation). The administration of high doses of ephedrine for a prolonged time is one of the factors that can contribute for the development of fetal acidosis because, despite its mixed action, it reduces uteroplacental perfusion. Currently, ephedrine cannot be considered the best vasoconstrictor to correct hypotension during cesarean sections, as suggested by a study in pregnant ewe[45]. Phenylephrine or metaraminol would be more adequate vasoconstrictors. Some measures to prevent fetal acidosis during anesthesia for cesarean section include: the UD time should be as short as possible (between 90 and 180 seconds); fast (in less than three minutes) and aggressive treatment of hypotension with volume replacement, moving the uterus to the left, avoiding repeated administration of ephedrine as the only corrective measure before fetal extraction; phenylephrine (pure á agonist) or metaraminol should be administered, before fetal extraction, to minimize the severity and duration of hypotension.

3. Fasting in Obstetrics

In 1946, Mendelson described a severe chemical pneumonitis in parturients who aspirated gastric contents due to vomiting or regurgitation during inhalational general anesthesia with ether for cesarean section (*Mendelson Syndrome*) [46]. During pregnancy relaxation of the gastrointestinal musculature, delayed gastric emptying, and reduction in the tonus of the gastroesophageal sphincter are observed. Thus, in pre-anesthesia, parturients are considered patients with a full stomach. However, in “humanized” labor, it is recommended that the parturient should eat during labor, which might represent additional anesthetic risk if urgent or emergency general anesthesia is indicated. Lewis and Crawford observed an increase in gastric volume and reduction in the pH of the stomach in parturients who had tea and toast four hours before the surgery[44]. Currently, it is recommended that the parturient refrain from eating for at least one hour (water), four hours (clear liquids), and eight hours (milk and solid food) before cesarean sections.

VII. Chronobiology of Dystocia – Circadian Variation

1) Pain

Effective control of labor pain was initiated in Scotland (Edinburgh) with inhalational anesthesia with ether (Simpson, 1847)[12-14]. Pain severity is secondary to uterine contraction and mechanical pressure of the fetus on structures of the birth canal, especially during expulsion of the fetus. However, pain perception is subjective, individual, and non-transferable. Unlike the matutinal and afternoon periods, labor pain is more severe at night due to neurohumoral changes, nocturnal acrophase of pro-nociceptive mediators (histamine, prostaglandins, oxytocin) associated with exhaustion or sleep deprivation of the parturient[7,8,12,13,47]. In the evolutionary point of view, a lower pain threshold at night has contributed for labor acceleration: faster delivery is aimed at protecting the newborn of the *Homo sapiens* against natural predators since his nomadic dislocation from central Africa thousands of years ago. Morning levels of â-endorphin, â-lipotrophin, and ACTH are elevated, while those of prostaglandins (PG) are reduced. Scores of the Visual analogue Scale (VAS) of parturients are lower in the morning as a consequence of an increase of anti-nociceptive mediators (ACTH, cortisol, endorphins, and enkephalins) and in greater $â_2$ sympathetic activity (tocolysis). Besides the greater nocturnal parasympathetic activity (uterotonic), the activity of neurotransmitters and pro-nociceptive mediators – histamine, prostaglandins, and oxytocin – is exacerbated, along with the deficit of endorphins, dynorphins, and enkephalins. One hour after vaginal delivery or cesarean section, the levels of all anti-nociceptive peptides are reduced. The chronobiological approach of toco analgesia does not exclude other co-variables that influence the reduction in pain severity, such as support of the husband, help from doulas (labor companion), massage, and breathing exercises alongside other complementary alternative toco analgesic methods. Besides, the widespread use of electrical light especially in urban areas and maternity hospitals changed the pattern of female activity by reducing melatonin levels, leading to a deficit in sleep induction, anti-nociceptive, and immunoprotective functions during labor[48]. Thus, nocturnal silence and social isolation of the parturient in nocturnal labor cannot be the only justification for the increased pain at night. Neurohumoral changes justify the lower intensity of matutinal and evening pain, since there is an abundance of central anti-nociceptive neurotransmitters: endorphins, enkephalins, and noradrenaline, during the day (light phase). Besides the nocturnal increase in melatonin, serotonin, and acetylcholine (anti-nociceptive), a drastic reduction in the levels of endorphins, corticosteroids, as well as the elevation of pro-nociceptive mediators (histamine, PG, oxytocin, cytokines) are also seen[47-49].

