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Review

Physiology and Pathology of Contractility of the Myometrium

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Abstract. *Uterine atony is a serious obstetrical complication since it is the leading cause of postpartum hemorrhage. Postpartum hemorrhage (PPH) is one of the 5 major causes of postpartum mortality; therefore, it requires immediate medical intervention, independent of whether delivery occurs normally or with a cesarean section. While in the past years most cases of postpartum hemorrhage were caused due to uterine atony following vaginal delivery, in recent years most PPH cases indicate a significant association with cesarean delivery. There are several methods used in order to avoid such a life-threatening complication, ranging from risk assessment to prevention, and finally medical intervention and management, if such an event occurs. In this scientific paper emphasis is given on the so-called "uterotonic" agents that are currently used, including oxytocin among others. It is, therefore, important to be familiar with these agents as well as understand the physiological mechanism by which they work, since they are used in everyday practice, not only for managing but also for preventing PPH. There are several potential questions that arise from the use of such "uterotonic" agents, and most specifically of oxytocin. Maybe one of the most important issues is the determination of optimal dosing of oxytocin in order to avoid PPH after a cesarean section.*

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Myometrial contractility depends on the ability of muscle cells to maintain the difference in the concentration of ions on either side of the cell membrane or its recreation after stimulation, *via* several metabolic processes (1). The intensity of myometrial contractility depends on the difference between the intracellular and extracellular concentration of the various ions. Under normal conditions, the resting membrane potential is -60 to -90 mV but this can be altered in the presence of steroid hormones, such as oxytocin and prostaglandins, which can affect the concentration of electrolytes in the cells of the myometrium (2).

An action potential results when the massive influx of Na^+ ions into the cell interior creates another potential, opposite to the resting one. Finally, the resting potential is restored by the activation of K^+ and K/Na ATPase pumps with the help of ATP (3). Progesterone and estrogen have a contraction inhibitory effect, while oxytocin and other prostaglandins promote muscle contraction (4-7). Uterine atony describes the inadequate contraction of the myometrial cells of the corpus uteri while responding to endogenous oxytocin, which is released during delivery and constitutes the basic cause of postpartum hemorrhage. Postpartum hemorrhage is considered an obstetric emergency, because it is one of the 5 principal etiological factors of maternal mortality (8).

Oxytocin (Pitocin), Methylergonovine (Methergine), 15-methyl-PGF2-alpha (Hemabate), Misoprostol (Cytotec) and Dinoprostone (Prostin E2) are some of the currently used pharmacological substances for the treatment of uterine atony (8), therefore is important to optimise the correct dosing of administration for these drugs, taking also into consideration whether the delivery is normal or by cesarean section.

Muscle Stimulation Process

Resting potential. Since the time of Bernstein (1911) it has been known that every living muscle cell has a bioelectric

membrane (9). In the resting phase, the relatively small size of potassium ions allows their bi-directional movement in and out of the cell, whereas the larger sodium ions remain mainly on the outer side of the cell membrane. Based on the function of the K^+-pump, which uses energy to bring back in the cell K^+ ions which have been transferred out of it, and the Na^+-pump, which also maintains a different intracellular and extracellular Na^+ ion concentration, a 40 to 50 times higher concentration of K^+ ions is created inside the cell at a resting phase (3). The tendency of the positive K^+ ions to diffuse towards the side of their lower concentration creates a diffusion potential, the so-called membrane potential or resting potential. The metabolic processes of muscle cells help maintain this difference in ion concentration on either side of the cell membrane or its recreation after stimulation. The intensity of the resting potential depends on the difference between the intracellular and extracellular concentration of various ions, and this mechanism ultimately regulates the total potential of myometrial contractility (1). Both steroid hormones as well as oxytocin and prostaglandins can affect the concentration of electrolytes in the cells of the myometrium. Thus, while under normal circumstances the resting potential is -60 to -90 mV, this can be differentiated by hormonal factors (2). The electrical stimulating action is referred to as “electromechanical coupling” (10).

