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Review Article

Does the use of Oxytocin in the Third Stage of Labour have an Impact on Breastfed Babies Health? Looking for a Viable Alternative

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Abstract

Synthetic oxytocin (SynOT) (Pitocin®, Syntocinon®) is a drug that is used regularly to prevent and to care post partum haemorrhage in childbirth. On the other hand oxytocin (OT) is also an important mediator of life processes; it has been defined "the Great Facilitator of Life". OT may affect behaviors and physiology to facilitate the propagation of species. Previous studies suggest there is likely to be a high level of OT in the first feed of colostrum after a woman has received SynOT for this purpose. This apparently transient exposure could have direct effects on the immunological development of the infant gut as, at this stage of life, the gut is particularly sensitive to OT and is pivotal in the development of the infant's immune system. The complexities of the developing immune system are only just being exposed, however, the notion that many autoimmune diseases may develop from this period is increasingly well accepted. From an epigenetic point of view, the establishment of a suitable commensal biome and exposure to appropriate antigens is essential in this postnatal period. Furthermore, in the perinatal period, there are times of particular sensitivity in which the correct receptor/hormone ratio develops. If the initial ratio is incorrect, the receptor/hormone ratio may be damaged throughout the whole life of the individual, this is the called 'Faulty Perinatal Hormonal Imprinting'. Another mechanism through which this process could take place is genomic imprinting. These complex developmental processes are critical to the ongoing health of the infant and are likely to be affected by the amount of SynOT introduced in the first feed. For these and other reasons it is important to evaluate different drugs to reduce postpartum haemorrhage in low-risk women. With this goal in mind we are currently testing tranexamic acid for post partum haemorrhage prophylaxis. This review explains the main reasons why, based on the principle of prudence, it is important to evaluate different drugs from oxytocin for prophylaxis of postpartum hemorrhage (PPH).This article presents conceptual arguments and empirical facts in support of this hypothesis.

ABBREVIATIONS

SynOT: Synthetic Oxytocin; **OT:** Oxytocin; **PPH:** Post Partum Hemorrhage; **TXA:** Tranexamic Acid

INTRODUCTION

SynOT given to mothers in the third stage of labour changes the amount of OT in human milk/colostrum [1-3]. This effect is probably mediated by a reduction in receptor sensitivity, as demonstrated at the level of uterine muscle, where, in biopsy, specimens of myometrium treated with oxytocin were desensitized to the oxytocin receptor [4]. Furthermore SynOT significantly decreased the likelihood of the baby suckling while skin to- skin with its mother during the first hour after birth [5],

With this in mind we have to ask three important questions that we will try to answer:

1. The different amount of OT in the colostrum/milk could have effects on the development of the immunological system of the neonate?
2. Could this fact have potential for life-long effects on health in general, and on autoimmune responses in particular?
3. Could this be part of the reason why we have an auto-immune epidemic?

The impact of SynOT in the neonate gut on the immune system of the infant is possible since:

SynOT is transferred from the mother's blood to the milk and preserved there [6]. Small amounts of SynOT, particularly when other hormones like oestrogens are present, can up or down regulate OT receptors [7]. The gut lining is initially open to molecules like OT, hence some may pass into the infant's system [8], where it can act on the intestine to modulate motility, secretion, blood flow, cell turnover, and contribute to release of neurotransmitters and hormones [9]. Indeed, in the gut there are both receptors for oxytocin and there is also an endogenous oxytocin production that can be altered by the SynOT coming from the outside [10]. With a change in OT receptors, the gut muscles may respond differently to a situation where no SynOT

is introduced, and will change their response to further exposure to OT, which will be in breast milk/colostrum [11,12]. A change in motility will change the time of exposure for a great number of different bacteria that have to establish themselves in the gut microbiome. This mechanism is demonstrated in mice [13] but, there is indirect evidence that it can also occur in humans [14]. SynOT plays a critical role in the rate of gut repair and maintenance in the first days of life and in the consequent establishment of tolerance to environmental antigens, this effect is known in mice [15], and in hamsters [16]. Changes in the endogenous oxytocin concentration induced by the administration of SynOT may have many immunological effects, since it is known that oxytocin has many effects on the immune system: OT suppresses the mRNA expression of TNFα, IL-1β, COX-2 and iNOS and elevates [Ca^{2+}] in LPS-stimulated microglia cells [17,18]. Other possible impacts include: the development of the ratio of T helper 1 to T helper 2 cells. Currently the bias of pregnancy is recognised as increasing the proportion of T helper 2 cells and has a tendency to remain this way in some infants; it is known that breastfeeding stimulates the proliferation of a well-balanced and diverse microbiota, which initially influences a switch from an intrauterine TH2 predominance to a TH1/TH2 balanced response, with activation of T-regulatory cells by breast milk-stimulated specific organisms [19]. Moreover, the fetal immune system is already mature and capable of recognizing numerous antigens starting at least from the second trimester of intrauterine life [20]. We know that eukaryote cells are able to learn, even at a unicellular level. This memory is epigenetically executed by the alteration and fixation of methylation pattern of genes without changes in base sequences [21]. In the perinatal period, there are so-called "developmental window", when drugs and hormones, at different concentrations, can act on the hormone receptors, determining the adjustment of receptors to their target hormones, the relationship of hormones and receptors for life takes place in this period [22]. If these first receptor hormone contacts are not adequate, the hormone and its receptor will suffer from an altered relationship for the rest of life. This phenomenon was named by Csaba "The Faulty Perinatal Hormonal Imprinting" [23]. Especially for oxytocin, it has been shown that, in rats, perinatal single-hormone treatment causes hormonal imprinting with lifelong consequences in receptor-binding capacity. Haschem and colleagues have shown that newborn rats, treated with a single dose of oxytocin, decreased dopamine turnover in the hypothalamus and decreased serotonin turnover in the hypothalamus, medulla oblongata, and striatum of females, for the whole life [24]. Of course, under certain circumstances, and on subjects with particular pathologies, SynOT can have positive effects, such as Magel2-deficient mouse mice, suffering from a high percentage of neonatal mortality, since they had an altered onset of suckling activity and subsequent impaired feeding, a single postnatal injection of oxytocin is able to rescues the lethal feeding behavior, by allowing mice to survive better [25].

Another mechanism through which this process could take place is the genomic imprinting. This is a phenomenon which is still unclear in its molecular details. Some maternal and paternal genes activate differently, some are silenced and others activated with an epigenetic mechanism, associated with the need to avoid heterogeneity and altered gene dosage effects. For example genomic imprinting in response to environmental stimuli, may be the driving force of the fetal growth [26]. Many other phenotypic phenomena in mammals may also be determined by genomic imprinting [27].