2) Uterine Contraction

The reduction in progesterone activity and increased estrogen activity in the last days of pregnancy favors the contractile activity of oxytocin and PG, which induce labor. The reduction in tocolytic sympathetic activity ($â_2$) and increase in uterotonic (muscarinic) effects of the parasympathetic system along with the greater nocturnal availability of oxytocin and PGs, especially PGE_2 and $PGF_2á$, increase the effectivity (and pain) of the uterine contraction. Pain scores are more elevated in nulliparas because multiparous women have prior experience and cervical dilation is faster (more than one centimeter per minute), favoring briefer labor[16,48]. Uterotonics are divided in long-acting alkaloids of rye (*Claviceps purpurea*), oxytocin (short-acting), and potent PGs (E_2 and $F_2á$). A metanalysis approach to toco-analgesia demonstrated that epidural blocks prolong labor, increases the administration of oxytocin, the incidence of instrument-assisted vaginal delivery, and it also causes a slightly increase in the incidence of cesarean sections (10%). Although oxytocin causes hypotension and oliguria, it has advantages over the uterine retractor – methylergometrine – which is less stable and can trigger vomiting, cardiac arrhythmias, and hypertension, especially when associated with ephedrine[48].

3. Blood Loss or Hemorrhage

The nocturnal increase in plasma levels of heparin and reduction in platelet aggregation justify the greater tendency of nocturnal hemorrhage in nocturnal non-obstetric surgeries[9-12,16,50]. Postpartum hemorrhage (PPH), with blood loss greater than 500 ml, is one of the five causes of maternal shock and death in developing countries, after both vaginal delivery (40%) and cesarean section (30%). The therapeutic use of oxytocin, ergometrin, and PG to control uterine hemorrhage after placental detachment is extremely important, unless the patient has bleeding disorders. The greater parasympathetic activity along with the greater potency of oxytocic drugs and uterine retractors guarantee better nocturnal control of uterine blood losses after vaginal delivery or cesarean section. Crushing of blood vessels in the myometrium by sustained muscular contraction, the classical “living ligatures”, controls bleeding by indirect vasoconstriction[49]. On the other hand, bleeding caused by autonomic sympathetic arterial dysfunction parallels circadian variations in blood pressure. Epidemiological data have demonstrated a tendency for increased blood pressure (BP) in the morning (sympathetic hyperactivity), with greater risk of intracranial and subarachnoid hemorrhages. A higher incidence of cerebral hemorrhage or aneurismal rupture, with peak incidence around noon, has been reported[51]. Nocturnal paroxysmal hemoglobinuria is a severe and rare disease secondary to a genetic mutation in the hematopoietic system (chromosome X), and 16% to 18% of the cases are diagnosed during pregnancy. The type of delivery is another important aspect in the care of pregnant women. The risk of hemorrhage is lower in vaginal deliveries than in cesarean sections. Labor analgesia is complicated in the presence of this coagulopathy, with the risk of epidural hematoma due to the use of the catheter. It is necessary to administer platelets in patients with increased risk of bleeding (platelets < 50,000 mm^3), regardless of the type of birth[9-12,52].

4. Hypertension (HTN)

Hemodynamic chronesthesia depends on a distinct circadian periodicity with a predominance of the sympathetic autonomous system during the day, and increased parasympathetic activity at night: during the day, it is necessary to search for water and food; flight and fight, rest, and the search for reproduction are associated with the dark phase, with or without moonlight. The morning rise in blood pressure depends on the levels of noradrenaline and angiotensin, and greater platelet aggregation and blood viscosity, associated with changes in baroreceptor reflex: high diuturnal blood pressure levels favor hemorrhagic processes, but the reduction in blood pressure explains brain ischemia during the night[9-12,53]. Circadian blood pressure patterns in parturients are similar to that of non-pregnant females: matutinal elevation and reduction during the night. In pre-eclampsia, the hemodynamic pattern changes, with smaller BP reduction at night. In severe pre-eclampsia, a reversion of this circadian pattern is observed, since nocturnal blood pressure does not decrease or increase[9-12,53].