Action potential. Following electrical muscle stimulation, the resting potential can be reduced below a limit value, which results in a massive influx of Na^+ ions inside the cell, resulting in a change in ion concentration on either side of the membrane. Thus, another potential is created, the so-called action potential, which is the opposite of the resting potential of the cell. Subsequently, after the gradual loss of Na^+ ions’ ability to easily penetrate the cell, the Na^+ and K^+ pumps, with the help of ATP and the ATPase enzyme, restore the concentration of ions to their resting state, thereby, restoring the resting potential (3). This "electrical" stimulation process leads to muscle cell contraction and is referred to as "electromechanical coupling" (10). A key precondition, of course, for this contraction to occur, is to ensure the ability of the cell to consume energy (*i.e.*, ATP and phosphocreatine), so as to allow a corresponding reaction in the contraction proteins, actin and myosin. Ca^{++} ions are also necessary for the reaction of these proteins, and following membrane depolarization enter the cell abruptly and in large quantities, and by hydrolysis of ATP (upon activation of an ATP molecule by Ca^{++} and Mg^{++} ions) cause the contraction of these proteins and consequently of the muscle cell (11). In the presence of calcium "antagonists" no muscle contraction is observed despite the presence of bioelectric stimuli. This phenomenon is also referred as "electromechanical decoupling" (12).

In order for the stimulus to cause a contraction in the muscle cell, it must be as intense as the resting potential. The value at which the resting potential has to be reduced in order to cause immediate contraction of the muscle cell is referred to as ‘limit potential’. The difference between the actual resting potential and the limit potential corresponds to the "stimulus range" (13).

Hormonal Effect

Progesterone increases the resting potential and inactivates the Na^+ pump (so-called "progesterone block"). The contraction inhibitory effect of progesterone is much more intense in the non-pregnant uterus and decreases during pregnancy (4). Estrogens also increase the resting potential of muscle cells by increasing the intracellular K^+, and, at the same time, they increase the concentration of phosphocreatine, actin and myosin, the activity of ATPase, and, consequently, the transmission speed of the stimulus. In this way, by increasing estrogen during the last trimester, the myometrium "prepares" for the active process of labor, while at the same time it is protected against symptomatic and unwanted contractions (5). Oxytocin, by contrast, reduces the resting potential to approximately the limits of the stimulus range, thereby, it increases the ability of the myometrium to be stimulated. Despite this, the stimulus transmission speed decreases under the effect of oxytocin (6). Prostaglandins, like oxytocin, reduce the cell’s resting potential, possibly by facilitating the transfer of Ca^{++} ions through the cell membrane, eventually leading to its depolarization (7).

Creation, Influence and Transmission of the Stimulus

The results of initial researches with micro-abductions on individual myometrial muscle fibers have shown that parts of them, such as the heart vein fibers, are capable of producing stimuli on their own (1). The typical action potentials that are produced in a pacemaker manner, are observed in various parts of the myometrium and are not identified exclusively in specific locations. These observations have been reported in many studies, where the main stimulus creation area comes from the left side of the lowest end of the human uterus, even though stimuli can also be produced elsewhere in the myometrium (14, 15).

Mosler and Czekanowski in 1973 found that contractile activity was greater at the lowest end of the non-pregnant uterus; however, the frequency of contractions was a bit higher, at the isthmus (16).

According to the same authors, the origin of the contractions starts from both the lowest end as well as the isthmus. These contractions in a non-pregnant uterus are not coordinated, they occur at other times and are of varying intensity. On the other hand, in a pregnant uterus contractions originating from the lowest end and isthmus are rather coordinated before and during labor (16).

Today there is no doubt that the myometrium is capable of producing stimuli autonomously – that is, with no nerve effect like the myocardial tissues – since local contractions of the myometrium can be caused by stimuli created in any area. “Uterine pacemaker” is a defined histological structure in which electrical potentials are triggered by the integration of fetal and maternal stimuli, the “myometrial-placental pacemaker zone”. The number and location of the so-called "pacemakers" can vary throughout the uterus. Knowing about these regions may explain many pathological forms of myometrial contractility during labor (6, 14).