The introduction of SynOT into hospitals across the 1960's [28], coincides well with the time and places of the current auto immunological issues. In first world countries, mothers would not have breastfed so frequently and artificial uterotonics were not so widely used in hospitals. There was an increase in breast feeding numbers in the 1980's [29], and more recently, feeding babies immediately after birth has became popular. (The use of different synthetic uterotonics is also a possible factor influencing the outcomes here). In some first world countries it seems that the increase in autoimmune related diseases like asthma has reached a saturation pattern. It will be interesting to see if these numbers will fall as women choose not to have active management of the third stage of labour. There is a general paucity of work on the levels of SynOT in humans. This may be because SynOT concentrations are much smaller than most of other measured hormones and it has a short half-life in the blood stream; it is pulsatile in its release and the methods used to measure it have been varied and not all are currently considered reliable [30]. Oxytocin receptor production is also influenced by steroids such as oestrogens [31], and by other less well documented local factors such as some interleukins [32]. These factors may also need to be considered when investigating SynOT effects in neonates as, for example, the amount of oestrogens and various interleukins at birth is different to that of an adult [33,34]. In the bloodstream OT half-life is 3 to 4 minutes, which results in it having little chance of impact on the infant. However, it is not the case in breast milk; in fact, in the highly fatty surroundings of breast milk oxytocin can last for longer periods of time [6]. These authors also showed that OT injected into the mother's bloodstream would accrue in the breasts and in observing the reduction in OT concentration in the mammary glands over time concluded that it is likely to be due to the increased milk production rather than to a change in OT production. This suggests there may be an even higher concentration of OT in the small amount of colostrum available in the first feed than is surmised from samples of breast milk in the days after birth. It seems likely that some colostrum is made when the alveolar linings are more permeable prior to parturition [35], thus making it likely that OT also moves into the colostrum forming at this stage in the breast, prior to the decreasing permeability of the alveolar membranes in response to changes in hormonal levels at birth. We have found no studies where samples of colostrum have been analysed for OT within the early hours after birth, from women who have been given post partum SynOT to insure prevention of PPH, in contrast to those who have not been given SynOT.

Studies available suggest that the normal, non-pregnant female and male typically have less than 10pg/ml of OT in blood plasma [30]. In pregnant females there is a peak of between 9 and 250pg/ml during advanced stages of labour. Lactating mother's peak is at about 24pg/ml. It was found that about 12.8% 3H-oxytocin labeled, administered to lactating mothers was found in the gut lumen of infants, and one third of this amount crossed into the baby's plasma [6]. Takeda et al also showed that OT was highly stable in breast milk and would easily last

for more than 2 hours. Women given SynOT in the third stage of labour are likely to have unusually high levels of OT in their colostrum. It is also important to recognise that infants at birth are likely to have a high level of oestrogens in their plasma and in the mother's milk to which they are exposed, along with OT. It is known that oestrogens have an impact on the number of OT receptors expressed [31].

Most women are given 10IUof SynOT in the third stage of labour regardless of mother's body mass [36]. This is equal to about 16.7 micrograms of SynOT recommended for a drip infusion. This does not include extra SynOT eventually used for augmentation of labour that is likely to be broken down as it is given to the mother when she is still producing the maximum amount of oxytocinase. However it should be noted that 1 microgram is equal to 1,000,000 picograms(pg). Average full term female blood volume is 6.5L = 6,500mL so there is potentially 16,700,000pg/6,500mL = 2,569pg/ml of blood of SynOT although it may be administered over some time frame.

WHAT HAPPENS TO THE LEVEL OF OT IN WOMEN DURING LABOUR?

This is not a trivial question and the answer is not clear. However, data collected in 1978 (Figure 1) showed a marked fall between the second and the third stage of labour [37]. They found that maternal plasma oxytocin increases significantly from the first stage to the second stage of labour, followed by an equally significant decline in the third stage of labour. At the time that this study was completed there was a sense that OT was responsible for the onset of labour. Today the onset of labour is recognised as a complex scenario, where other hormones are involved, the foetus is known to send signals to the mother and there is an element of immune inflammatory response assisting the changes that occur [38].

It is apparent from this graph that the OT level falls after the second stage of delivery, when the baby is born, and thus is relatively low when the placenta is delivered. Current studies suggest the uterus itself may produce locally manufactured OT, in response to being stretched and to the hormonal milieu at the time, especially to estradiol. This could contribute to a sudden drop in OT levels after chilbirth. It is important to recognise the increase in OT receptor over this period which increases the sensitivity of the uterus to OT at this time [39].

Effective use of uterotonics has had a profound impact on the survival rate of mothers around the world since 1955 when the first synthetic oxytocin was produced. Therapeutic use of SynOT does save lives because PPH is a significant cause of maternal death [40]. Although there has been vast improvements in managing the loss of life, deaths in impoverished poorly educated communities have remained high with more than 50,000 maternal deaths world wide in 2012 [41].

Administration of a uterotonic agent, such as SynOT, immediately after childbirth has been shown to reduce the risk of postpartum haemorrhage [42]. If SynOT is so efficient in reducing PPH [43], why has a persistence of elevated OT in mothers not developed evolutionarily? Generally we make it when needed. Since it is not occurring naturally, there would seem to be very

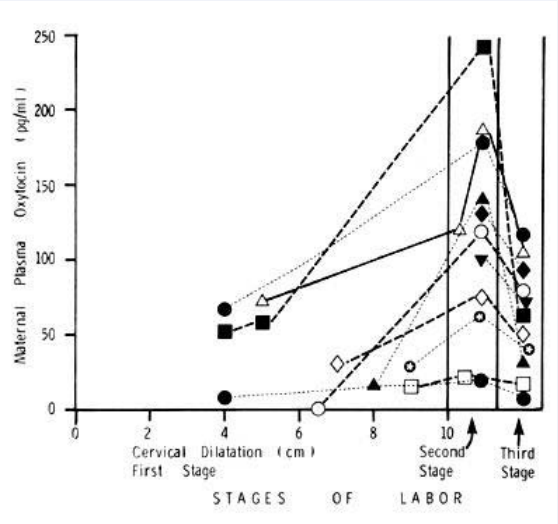

Figure 1 Serial maternal plasma oxytocin during the first, second, and third stages of labour in 11 women with spontaneous normal labour and vaginal delivery. In every patient, there was an increase in plasma oxytocin from the first to the second stage and a fall during the third stage. The plasma samples taken during the second stage of labour were timed to coincide with the crowning of the fetal head." Modified From Dawood et al.,1978.