5. The Risk of Allergies and Asthma Attacks

The greater nocturnal activity of allergens is secondary to the higher potency of histamine, SRS (autacoids), and other cytokines during the night. Besides the greater cutaneous reactivity to topical histamine at night, the chronesthetic activity of other allergic diseases, such as asthma and rhinitis, is greater during dawn. In the case of asthma, a reduced responsivity to the action of bronchiolar anti-inflammatories with respiratory repercussions, justifying the difficulty of nocturnal pharmacologic treatment with xanthenes, $\hat{a}_2$ agonists, and corticosteroids, has been observed. It is also relevant to know that forced exercise and hyperventilation increase dyspnea, especially at night. Since 10% of asthmatic parturients have problems with prematurity, low weight, and even pre-eclampsia, proper treatment to reduce the incidence of asthma attacks is mandatory. Pregnancy itself can worsen asthma, and status asthmaticus or non-controlled asthma attacks can delay anesthesia[54,55].

VIII. The Chronopharmacology of Obstetric Anesthesia

Regional blocks guarantee that the mother-to-be will remain conscious, analgesia, preservation of muscular contractility (differential blockade), ensuring the first touches and caresses with her baby. Spinal blocks and general balanced anesthesia guarantee toco analgesia, besides sedation and muscular relaxation, which are indispensable for the comfort and safety of delivery, may it be vaginal or cesarean section. The definitive influence of chronopharmacology in anesthesiology is not determined. Without a doubt, recent studies confirm the great anesthesiologic interest by verifying the impact of chronopharmacological and biological biorhythms in general anesthesia and in computerized pharmacokinetic models for total intravenous anesthesia with propofol and/or remifentanil[16,56].

1) Local Anesthetics

As can be seen in Chart I, the spinal administration of local anesthetics (LA) associated with other pharmacological agents or not has been the main technique in toco analgesia for vaginal delivery or cesarean section for over a century[12,17,56-61]. Blockade of voltage-dependent sodium channels is responsible for the analgesic property of LAs at the site of administration in the nerve fiber, by inhibiting the action potential (afferent sensory blockade). The spinal injection of LA reduces the plasma levels of adrenaline, contributing for an increase in uteroplacental perfusion by reducing autonomous response to stress. The local anesthetic action (latency, duration of analgesia, and toxicity) shows circadian variability: greater diuturnal potency, especially in the evening. Reinberg and Reinberg observed that the duration of the local anesthetic effect of infiltrative anesthesia in the forearm with equal doses of lidocaine, i.e., 21 minutes (9 a.m.) versus 51 mint (4 p.m.), was increased two-fold[59]. It also has been observed a reduction in the latency of spinal block with 0.5% bupivacaine and 5% lidocaine in the evening than in the morning (Table I) [60]. Debon et al. detected a maximal analgesic effect of the epidural administration of ropivacaine between 1 and 7 p.m. (117 min), and shorter nocturnal analgesia (91 min) between 7 p.m. and 1 a.m.[61]. Several mechanisms would be involved in the greater toxicity and analgesic efficacy in the evening of the LAs used more often in toco analgesia: bupivacaine, ropivacaine, and lidocaine. First, faster conduction in nerve fibers in the evening makes the voltage-time-dependent blockade of LAs more evident; circadian changes in the ionic permeability of axonal membrane as a function of the higher sympathetic activity in the evening, since axonal efflux of potassium is lower at 3 p.m.; increase in CSF temperature in late afternoon can reduce the pKa of LAs (lower dissociation), increasing the diffusion capacity, ensuring shorter latency; finally, the variability of the negative participation of progesterone in cardiac inotropism can increase the evening cardiotoxicity of bupivacaine. Do not forget that pain is less severe in the afternoon than at night, and that the analgesic action of adjuvant drugs (opioids, adrenaline, clonidine) follows a different circadian pattern than LAs. One can conclude that the time of the spinal injection of LAs influences maximal toco analgesia in the afternoon due to the shorter duration in the morning and at night (approximately 28%)[56-61].