As with individual muscle fibers, we can assume that throughout the entire myometrium there is a ‘limit potential’, which reduces the individual ‘resting potential’ of the myometrium with an "irritant" substance, transmitting the stimulus throughout the myometrium. Thus, the greater the "stimulus range", the lower is, correspondingly, the irritability of the uterus. Although stimulus production is exclusively performed on individual muscle fibers of the myometrium, the process of releasing the stimulus does not depend solely on local myometrial parameters, but may be the result of autonomous nervous and/ or neuromuscular stimuli or even hormonal changes (7, 17).

The autonomous nervous system with the sympathetic and parasympathetic nerves, its neurotransmitters (acetylcholine, noradrenaline, and adrenaline) and their corresponding cellular receptors, together with the steroid hormones, oxytocin and prostaglandins, plays, through complex neuroendocrine mechanisms, a very important role on the contractility of the pregnant uterus (17). During pregnancy, while the parasympathetic nervous system remains unchanged, available adrenergic receptors and the myometrial content in noradrenaline are significantly reduced (18-22).

Interestingly, the levels of catecholamines in maternal serum remain unchanged until the onset of labor, when they increase. Fear, pain and stress, as it is well known, disturb the balance of the autonomous nervous system during labor (23, 24). The relationship between a change in psychosomatic health in the mother and the occurrence of late or premature labor has been demonstrated after measurements of neuromuscular readiness of the mother’s lower limbs muscles (Rheobase). The increased adrenergic activity results, through increased sensitivity to oxytocin, increased synthesis of prostaglandins and its own action, in vasoconstriction and induction of labor (19, 24). The adrenergic action is carried out in the uterus through alpha-adrenergic contractile response and beta-adrenergic receptor blockade. According to Alquist’s research, who was the first to separate the α- and β-receptors in 1948, noradrenaline acts as a neurotransmitter between the sympathetic nerve endings and α-receptors in smooth muscle fibers, leading to their contraction (24). Substances similar to adrenaline have since been found with an greater β_2-mimetic action, and due to their selective action they were gradually used in obstetrics as "tocolytic" (meaning termination of pregnancy), causing myometrial rupture (25). The research on β_2-blockers has evolved correspondingly. In addition to their application in cardiology and the treatment of hypertension, they are also administered as antidotes to the side effects of β_2-mimetic substances (26).

The α_2 adrenergic receptors are located in postsynaptic but also in the presynaptic membrane of adrenergic synapses as well as at the ends of the sympathetic and noradrenergic nerves of the brain. The suspension of α_2 adrenergic receptors is also sensitive to potassium ion (K +) channels. It has been found in experiments in human osteoblasts that noradrenaline can change the response of the K + channels through α (1B) adrenergic receptors. When the α_2 receptors are stimulated by noradrenaline in the synaptic cleft they inhibit their extracellular secretion of synaptic vesicles and noradrenaline secretion (self-inhibition mechanism) (8, 17, 20, 27).

All of these receptors can now be found in the myometrium as well as other organs, by different techniques including radioligand binding techniques and situ hybridization histochemistry. Adrenergic receptors show a variation in their number depending on the level of catecholamines present in the blood (24). They are also affected by steroids and prostaglandins. The number of α_1-receptors increases with the action of progesterone and decreases with the effect of estrogens. In contrast, α_2-receptors increase following estrogenic activity (28). It is currently assumed that the activity of α-mimetic substances and their sensitivity to α-receptors increase more with the effect of estrogens, while β-mimetic substances activity and β-receptor sensitivity increase with the effect of progesterone. Both hormones result, simultaneously, in decreased sensitivity and activity of the "opposite" receptors, *i.e.* the estrogen in β-receptors and the progesterone in α-receptors (7, 29).