strong selective pressure acting against the sustained production of oxytocin over this period. Could it be that the level of OT in the newborn gut needs to be low so that the first feed of colostrum does not contain too much OT and the OT receptors in the gut are not internalised? When feeding an infant for the first time, the introduction of the extra SynOT in colostrum may change the number of Oxytocin receptors along the gut and this in turn will change the gut sensitivity to oxytocin. This may have long term consequences for the developing immune system. It has been shown that long exposure to OT in the uterine muscle, as well as altering mRNA levels of the OT receptor may cause internalisation of OT receptors [44]. A biphasic response of OT Receptor formation in response to the concentration of OT has been found in gut cells [45], and indicates the sensitivity of gut cells not only to the presence or absence of OT, but also to the amount of OT. It could be possible that there is an ideal concentration of OT in the gut lumen required to get the optimum effect of OT Receptor development in a neonate; too much or too little could have unforeseen consequences through both faulty Perinatal Hormonal Imprinting and immune development. As the mother will have different OT and oestrogen levels [46], as found in other mammals [47], it is likely that the cells in the infant gut will be affected by an unexpectedly different exposure to OT at this critical stage of development. After studying the regulation of the OT receptor in peripheral organs, Kimura [48] concluded that OT receptor is regulated in a very complex manner that is not yet determined. The role of hormones at levels below regulated standards with respect to the endocrine-disrupting chemicals with estrogenic activity has been called into question in recent years. This is pertinent to this discussion because it emphasises the relative amount of these hormones that occur naturally and how they operate in the body in contrast to the manner that toxicological boundaries are established [49].

THE IMPORTANCE OF THE NEONATAL GUT ROLE IN THE IMMUNE SYSTEM DEVELOPMENT

Neonatal immune tolerance is well recognized and has been described in the past as "defective", due to the increased tendency for infants to die from disease [50]. However, increasingly it has been seen as an essential state for the infant to adopt while the acquired immune system samples and sorts its responses to the massive influx of new antigens. The enlarged thymus at this stage of life, as large to body size as it will ever be [51], indicates the enormity of the T cell related activity in response to the great number of new antigens being introduced to the body. In the first month of life there is a marked increase in the rate of Thymocyte cell death, observed as early as day 1 after birth [52]. This cell death has been identified as necessary to increase the T regulation population [53]. The neonate initially has its mother's antibodies reflected in its own system; this is a unique opportunity for the establishment of tolerance and while this is happening it seems that the neonate relies mostly on innate rather than on acquired immunity. It takes two weeks for a new T cell to mature in the Thymus. From the time an infant is born it is exposed to a vast array of new antigens, from foods and bacteria to dust and compounds in the air. The immune response of the infant is assisted by the mother's antibodies, particularly Immunoglobulin G mostly from across the placenta and Immunoglobulin A, transmitted in the earliest breast feeds, so that it can line the neonate gut. The interactions that take place at this time have been shown to be important to maintain health over a life-time [54]. It is now recognised that the gut is an important organ in immune system development [55], and this neonatal period is extremely critical and markedly different from the adult norm. For example, despite the murine neonatal dendritic cells, having enhanced Toll Like Receptor responses in contrast to adult counterparts, in vitro the B cells of these neonates will impair dendritic cell responses to Toll Like Receptor activation in an Interleukin-10 dependent fashion (Interleukin-10 and T regulatory cells can maintain tolerance to intestinal microorganisms). It was also shown that Toll Like Receptors activated neonatal, but not adult, B cells, and impaired Th1, but not Th2, cell alloimmune responses in vitro and in vivo [56].The importance of timing can be seen in many other mammals. For example, in dogs there is a critical period after birth in which the pup must feed on the colostrum. It must gain access to the mother's antibodies and other immune factors. If the pup is born too early, the mother will not have the appropriate antibodies in her milk due to the leakiness of the alveolar lining; if the pup is accessing the milk too late it will suffer due to its digestive tract closing, and thus not gaining the appropriate antibodies required [57]. Humans are a little different since they have gained most of the antibodies directly across the mother's placenta; however, the timing of gut closure and exposure to colostrum are still important.

SYNOT RECEIVED AT CHILDBIRTH CAN HAVE A LONG TERM IMPACT ON THE INFANT'S DEVELOPMENT

Interesting are the results of recent studies about oxytocin effects on neurohormonal maternal system. The studies suggest that exposure to peripartum maternal oxytocin can alter the neural response to stimulation of the child [58,59]; neuroimaging studies indicate that oxytocin supports the sensitive care giving, in fact breastfeeding mothers have a greater activation of the insula and of the prefrontal cortex in response to the baby's crying. It is shown to be the same for mothers who deliver vaginally, compared to those who give birth by caesarean section [60]. Long term effects of OT on neonates have been demonstrated in diverse areas of research. For example, the chance of successfully establishing breastfeeding and attachment patterns of the neonate were shown to be significantly less likely in women who had received SynOT in the third stage of labour [61]. There is a direct correlation between the level of SynOT in infusions with epidural analgesia and the lowest median level of OT in the mother's blood plasma when breast feeding on the second day post partum [2,3]; there was also a significant rise of prolactin observed after 20 minutes in all women, but after only 10 minutes in mothers who received OT infusion during labor. Furthermore intrapartum exposure to SynOT significantly decreased the likelihood of the baby suckling while skin-to-skin with its mother during the first hour after birth [5]. SynOT given to the mother might act indirectly on the infant, through an effect mediated by maternal depressive symptoms. In fact in mothers who experienced high levels of psychosocial stress, high levels of oxytocin are related to a reduction of depressive symptoms [62]. The data from a study conducted on 288 breastfeeding mothers undergoing treatment with uterotonic during the third stage of labor, after vaginal delivery, suggest that the injection of prophylactic uterotonic may reduce the duration of breastfeeding, but not the initiation. This may be attributable to SynOT effects on the physiology of lactation (oxytocin reflex), with consequent difficulties in attachment to the breast and the production of milk. The authors conclude that there is the need to explore this hypothesis with randomized controlled trials [59]. However, it is known that there is a clear association between the peripartum administration of SynOT and the subsequent development of depressive and anxiety symptoms in puerpers [63].

The results of recent studies [64], that investigated the long-term effects, breast-feeding and maternal mental and physical balance, where SynOT was administered intrapartum, on endogenous synthesis of oxytocin, revealed a significant and positive correlation between dose and synOT symptoms of depression and anxiety, two months after giving birth. This was likely to be due to synOT causing endogenous system dysregulation. The hypothesis is that, as the insulin resistance in diabetes, after administration of SynOT, can be activated by positive feedback mechanisms on oxytocin receptors, responding with a greater production of endogen circulating OT , and maintaining levels high and persistent after childbirth; it is also plausible that exposure to SynOT can reset the system to a higher base level (compensatory mechanism). There has also been a lot of research on prairie voles and other animals, that would also suggest that changing the level of OT that a neonate is exposed to has profound and long term consequences on the physiology and behaviour of these animals. "Even brief neonatal exposure to an oxytocin antagonist may disrupt subsequent social behaviours, including the tendency to form social bonds, to exhibit parental behaviours, and to manage anxiety or stress" [65]. In female prairie voles treated with a dose of 3 μg of OT or OT antagonist on postnatal day 1 a marked increase was observed

in oxytocin immunoreactivity on day 21 in the supraoptic and paraventricular nuclei (PVN) of the hypothalamus. In contrast, males treated with an antagonist tended to have decreased vasopressin immunoreactivity in the same region. "These results suggest that the effects of neonatal manipulation of oxytocin are age-dependent, site-specific and sexually dimorphic" [66]. There have been at least 30 studies where OT has been given to prairie voles, rats, mice or pigs and longer term behavioural consequences have been recorded [67]. It seems possible that a transient increase in OT can impact on the long term development of a neonate, if given at this critical period immediately after birth: This is what has already been discussed as epigenetic effects of oxytocin.