Table I – Analgesia Latency (Seconds) of the Matutinal and Evening Subarachnoid Administration of 5% Lidocaine and 0.5% Hyperbaric Bupivacaine[148].

	Lidocaine	Bupivacaine
Matutinal	132.1 ± 63	179.4 ± 48
Evening	85.0 ± 25 *	110.0 ± 68 *

Student *t* test; * $p < 0.05$

2. Opioids

Labor pain is more severe at night because of the nocturnal acrophase of pro-nociceptive mediators (histamine, PGE, oxytocin, cytokines) and reduction of melatonin by excessive artificial illumination, associated with the exhaustion and sleep deprivation of the parturient[7,8,16]. Three points are relevant: placebos can have 30 to 40% of analgesic efficacy; the difference in duration of the analgesic effect is about 30% between acrophase and batiphase; finally, the greater intensity of nocturnal pain requires larger doses of opioids[62]. Consumption of opioids as surgical analgesics is lower in the morning: a 15% to 40% day-night difference. In spinal blocks for labor analgesia, Pan et al. detected a 27% variation in analgesia, with longer duration (93 min) of the effects of subarachnoid fentanyl during the day (from noon to 6 p.m.) and shorter duration (69 min) at night between 8 p.m. and 2 a.m., probably due to variation in pain mediators or changes in the circadian affinity of opioid receptors[64]. For subarachnoid sufentanil, two peaks of maximal analgesic effect, with a 30% variation, were observed: shorter duration at midnight (78 min) and longer duration at noon (127 min) [62-64].

3. Hypnotics

Hypnotics are used to induce sleep and general anesthesia, as well as to maintain sleep and as sedatives. Circadian changes in the depressive activity of the CNS depend on the neuronal influx of chloride through $GABA_A$ receptors, whose susceptibility shows circadian and seasonal rhythmicity:

3.1 Barbiturates – Thiopental: in volunteers, it was more effective and long-lasting at night due to facilitation of biological sleep, corresponding to the period of greater postsynaptic cerebral GABAergic activity.

3.2 Ethomidate and Propofol: Hypnotic activity depends on the circadian rhythmicity of GABAergic receptor type A. Vale et al. observed greater hypnotic activity of ethomidate during nocturnal uterine curettage, with reduced incidence of myoclonia, and greater hypnotic activity (sleeping time) of propofol during rest in mice (Table II).

Table II – Time of Anesthetic Induction (Seconds), Sleep Duration (Minutes), and Time of Awakening (Minutes) with the Association of Ethomidate and Fentanyl (Preanesthetic).

	Induction (sec)	Sleep (min)	Unconsciousness (min)
Morning	60.0 ± 14	9.5 ± 2	11.1 ± 1
Afternoon	65.8 ± 5	8.3 ± 2	10.0 ± 3
Night	49.5 ± 12	8.0 ± 2	10.3 ± 3
Dawn	43.3 ± 6*	12.2 ± 2*	13.2 ± 2*

Student *t* test; * $p < 0.05$)

3.3 Benzodiazepines: The time of the day influences the hypnotic, amnestic, and sedative activities of midazolam and diazepam, since the greater encephalic GABAergic activity in rodents is seen during rest. In short-term sedation, shorter elimination half-life of midazolam was observed at 2 p.m. (1.26h) and longer at 2 a.m. (1.57h). The duration of diazepam-induced hypnosis at night surpasses that of midazolam, especially due to the presence of several active metabolites, such as desmethyldiazepam. In NB, midazolam has a half-life of 6.3 h, and thiopental, 14.7h[65-67].