The exact configuration during the biochemical reaction of the receptors and the exact biochemical processes that cause the receptor’s activation are not fully known. B-receptor stimulation results in an increase in cyclic adenosine monophosphate (cAMP), which induces specific responses within the cell (29). Finally, it is certain that receptors will only bind with ligands of a particular structure (7, 30). Thus, the readiness of the cell membrane of the myometrial muscle fibers to be stimulated, is significantly affected by both the presence of sympathetic mimetic or sympathetic antagonist substances, as well as other substances, such as oxytocin, estrogen, progesterone and prostaglandins. Within the general context of the mother’s chemical and neurophysiological status as well as the fetal-placental regulatory mechanisms, it is clear that efficient labor-inducing stimulation of the pregnant uterus at the end of pregnancy is a complex process (30). As a result, incomplete and inadequate coordination and incorrect antagonism

between stimulus-triggering and stimulus-counteracting regulators often lead to pathological forms of uterine contractility during labor (30, 31).

As already mentioned, the muscle fiber stimulation processes are autonomous and independent of nerve fibers. In both isolated and in *in situ* uteri there is a coordination of stimulus dynamics between adjacent areas of the myometrium and the completion of this coordination is associated with the direction of the elongated axis of the myometrium muscle fibers (32). It is now accepted that the spread and transmission of the stimulus in individual areas of the myometrium is performed *via* local stimulation from the neighboring cells, while larger areas of the myometrium are coordinated in their contraction through a general signaling stimulus (15).

The myogenic spread of the stimulus corresponds to the speed of the stimulus transmission. The rate of stimulus transmission may also be affected by α- or β-adrenergic substances, as well as by oxytocin, which in large doses reduces this rate by depolarizing the cell membrane (30). Garfield et al., have shown that at the end of pregnancy there is a particularly high number of cell bridges in the form of gap junctions between myometrial cells, in contrast to earlier stages of pregnancy, where these bridges are either not present or are found in a small numbers (33-36). About 24 h following labor, these gap junctions gradually begin to disappear again. In premature births, whether automatic or induced, these junctions are also observed. The presence of one or more gap junctions between two adjacent cells of the myometrium, leads to the transmission of the action potential from one cell to another by varying their ion concentration (35).

It is now believed that the sharp increase in these gap junctions in myometrial cells at the end of pregnancy contributes to the ability to transmit stimuli at the onset of and during labor, as well as to coordinate the various stimuli, which is characteristic as well as crucial for a successful labor (37). There is evidence that estrogen promotes the appearance of gap junctions in the myometrium, while progesterone inhibits them. Also, some prostaglandins, such as prostaglandin E2 (PGE2), prostaglandin F2a (PGF2a) and thromboxanes, promote the formation of these cell bridges, while others, such as prostacyclin inhibit it (38).

Uterine atony after delivery. Uterine atony is characterized by inadequate contraction of the myometrial cells of the corpus uteri while responding to endogenous oxytocin, which is released during delivery (39).

The placenta delivery causes disruption of the spiral arteries, which results in postpartum hemorrhage (PPH). During pregnancy, these arteries get rid of their smooth muscle cell coverage and so they depend onother muscle contractions for maternal blood flow to the fetus (40). Due to severe loss of blood during uterine atony immediate actions are required to prevent severe adverse outcomes. Universally, it is one of the principal causes that lead to maternal mortality (8).

Important risk factors causing uterine atony include: i) prolonged labor, ii) uterine distension (fetal macrosomia, polyhydramnios, and multi-fetal gestation), iii) precipitous labor, iv) magnesium sulfate infusions, v) fibroid uterus, vi) prolonged use of oxytocin, and vii) chorioamnionitis (41). Moreover, the uterus not contracting in an effective way (diffusely or focally) can be associated with various etiologies, such as i) retained placental disorders (*i.e.*, placenta previa, morbidly adherent placenta, and abruption placentae), ii) invasive placenta iii) uterine inversion and iv) coagulopathy-increased products due to fibrin degradation (plasmin has been formed and it cleaves soluble fibrinogen, fibrin, or insoluble cross-linked fibrin). Last but not least, when there is a class III obesity problem with a body mass index (BMI) above 40, this can also be an important postpartum uterine atony risk factor (42).