Gene transcription can only alter in defined brain areas, as in the case of the ventromedial nucleus of the hypothalamus, in case of control of anxiety and sex behaviors in rats [68], or ventral tegmental area, in case of early life stress, that may increase risk for depression in adult mice [69].

Changes in the OT concentration also affect gut activity. The impact of OT on uterine contractility has long been known. Acting through its G-coupled protein receptors, OT exerts its influence on the uterine myometrium in the presence of other hormones and compounds. However, what the effects of OT exactly are on gut motility is surprisingly unclear. Qin [70], found that the OT receptor is expressed on the smooth muscle of the stomach and mediates an excitatory effect of OT on gastric motility. OT induces an early transient decrease and a subsequent increase on intragastric pressure. Welch [10] found OT and OT receptors on enterocytes in the gut, peaking postnatally at day 7 in rats. Villus enterocytes were OT receptor immunoreactive until day 19 postnatally, and then immunoreactivity was restricted to crypts and concentrated at the crypt-villus junction. In a further study they observed OT/OT Receptor interactions acted as a brake on intestinal motility and, amongst other things, decreased mucosal activation of enteric neurons and promoted enteric neuronal development [45]. Some groups determined that OT is necessary to accelerate skin closure and improve the rate at which wounds heal. One author found the role of OT in translating the impact of bacteria like *Lactobacillus reuteri* in the gut though its ability to trigger CD4+Foxp3+CD25+ immune T regulatory cells [71]. Chen [72] showed the impact of OT in rat ileum mucosa causing the pulsatile release of Prostaglandin E2, which together with OT reduces the impact of intestinal injury. Prostaglandin E2 and proteins that suppress cytokine-1 signalling (SOCS1) have been shown to have a role in organising tolerance in the intestinal innate immune system [73].Therefore it seems that OT could have an impact on the gut. This may be directly due to the OT receptors impact on the gut lining or could be induced in part through the nervous system and the macrophages, some of which scavenge from the gut lumen and thus are affected by the microbiota in the lumen [74]. The exact age, the area of the gut and the type of exposure alters the outcome of experiments in OT responsiveness. There is a lack of clarity in this area but the impact of OT directly on the gut has been demonstrated. Changes in the OT concentration could affect the rate of gut closure. Many mammals are known to reduce permeability of the gut more completely after birth, along with the formation of the mucosal barrier. The integrity of the mucosal barrier of rabbits was tested by allowing the passage of radioactive serum albumin to cross the gut lining [75]. It has been known for some time that newborn infants absorb greater quantities of macromolecules than older infants or adults [76]. Gut closure occurs in the first postnatal week and it is recognised that any delay or disruption to this process, predisposes the infant to infection, inflammation and allergic sensitisation [77]. The gut closure process is assisted by human milk hormones and growth factors that are important in stimulating intestinal epithelial growth and maturation [78].

Anderson et al reported that the controlled regulation of the intestinal barrier in the healthy intestine leads to antigenic tolerance. However, disruption of the intestinal barrier, in particular of the tight junctions of the physical barrier, results in increased permeability. This allows direct access of antigens to the dendritic cells in the lamina propria, as opposed to the dendritic cells sampling the lumen, and results in an aberrant immune response that can target any organ or tissue in genetically predisposed individuals. This in turn can lead to inflammatory and autoimmune diseases both during infancy and adulthood. In goats it has been shown that the tight junctions will become leaky if artificially high levels of OT are created, this in turn will reduce the volume of milk produced [35]. It is likely to be a combination of factors that affect the rate of gut closure. Vukavić has found that the timing of the introduction to breastfeeding makes a difference with postponement of introduction to colostrum for more than 24hours resulting in a marked delay in spontaneous gut closure [79]. Lastly, another manner in which OT is potentially significant in establishing the gut microbiome and influencing the gut closure has been established. Klein [45], showed that the P13/Akt/mTORC1 pathway in gut cells is controlled by OT activation of the P13/Akt pathway in gut cells and peaked at 62.5nM OT after 30 minutes, coinciding with OT receptor internalization. This pathway controls the production of the secretory (or extra-cellular) component of the immunoglobulin, that will act as a receptor for molecules like Immunoglobulin A [80]. This mechanism in turn has been shown to increase the adhesion of Lactobacillus or *Bifidobacterium* to the gut lining by 3.4 times [81]. As Immunglobulin A is the main protective immunoglobulin available in colostrum, the advantage of this particular pathway is clear. In the paper by Mathias [81], these bacterial attachments were also shown to increase the phosphorylation of tight junction proteins occludens-1 and occluding, increasing transepithelial resistance. Many other aspects of immunologic functions that link oxytocin in a pivotal role to immune development are being investigated currently. For example OT may be critical in the differentiation of T cells due to its ability to act as a signalling substance in the thymus network. OT helps focal adhesion and may establish immunological junctions between Thymal epithelial cells and immature T cells [82].

CONCLUSION

OT has been found to be expressed in many parts of the human body and has been a stable molecule in vertebrates for over 500 million years [31]. Interestingly, for approximately the same length of time as the RAG gene, fundamental to the acquired immune system, have been a part of our genetic code [83], and the development of the thymus [82]. SynOT may need to be given in some cases to reducing post partum bleeding. However, SynOT

given to assist in the third stage of parturition is likely to result in higher levels of OT in the colostrum than normal. We have found no studies on this topic, despite the widespread use of SynOT in the third stage of labour. It would seem that OT levels that protect the mother from post partum haemorrhage would have been strongly selected for and so the question "at what cost does SynOT reduce PPH of mothers?" must be asked. Growing evidence suggests that the level of OT in the first colostrum delivered to an infant is significant for the infant's future immunological health. Possibly by affecting the number of OT receptors available and consequently reducing the impact of OT in the gut.