4. General Anesthetics

Temporal variations the analgesic and toxic effects of inhalational halogenated or intravenous anesthetics as a function of changes in the susceptibility of GABAergic type A and glutamate (NMDA and AMPA) receptors, the main targets of anesthetics, have been observed. In rodents, susceptibility and minimal alveolar concentration (MAC) of halothane showed circadian variability, with higher toxicity and mortality during the resting period and an increase in MAC in the hours of greatest motor activity. Fukami et al. detected lower halothane consumption at night (between midnight and 6 a.m.) [68].

5. Neuromuscular Blockers (NMB)

The natural choice is between the shorter acting neuromuscular blocker (cisatracurium) or faster induction (rocuronium and succinylcholine). Tiredness and muscular fatigue are present in parturients with diurnal activities, which would indicate a lower dose of NMB for tracheal intubation in general anesthesia for cesarean section. Rocuronium caused shorter muscular relaxation during the activity period in mice[69].

Reginal blocks caused a revolution in obstetric care, especially in cesarean sections, because the mother remains conscious for the first contacts and caresses. The impact of timing in obstetric anesthesiology routine is apparently minimal. However, studies on the presence of oscillators (pacemakers) in the CNS capable of influencing temporal organic variability (chronesthesia) and the evolution to internal temporal disorder have contributed for better understanding of the variability of the pharmacokinetics and pharmacodynamics of anesthetics and their adjuvant regarding pain, memory, muscle strength, and labor. Ignoring existing chronopharmacological information on analgesics or chronobiological modifications regarding physiological parameters or morbid states can induce errors type I and/or II on studies, since biological rhythms are always present in cells, tissues, and systems of all parturients. Chronobiological studies on chronesthesia, chrono-energy, and chronotoxicity emphasize and disseminate the medical and obstetric importance of circadian rhythmicity, as well as the study on the impact of the routine inclusion of time in the protocols of future basic and clinical studies on the cost/benefit ratio of general and regional anesthesia in obstetrics.

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RESUMEN

Vale NB, Vale LFB, Cruz JR - El Tiempo y la Anestesia Obstétrica: de la Cosmología Caótica a la Cronobiología.

JUSTIFICATIVA Y OBJETIVOS*: Ciclos temporales (claro/oscuro; nacer/morir, etc.), y las condiciones ambientales (sincronizadores), influyen en la fisiología del parto en función de la existencia de relojes endógenos (osciladores), que interactúan con pistas sociales diuturnas. En esta revisión, fueron abordados los parámetros anestésico-obstétricos cíclicos más importantes en la atención a la parturiente.*

CONTENIDO*: Análisis cronobiológico de los principales eventos de la fisiopatología obstétrica de la Mulier sapiens: I) Período de la embriogénesis y riesgo de teratogénesis; II) de la prematuridad al postdatismo: del parto eutócico al cerclaje uterino; III) La noche y el parto: mayor incidencia nocturna del parto (facilitación fisiológica), y diurna de la cesárea (opción del obstetra); IV) La luna y el parto (resultado no conclusivo); V) guardia nocturna en la Anestesia Obstétrica: contingencia profesional de más riesgos; VI) Tiempos de la cesárea: retirada fetal: tiempo UD (uterotomy – delivery), el más corto posible; corrección eficaz de la hipotensión arterial y valorización del tiempo de ayuno preanestésico; VII) Variación circadiana de la distocia: dolor; contracción uterina; pérdida sanguínea; hipertensión arterial sistémica (HAS); riesgo de alergia y asma brónquica. En la fase nocturna, existe una mayor intensidad de contracción y más riesgos de hemorragia, de alergia y de asma. En contraposición, hay una falta de variación circadiana de la HAS en la eclampsia; VIII) Cronofarmacología obstétrica: anestésicos locales, analgésicos, hipnóticos, anestésicos generales y bloqueadores neuromusculares. La cronergia explica el pico analgésico matinal de los opioides, el vespertino de los anestésicos locales y el nocturno de los anestésicos generales inhalatorios.*

CONCLUSIONES*: El abordaje cronobiológico de la atención anestésica al parto en la maternidad, enfatiza la importancia obstétrica del ritmo circadiano en la humanización y seguridad del parto.*