What is considered key in good practice of prenatal examination and risk management is discernment of risk factors. When identifying risks, resource availability and planning, such as medication, adequate intravenous access, personnel, blood products (fresh frozen plasma and red blood cells) and equipment. Before giving birth, women should be identified as extremely prone to postpartum hemorrhage when indicating the following: i) presence of the accreta spectrum in the placenta, ii) a pre-pregnancy BMI >50, iii) a clinically important bleeding disorder, and/or iv) other surgical/medical factors of high risk, according to the American College of Obstetricians (43). In addition, there should be a plan for the type of delivery, and at an appropriate facility with a respective care level for the mother's needs (8).

Initial medical treatment. In case of uterine atony, medical management should be initiated to induce and regulate uterine contractions, in addition to uterus massage, which can also be effective. Furthermore, intravenous (IV) fluids are given *via* a u8-gauge intravenous catheter. Additionally, the attending staff should be alarmed *via* a fixed built-in alert system. Medication that can be used in the case of postpartum hemorrhage for uterine atony include (8):

- Oxytocin (Pitocin): IV 10 to 40 units/1,000 ml or 10 units intramuscularly (IM). Caution is required as hypotension is possible due to rapid undiluted infusion.
- Methylergonovine (Methergine): IM 0.2 mg can be given every two to four hours. It should be avoided in patients suffering from hypertension.
- 15-methyl-PGF2-alpha (Hemabate): IM 0.25 mg can be given every fifteen to ninety minutes (max. 8 doses). This medication should be avoided in people suffering from asthma. It can cause fever, diarrhea, and/or tachycardia and is rather expensive.

- Misoprostol (Cytotec): 800 to 1000 mg can be placed rectally. This medication may cause a low-grade fever and has delayed action.
- Dinoprostone (Prostin E2): 20 mg rectal or vaginal suppository, it could be given every two hours.

Vaginal delivery. As mentioned previously, the obstetric history, the aspects of delivery before postpartum hemorrhage (PPH), the hospital status and any possible delay in care initially, are factors that adjust the grade of how simple or severe the PPH could be.

Women that require immediate management and really careful attention, such as those that i) have a history of postpartum hemorrhage, ii) experience their first birth, iii) have labor by induced cervical ripening, iv) have a prolonged labor, v) have previously had an episiotomy, as these have high risk for severe PPH (44). What is really interesting is that even in physiological labor there is an increased risk of PPH due to episiotomy or uterine atony and this finding emphasizes on the need to limit the use of episiotomy during vaginal birth. Moreover, there is a great risk of blood loss for women with PPH after giving vaginal birth in non-university public hospitals compared to private or university public hospitals. This factor is important, not because of the demographics of the women in labor, but because to the delayed or even inappropriate second-line management of PPH in the former hospitals, due to limited supplies or human resources. Nevertheless, these PPH management steps are less standardized in these establishments and it is really difficult to assess their procedures due to imprecisions in the corresponding guidelines (45).

Cesarean section. While in past years most cases of PPH were caused by uterine atony following vaginal delivery, in recent years there is a significant association between PPH and cesarean delivery. In addition, there is an important risk of peripartum hysterectomy in pregnancies with placenta previa since during the cesarean section numerous patients are diagnosed with invasive placenta (46-49). It should be pointed out that PPH refers to blood loss of >500 ml within the first 24 h from the genital tract after giving birth (50). This definition, though, is problematic as the mean blood loss from an elective lower segment caesarean birth is 487 ml while from an emergency caesarean following a labor period is 1000 ml (51-53). There is no recent study quantifying exactly the blood loss taking placing following emergency caesarean.

Regarding uterine atony, this is a predominant side-effect resulting in PPH after Cesarean section. The myometrium cannot contract adequately and it is not able to limit blood loss. This could happen due to several reasons: i) exhaustion of the myometrium (augmented or prolonged labor), ii) over distension (multiple pregnancy, polyhydramnios), iii) functional or anatomic distortion (placenta previa, fibroids, or not so frequent anomalies of the uterus, such as arteriovenous malformations), and iv) infection. In addition, possible risk factors for postpartum hemorrhage at cesarean entail i) amnionitis, ii) general anesthesia, iii) pre-eclampsia, iv) fetal macrosomia, v) multiple pregnancy, vi) leiomyomas, vii) blood disorders, viii) placenta previa, ix) intrapartum or antepartum bleeding, x) preterm birth, and xi) prolonged labor (52-54).