It is of particular importance that many immunological effects are found only in the period just after birth and that sensitivity to a hormone like OT is very high in the rapidly developing neonate. Recognition is now given to the need for the immune system to defend against potential pathogens and to accept and tolerate the commensal bacteria and all the other new antigens introduced to the infant in the days postnatally without an immune mediated inflammatory response. This process is critical to the ongoing health of the infant and is likely to be affected by the amount of OT introduced in the first feed. Epidemiologically, evidence needs to be considered also, however this paper is already broad in it coverage, crossing several medical research boundaries and so has not considered this area here. We must also take into account the possible effect of perinatal imprinting on OT receptors, OT which is a fundamental and important hub in the hormonal network that is established at birth, when hundreds of genes are activated in the neonatal organism (Figure 2). For example, it is recognized that DNA Methylation at the Neonatal State may influence the future development of Obsessive-compulsive disorder in adulthood [84], We also know that Obsessive-compulsive disorder is associated with epigenetic involvement of oxytocin receptors through a significant change in methylation in two target sequences located in the exon III of the oxytocin receptor gene (OXTR) in patients with obsessive- compulsive disorder [85]. An increasing body of evidence suggests that dysregulation of the oxytocinergic system might be involved in the pathophysiology of neurodevelopmental disorders such as ASDs [86]. After all, if maternal nutrition at the time of conception can affect the regulatory tagging of neonatal's DNA from the earliest embryonic stages, as argues a study, focused on a population of women and children in Gambia [87]. We must think that even the time of Birth, is a time when many genes are activated [88].

As we have seen in this review, there are many reasons to start evaluating the effectiveness of alternative drugs for postpartum haemorrhage prophylaxis. We have considered some of these reasons. We have identified tranexamic acid (TXA) as an alternative molecule to SynOT, to be administered for postpartum haemorrhage prophylaxis. We have therefore designed a longitudinal phase III, open, randomized, clinical trial named "TRANOXY 2016" The trial is registred on EudraCT whit the code number 2016-002047-42. The study includes two treatment groups: group A: TXA 500 mg / 2 vials (1 g) by slow intravenous infusion (max 5ml / min) within 5 minutes after delivery and group B (control): SynOT 5UI / ml / 2 vials (10 Units) intramuscularly within 5 minutes after delivery. The primary outcome of the study will test a hypothesis of equivalence between the two treatments. Therefore, the following hypothesis

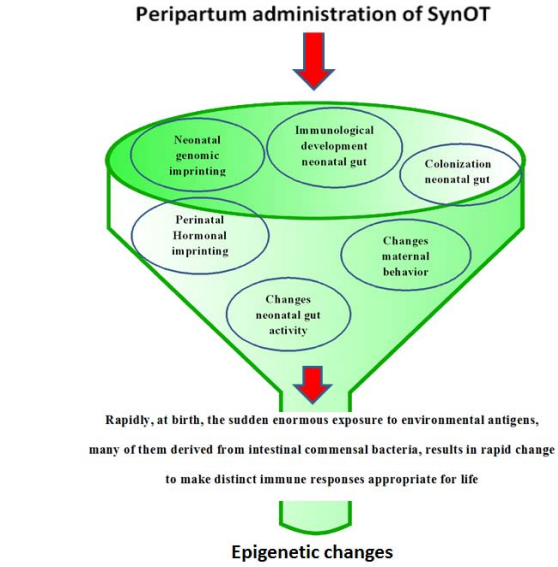

Figure 2 Hypothetical mechanisms through which the administration of SynOT peripartum can lead to modifications of the neonatal epigenetic expression profile.

of equivalence: Group A vs Group B will be tested. The primary aim will be to understand if TXA (ev) is equivalent to SynOT (im) in reducing post partum blood loss (mL) in term patients (37-42 w) at low risk of postpartum haemorrhage. Finally, we will try to demonstrate a considerable advantage of TXA compared to SynOT. TXA is stable over a wide temperature range, from -20° C to + 50°C for more than 12 weeks [89] while SynOT needs to be stored at a controlled temperature (refrigeration between 2-8°C). Furthermore TXA maintains its stability (measured as the activity loss of the block streptokinase (SK) induced by fibrinolysis in 30 ml of plasma for each T° (-20°, -4 °, + 22°, + 50° C) and evaluated with thrombelastography (measure of the units / ml of SK necessary to obtain 100% of the fibrinolysis to 60 min). Therefore, from the time that the drug remains effective for at least 12 weeks out of the temperature recommended by the manufacturer outside hospitals TXA could be used in countries such as sub-Saharan Africa, where about 50% of births take place at home and where the availability of this drug at home of mothers could reduce maternal mortality from PPH, if used on a large scale for prophylaxis of PPH.

1) Finally, it is important to introduce the concept of precautionary principle. The precautionary principle is defined as a risk management strategy in cases where there are indications of adverse effects on the environment or on the health of humans, animals and plants, but available data do not allow a complete risk assessment. The application of the precautionary principle requires three keyThe identification of potential risks

2) A scientific assessment, carried out strictly and comprehensively on the basis of all existing data

3) The lack of scientific certainty that would reasonably exclude the presence of identified risks

For the prophylaxis of postpartum haemorrhage, there are

many studies that compare different oxytocics but very few trials with an arm that receives no treatment or placebo [90]. In fact the evidence that prophylaxis against PPH reduces maternal mortality exists only for misoprostol and not for oxytocin [91]. In an appropriate setting, holistic psychophysiological third stage care compared with Active management of the third stage of care, is safe and leads to a seven fold reduction in PPH [92]. Probably the future will be characterized by the abandonment of the concept that "one size fits all" and the prophylaxis will be reserved for certain groups of patients at risk of PPH. The drugs used for this prophylaxis will have to be differentiated according to the most probable cause of PPH in that particular category of patients.

We think that in the case of SynOT we are faced with a generalized use on a planetary scale of a drug which, although SynOT, at any dose, decreases both PPH greater than 500/1000 mL and the need for therapeutic uterotonics, compared to placebo alone [40]. SynOT still lacks reasonable assurance that it is non-harmful for perinatal and immunological development. We should be guided by the precautionary principle, as it was enshrined in the 1992 Rio de Janeiro Earth Summit Conference, involving more than 120 governmental delegations, from around the world [93].The Rio Declaration was also ratified by the Italian Government in 2004 [94]. For all of the reasons listed above, we think there is an urgent need to test new drugs for post-partum hemorrhage prophylaxis, drugs that are effective and at the same time lack immunologic and perinatal effects on the infant.