Finally, there are various methods to manage atony of the uterus during cesarean birth. Along with medical treatments using uterotonic agents, doctors perform surgical or interventional procedures (*e.g*., embolization of the uterine artery, uterine compression sutures, uterine tamponade by applying a balloon, packing uterus with gauze and uterine artery ligation) as well as manual massage/compression of the uterus. The main objective of the aforementioned treatments is blood loss reduction and hysterectomy avoidance for the benefit of preserving maternal fertility (55, 56).

Optimal Dose of Oxytocin after CS for Prevention of Uterine Atony and PPH

The use of the aforementioned uterotonic agents is prophylactic as it prevents atony of the uterus and leads to PPH reduction by 40% to 50% (55-57). Regarding the use of oxytocin (when compared to misoprostol and methylergometrine), this induces few side effects (if any) and, generally, exhibits a very good safety profile. In the USA, oxytocin is the most frequently used uterotonic drug for prophylaxis. Despite its extensive use and the fact that more than two-thirds of deliveries are vaginal births, the optimal dose-regimen or even if a higher oxytocin dose could be more effective in vaginal deliveries is not known. Thus, considering vaginal delivery, no specific oxytocin dose is related to lower risk for PPH (58-61).

However, considering cesarian birth, the higher the prophylactic oxytocin dose the more beneficial it proves to be for the prevention of PPH (62-63). This is why a high dose of 80 units of oxytocin is used in cesareans. Nevertheless, vaginal birth does not reduce the frequency of uterine atony that can cause a drop in the haematocrit of more than 6 units. So, taken together, it could be noted that practitioners would not use a high oxytocin dose in vaginal delivery but use a high dose of 80 units for cesarian delivery in order to protect their patients.

In fact, the most important consideration regarding the 80-unit dose of oxytocin efficiency for postpartum prophylaxis is related to its stability as a drug. In detail, a ≤40 units/500 cc concentration of oxytocin is proven to be beneficial when administered iv for at least one week, but there is no data available confirming its usefulness when concentrated at 80 units per 500cc, since no specific data have provided the metabolic course of such a large oxytocin dose (64-66). This

indicates that more studies are needed to evaluate the ideal doses of oxytocin administered postpartum, since all the possible adverse outcomes are still not fully appreciated.

In conclusion, since the time of Bernstein (1911) who discovered that every living muscle cell has a bioelectric membrane (9), significant advances have been achieved in the field of muscle stimulation, the hormonal effect on this process as well as the creation, influence and transmission of the stimulus. Despite all these accomplishments in the biology field, in everyday clinical practice serious and unknown health conditions arise, requiring an immediate medical response. Uterine atony, as the principal etiological factor of postpartum hemorrhage and one of the five main causes of maternal mortality, is considered an obstetrics emergency. During the past years most cases of PPH have been due to uterine atony following vaginal delivery, while recently PPH is also highly associated with cesarean delivery. Given the emergency of PPH, medical intervention is required in order to prevent and treat such a serious complication. Several pharmacological agents, apart from oxytocin (Pitocin) are currently used as prophylactic against PPH, preventing atony of the uterus and leading to a PPH reduction of 40% to 50% (67), even though oxytocin remains the medicine of choice. Oxytocin induces only few side effects, if any, and generally exhibits a very good safety profile when compared to other agents. While oxytocin is abundantly used in everyday clinical practice due to its advantages, its correct dosing is yet to be determined in order to achieve the maximum efficacy on preventing uterine atony after a cesarean section. Future research will shed light in this field.

Conflicts of Interest

The Authors declare that they have no competing interests.

Authors' Contributions

KA, FZ, TN and KNE contributed to conception and design. KA, KNE and SA were responsible for overall supervision. KA, PA, and GN drafted the manuscript, which was revised by GN. All Authors read and approved the final manuscript.

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