REFERENCES

1. Lee HJ, Macbeth AH, Pagani JH, Young WS 3rd. Oxytocin: the great facilitator of life. Prog Neurobiol. 2009; 88: 127-151.
2. Jonas K, Johansson LM, Nissen E, Ejdebäck M, Ransjö-Arvidson AB, Uvnäs-Moberg K. Effects of intrapartum oxytocin administration and epidural analgesia on the concentration of plasma oxytocin and prolactin, in response to suckling during the second day postpartum. Breastfeed Med. 2009; 4: 71-82.
3. Handlin L. Human-Human and Human-Animal Interaction Some Common Physiological and Psychological Effects. Faculty of Veterinary Medicine and Animal Science Department of Animal Environment and Health Skara Doctoral Thesis; Swedish University of Agricultural Sciences. Skara. 2010.
4. Robinson C, Schumann R, Zhang P, Young RC. Oxytocin-induceddesensitization of the oxytocin receptor. Am J Obstet Gynecol. 2003; 188: 497-502.
5. Brimdyr K, Cadwell K, Widström AM, Svensson K, Neumann M, Hart EA, et al. The Association Between Common Labor Drugs and Suckling When Skin-to-Skin During the First Hour After Birth. Birth. 2015; 42: 319-328.
6. Takeda S, Kuwabara Y, Mizuno M. Concentrations and origin of oxytocin in breast milk. Endocrinol Jpn. 1986; 33: 821-826.
7. Kota SK, Gayatri K, Jammula S, Kota SK, Krishna SV, Meher LK, et al. Endocrinology of parturition. Indian J Endocrinol Metab. 2013; 17: 50-59.
8. Power ML, Schulkin J. Maternal regulation of offspring development in mammals is an ancient adaptation tied to lactation. Appl Transl Genom. 2013; 2: 55-63.
9. Işeri SO, Sener G, Sağlam B, Gedik N, Ercan F, Yeğen BC. Oxytocin ameliorates oxidative colonic inflammation by a neutrophil-dependent mechanism. Peptides. 2005; 26: 483-491.
10. Welch MG, Tamir H, Gross KJ, Chen J, Anwar M, Gershon MD. Expression and developmental regulation of oxytocin (OT) and oxytocin receptors (OTR) in the enteric nervous system (ENS) and intestinal epithelium. J Comp Neurol. 2009; 512: 256-270.
11. O'Sullivan A, Farver M, Smilowitz JT. The Influence of Early Infant-Feeding Practices on the Intestinal Microbiome and Body Composition in Infants. Nutr Metab Insights. 2015; 8: 1-9.
12. Che T, Sun H, Li J, Yu X, Zhu D, Xue B, et al. Oxytocin hyperpolarizes cultured duodenum myenteric intrinsic primary afferent neurons by opening BK(Ca) channels through IP_3 pathway. J Neurochem. 2012; 121: 516-525.
13. Yajima M, Karaki SI, Tsuruta T, Kimura S, Nio-Kobayashi J, Kuwahara A, et al. Diversity of the intestinal microbiota differently affects non-neuronal and atropine-sensitive ileal contractile responses to short-chain fatty acids in mice. Biomed Res. 2016; 37: 319-328.
14. Gungor B, Adiguzel E, Gursel I, Yilmaz B, Gursel M. Intestinal Microbiota in Patients with Spinal Cord Injury. PLoS One. 2016; 11: e0145878.
15. Campos-Rodríguez R, Quintanar-Stephano A, Jarillo-Luna RA, Oliver-Aguillón G, Ventura-Juárez J, Rivera-Aguilar V, et al. Hypophysectomy and neurointermediate pituitary lobectomy reduce serum immunoglobulin M (IgM) and IgG and intestinal IgA responses to Salmonella enterica serovar Typhimurium infection in rats. Infect Immun. 2006; 74: 1883-1889.
16. Hernández-Cervantes R, Quintanar-Stephano A, Moreno-Méndoza N, López-Griego L, López-Salazar V, Hernández-Bello R, et al. Regulation of intestinal immune response by selective removal of the anterior, posterior, or entire pituitary gland in Trichinella spiralis infected golden hamsters. PLoS One. 2013; 8: e59486.
17. Yuan L, Liu S, Bai X, Gao Y, Liu G, Wang X et al. Oxytocin inhibits lipopolysaccharide-induced inflammation in microglial cells and attenuates microglial activation in lipopolysaccharide-treated mice. J Neuroinflammation. 2016; 13: 77.
18. Clodi M, Vila G, Geyeregger R, Riedl M, Stulnig TM, Struck J, et al. Oxytocin alleviates the neuroendocrine and cytokine response to bacterial endotoxin in healthy men. Am J Physiol Endocrinol Metab. 2008; 295: E686-691.
19. Walker WA, Iyengar RS. Breast milk, microbiota, and intestinal immune homeostasis. Pediatr Res. 2015; 77: 220-228.
20. McGovern N, Shin A, Low G, Low D, Duan K, Yao LJ, et al. Human fetal dendritic cells promote prenatal T-cell immune suppression through arginase-2. Nature. 2017; 546: 662-666.
21. Csaba G. Complex multicellular functions at a unicellular eukaryote level: Learning, memory, and immunity. Acta Microbiol Immunol Hung. 2017; 64: 105-120.
22. Csaba G. The Faulty Perinatal Hormonal Imprinting as Functional Teratogen. Curr Pediatr Rev. 2016; 12: 222-229.
23. Csaba G. The biological basis and clinical significance of hormonal imprinting, an epigenetic process. Clin Epigenetics. 2011; 2: 187-196.
24. Hashemi F, Tekes K, Laufer R, Szegi P, Tóthfalusi L, Csaba G. Effect of a single neonatal oxytocin treatment (hormonal imprinting) on the biogenic amine level of the adult rat brain: could oxytocin-induced labor cause pervasive developmental diseases? Reprod Sci. 2013; 20: 1255-1263.
25. Schaller F, Watrin F, Sturny R, Massacrier A, Szepetowski P, Muscatelli F. A single postnatal injection of oxytocin rescues the lethal feeding behaviour in mouse newborns deficient for the imprinted Magel2 gene. Hum Mol Genet. 2010; 19: 4895-4905.

26. Lambertini L. Genomic imprinting: sensing the environment and driving the fetal growth. Curr Opin Pediatr. 2014; 26: 237-242.

27. Barlow DP, Bartolomei MS. Genomic imprinting in mammals. Cold Spring Harb Perspect Biol. 2014; 6. pii: a018382.

28. Becker RM. Labor and Luck: The Birth of Modern Oxytocics. 2012.

29. Nathoo T, Ostry A. The One Best Way? Breastfeeding History, Politics, and Policy in Canada. Canadian Public Policy. 2012; 38: 611-613.

30. McCullough ME, Churchland PS, Mendez AJ. Problems with measuring peripheral oxytocin: can the data on oxytocin and human behavior be trusted? Neurosci Biobehav Rev. 2013; 37: 1485-1492.

31. Gimpl G, Fahrenholz F. The oxytocin receptor system: structure, function, and regulation. Physiol Rev. 2001; 81: 629-683.

32. Schmid B, Wong S, Mitchell BF. Transcriptional regulation of oxytocin receptor by interleukin-1beta and interleukin-6. Endocrinology. 2001; 142: 1380-1385.

33. Sarandakou A, Giannaki G, Malamitsi-Puchner A, Rizos D, Hourdaki E, Protonotariou E, et al. Inflammatory cytokines in newborn infants. Mediators Inflamm. 1998; 7: 309-312.

34. Young LJ, Muns S, Wang Z, Insel TR. Changes in Oxytocin Receptor mRNA in Rat Brain During Pregnancy and the Effects of Estrogen and Interleukin-6. J Neuroendocrinol. 1997; 9: 859-865.

35. Nguyen DA, Neville MC. Tight junction regulation in the mammary gland. J Mammary Gland Biol Neoplasia. 1998; 3: 233-246.

36. Peckforton Pharmaceuticals. 2015.

37. Dawood MY, Raghavan KS, Pociask C, Fuchs F. Oxytocin in human pregnancy and parturition. Obstet Gynecol. 1978; 51: 138-143.

38. Ravanos K, Dagklis T, Petousis S, Margioula-Siarkou C, Prapas Y, Prapas N. Factors implicated in the initiation of human parturition in term and preterm labor: a review. Gynecol Endocrinol. 2015; 31: 679-683.

39. Knobil E, Neill JD. Knobil and Neill's Physiology of reproduction. Elsevier. 2006; 2.

40. Begley CM, Gyte GM, Devane D, McGuire W, Weeks A. Active versus expectant management for women in the third stage of labour. Cochrane Database Syst Rev. 2015; 3: CD007412.

41. Barbieri RL. Routine use of oxytocin at birth: just the right amoung to prevent post-partum hemorrhage. OBG Manag. 2012; 24: 8-11.

42. Westhoff G, Cotter AM, Tolosa JE. Prophylactic oxytocin for the third stage of labour to prevent postpartum haemorrhage. Cochrane Database Syst Rev. 2013; 10: CD001808.

43. Atrash HK. Parents' Death and its Implications for Child Survival. Rev Bras Crescimento Desenvolv Hum. 2011; 21: 759-770.

44. Phaneuf S, Rodríguez Liñares B, TambyRaja RL, MacKenzie IZ, López Bernal A. Loss of myometrial oxytocin receptors during oxytocin-induced and oxytocin-augmented labour. J Reprod Fertil. 2000; 120: 91-97.

45. Klein BY, Tamir H, Hirschberg DL, Glickstein SB, Welch MG. Oxytocin modulates mTORC1 pathway in the gut. Biochem Biophys Res Commun. 2013; 432: 466-471.

46. Zingg HH, Rozen F, Breton C, Larcher A, Neculcea J, Chu K, et al. Gonadal steroid regulation of oxytocin and oxytocin receptor gene expression. Adv Exp Med Biol. 1995; 395: 395-404.

47. Voss AK, Fortune JE. Estradiol-17 beta has a biphasic effect on oxytocin secretion by bovine granulosa cells. Biol Reprod. 1993; 48: 1404-1409.

48. Kimura T, Saji F, Nishimori K, Ogita K, Nakamura H, Koyama M, et al. Molecular regulation of the oxytocin receptor in peripheral organs. J Mol Endocrinol. 2003; 30: 109-115.

49. Welshons WV, Thayer KA, Judy BM, Taylor JA, Curran EM, vom Saal FS. Large effects from small exposures. I. Mechanisms for endocrine-disrupting chemicals with estrogenic activity. Environ Health Perspect. 2003; 111: 994-1006.

50. Fanaroff AA, Martin RJ, Walsh MC. Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant. Elsevier. 2011.

51. Kurobe H, Tominaga T, Sugano M, Hayabuchi Y, Egawa Y, Takahama Y, et al. Complete but not partial thymectomy in early infancy reduces T-cell-mediated immune response: three-year tracing study after pediatric cardiac surgery. J Thorac Cardiovasc Surg. 2013; 145: 656-662.

52. Alberto V, Eva J, Rosa S, Margarita RM, Enrique M, Agustín GZ, et al. Analysis of the human neonatal thymus: evidence for a trasient thymic involution. J Immunol. 2000; 164: 6260-6267.

53. Konkel JE, Jin W, Abbatiello B, Grainger JR, Chen W. Thymocyte apoptosis drives the intrathymic generation of regulatory T cells. Proc Natl Acad Sci U S A. 2014; 111: E465-473.

54. Parigi SM, Eldh M, Larssen P, Gabrielsson S Villablanca EJ. Breast Milk and Solid Food Shaping Intestinal Immunity. Front Immunol. 2015; 6: 415 .

55. Newburg DS, Walker WA. Protection of the neonate by the innate immune system of developing gut and of human milk. Pediatr Res. 2007; 61: 2-8.

56. Walker WE, Goldstein DR. Neonatal B cells suppress innate toll-like receptor immune responses and modulate alloimmunity. J Immunol. 2007; 179: 1700-1710.

57. Mila H, Feugier A, Grellet A, Anne J, Gonnier M, Martin M, et al. Inadequate passive immune transfer in puppies: definition, risk factors and prevention in a large multi-breed kennel. Prev Vet Med. 2014; 116: 209-213.

58. Kim P, Strathearn L, Swain JE. The maternal brain and its plasticity in humans. Horm Behav. 2016; 77: 113-123.

59. Riem MM, Bakermans-Kranenburg MJ, Pieper S, Tops M, Boksem MA, Vermeiren RR, et al. Oxytocin modulates amygdala, insula, and inferior frontal gyrus responses to infant crying: a randomized controlled trial. Biol Psychiatry. 2011; 70: 291-297.

60. Swain JE. The human parental brain: in vivo neuroimaging. Prog Neuropsychopharmacol Biol Psychiatry. 2011; 35: 1242-1254.

61. Brown A, Jordan S. Active management of the third stage of labor may reduce breastfeeding duration due to pain and physical complications. Breastfeed Med. 2014; 9: 494-502.

62. Zelkowitz P, Gold I, Feeley N, Hayton B, Carter CS, Tulandi T, et al. Psychosocial stress moderates the relationships between oxytocin, perinatal depression, and maternal behavior. Horm Behav. 2014; 66: 351-360.

63. Kroll-Desrosiers AR, Nephew BC, Babb JA, Guilarte-Walker Y4, Moore Simas TA5, Deligiannidis KM6, et al. Association of peripartum synthetic oxytocin administration and depressive and anxiety disorders within the first postpartum year. Depress Anxiety. 2017; 34: 137-146.

64. Gu V, Feeley N, Gold I, Hayton B, Robins S, Mackinnon A, et al. Intrapartum Synthetic Oxytocin and Its Effects on Maternal Well-Being at 2 Months Postpartum. Birth. 2016; 43: 28-35.

65. Carter S, Perges SW. Evolution, Early Experience and Human Development: From Research to Pactice to Policy, chapter 5;

Neurobiology and the Evolution of mammalian Social Behaviour. Oxford University Press. 2013.

66. Yamamoto Y, Cushing BS, Kramer KM, Epperson PD, Hoffman GE, Carter CS. Neonatal manipulations of oxytocin alter expression of oxytocin and vasopressin immunoreactive cells in the paraventricular nucleus of the hypothalamus in a gender-specific manner. Neuroscience. 2004; 125: 947-955.

67. Miller TV, Caldwell HK. Oxytocin during Development: Possible Organizational Effects on Behavior. Front Endocrinol. 2015; 6: 76.

68. Bale TL, Davis AM, Auger AP, Dorsa DM, McCarthy MM. CNS region-specific oxytocin receptor expression: importance in regulation of anxiety and sex behavior. J Neurosci. 2001; 21: 2546-2452.

69. Peña CJ, Kronman HG, Walker DM, Cates HM, Bagot RC, Purushothaman I, et al. Early life stress confers lifelong stress susceptibility in mice via ventral tegmental area OTX2. Science. 2017; 356: 1185-1188.

70. Qin J, Feng M, Wang C, Ye Y, Wang PS, Liu C. Oxytocin receptor expressed on the smooth muscle mediates the excitatory effect of oxytocin on gastric motility in rats. Neurogastroenterol Motil. 2009; 21: 430-438.

71. Poutahidis T, Kearney SM, Levkovich T, Qi P, Varian BJ, Lakritz JR, et al. Microbial symbionts accelerate wound healing via the neuropeptide hormone oxytocin. PLoS One. 2013; 8: e78898.

72. Chen D, Zhao J, Wang H, An N, Zhou Y, Fan J, et al. Oxytocin evokes a pulsatile PGE2 release from ileum mucosa and is required for repair of intestinal epithelium after injury. Sci Rep. 2015; 5: 11731.

73. Chinen T, Komai K, Muto G, Morita R, Inoue N, Yoshida H, et al. Prostaglandin E2 and SOCS1 have a role in intestinal immune tolerance. Nat Commun. 2011; 8; 2.

74. Welch MG, Margolis KG, Li Z, Gershon MD. Oxytocin regulates gastrointestinal motility, inflammation, macromolecular permeability, and mucosal maintenance in mice. Am J Physiol Gastrointest Liver Physiol. 2014; 307: G848-862.

75. Udall JN, Pang K, Fritze L, Kleinman R, Walker WA. Development of gastrointestinal mucosal barrier. I. The effect of age on intestinal permeability to macromolecules. Pediatr Res. 1981; 15: 241-244.

76. GRUSKAY FL, COOKE RE. The gastrointestinal absorption of unaltered protein in normal infants and in infants recovering from diarrhea. Pediatrics. 1955; 16: 763-769.

77. Maheshwari A, Zemlin M.Ontogeny of the intestinal immune system. Haematologica reports. 2006; 2: 18-26.

78. Anderson RC, Dalziel JE, Gopal PK, Bassett S, Ellis A, Roy NC. The Role of Intestinal Barrier Function in Early Life in the Development of Colitis. Gastroenterol. 2012.

79. Vukavić T. Timing of the gut closure. J Pediatr Gastroenterol Nutr. 1984; 3: 700-703.

80. Liu D, Wang S, Jiang T, Ding P. TNF-α Mediated Secretory Component is Positively Regulated by PI3K/AKT/MTOR in CACO-2 Cells. J Med Biochem. 2013; 32: 116-120.

81. Mathias A, Duc M, Favre L, Benyacoub J, Blum S, Corthésy B. Potentiation of polarized intestinal Caco-2 cell responsiveness to probiotics complexed with secretory IgA. J Biol Chem. 2010; 285: 33906-33913.

82. Geenen V, Bodart G, Henry S, Michaux H, Dardenne O, Charlet-Renard C, et al. Programming of neuroendocrine self in the thymus and its defect in the development of neuroendocrine autoimmunity. Front Neurosci. 2013;7: 187.

83. Kapitonov VV, Koonin EV. Evolution of the RAG1-RAG2 locus: both proteins came from the same transposon. Biol Direct. 2015;10: 20.

84. Nissen JB, Hansen CS, Starnawska A, Mattheisen M, Børglum AD, Buttenschøn HN, et al. DNA Methylation at the Neonatal State and at the Time of Diagnosis: Preliminary Support for an Association with the Estrogen Receptor 1, Gamma-Aminobutyric Acid B Receptor 1, and Myelin Oligodendrocyte Glycoprotein in Female Adolescent Patients with OCD. Front Psychiatry. 2016; 7: 35.

85. Cappi C, Diniz JB, Requena GL, Lourenço T, Lisboa BC, Batistuzzo MC, et al. Epigenetic evidence for involvement of the oxytocin receptor gene in obsessive-compulsive disorder. BMC Neurosci. 2016; 17: 79.

86. Romano A, Tempesta B, Micioni Di Bonaventura MV, Gaetani S. From Autism to Eating Disorders and More: The Role of Oxytocin in Neuropsychiatric Disorders. Front Neurosci. 2016; 9: 497.

87. Dominguez-Salas P, Moore SE, Baker MS, Bergen AW, Cox SE, Dyer RA, et al. Maternal nutrition at conception modulates DNA methylation of human metastable epialleles. Nat Commun. 2014; 5: 3746.

88. Kanherkar RR, Bhatia-Dey N, Csoka AB. Epigenetics across the human lifespan. Front Cell Dev Biol. 2014; 2: 49.

89. de Guzman R, Polykratis IA, Sondeen JL, Darlington DN, Cap AP, Dubick MA. Stability of tranexamic acid after 12-week storage at temperatures from -20°c to 50°c. Prehosp Emerg Care. 2013; 17: 394-400.

90. Weeks AD, Neilson JP2. Rethinking our approach to postpartum haemorrhage and uterotonics. BMJ. 2015; 351: h3251.

91. Hofmeyr GJ, Gülmezoglu AM, Novikova N, Lawrie TA. Postpartum misoprostol for preventing maternal mortality and morbidity. Cochrane Database Syst Rev. 2013; 7: CD008982.

92. Fahy K, Hastie C, Bisits A, Marsh C, Smith L, Saxton A. Holistic physiological care compared with active management of the third stage of labour for women at low risk of postpartum haemorrhage: a cohort study. Women Birth. 2010; 23: 146-152.

93. Stirling A. The precautionary principle. 2009.

94. COMITATO NAZIONALE PER LA BIOETICA, Il principio di precauzione: profili bioetici, filosofici, giuridici. Roma. 2004.