Review

Neuroendocrinology of childbirth and mother–child attachment: The basis of an etiopathogenic model of perinatal neurobiological disorders

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1. Introduction: Childbirth as a neurobiological and neuroendocrine event

Physiological changes in the dynamics and mechanics of labor in women have been thoroughly studied (Liao et al., 2005). However, the peripartal neurohormonal scenery in the brain of the mother, the fetus and the newborn has received little attention. Here we will approach human childbirth as a neurohormonal event rather than a mechanical one and we will specifically focus on the peripartal neuroendocrine mechanisms that participate in the generation of mother–child attachment. We will also consider possible disrupting effects that some obstetrical interventions during the peripartal period may have on the neuroendocrine mechanisms of mother–child attachment, as well as its possible long-term consequences for the newborn. Birth outcomes have traditionally been measured in terms of maternal and neonatal morbidity in the short term, indicators that may not be valid to study the impact of hypothetical changes in the brain during childbirth or the early postnatal period. This impact may only be manifested later in life, during adolescence or even in adulthood. Understanding the neuroendocrine events involved in mother–child attachment that happen in both maternal and fetal brains during the peripartum period may allow the building of an etiopathogenic model of some mental disorders that would be better understood as the consequence of peripartal neuroendocrine alterations.

Motherhood entails neurochemical, morphological and functional brain changes designed to ensure the survival of newborns. Understanding the neuroendocrine events involved in mother–child attachment that happen in both maternal and fetal brains during the peripartum period may allow the building of an etiopathogenic model of some mental disorders that would be better understood as the consequence of peripartal neuroendocrine alterations.

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In this review we will specifically focus on the hormonal cascade in the maternal and the newborn brain at parturition, the early postpartum period and lactation, which primes the mother and the newborn for attachment initiation and consolidation (Fig. 1). Attachment theory, proposed by Bowlby, has become the dominant model of human emotional and social development. According to Bowlby, attachment between the infant and his or her mother is an innate biological response that increases the probability of survival (Bowlby, 1978). Our hypothesis is that in humans, like in other mammalian species (Mogi et al., 2011), peripartal neuroendocrine events play an essential role in the initiation of the bonding of the mother and the newborn immediately after birth. A disruption in these neuroendocrine events, even when intervention is necessary due to serious medical reasons, is likely to have not only a short-term impact on mother–child attachment but also long-term effects in the newborn, increasing the risk of behavioral alterations or mental health problems that may have not yet been causally related to a peripartal origin. Thus, we will also review in the present paper several potential etiopathogenic neuroendocrine scenarios during labor and the early postpartum period that are associated with neuroendocrine modifications, such as elective Cesarean section, intrapartum hormonal manipulations, preterm delivery, mother–infant postpartum separation and bottle-feeding instead of breastfeeding (Fig. 2).

2. Neuroendocrine events at parturition that affect mother–child attachment

2.1. Neuroendocrine events in the mother at parturition

2.1.1. Oxytocin

Studies in rodents and sheep indicate that the stimulation of the vagina and cervix at birth plays an important role in the induction of maternal behavior (Keverne et al., 1983; Yeo and Keverne, 1986; Kendrick and Keverne, 1991). Vaginal and cervix stimulation also triggers in sheep the formation of olfactory recognition memory that is essential for the selective recognition of lambs and for the formation of maternal bonding (Keverne et al., 1983; Kendrick et al., 1991b). These effects on maternal behavior and olfactory recognition may be mediated by the increased levels of oxytocin in the brain caused by the stimulation of the vagina and cervix. Indeed, one of the most important neuroendocrine events in the mother at parturition in relation with mother–child attachment is the activation of the oxytocinergic system. In rodents, gonadal steroids prime the oxytocin system to become activated in preparation of birth and maternal behavior (Crowley et al., 1995; Amico et al., 1997; Windle et al., 2006; Donner et al., 2007). However, oxytocinergic neurons remain at rest during pregnancy, avoiding premature birth (Brunton and Russell, 2010). Several mechanisms and hormonal systems contribute to maintain oxytocinergic neurons at rest until parturition (Brunton et al., 2014). These include actions of central opioids, which contribute to restrain premature oxytocin release by acting on μ-receptors on magnocellular oxytocinergic neurons or on presynaptic inputs to these neurons (Dondi et al., 1991; Douglass et al., 1993, 1995; Wigger et al., 1999). In addition, the progesterone metabolite allopregnanolone, prevents the release of oxytocin in late gestation through potentiation of the inhibitory effect of GABA_{A} receptors on magnocellular oxytocinergic neurons (Brunton and Russell, 2010; Brunton et al., 2014) and by inducing opioid inhibition over these neurons (Brunton et al., 2012, 2014).

While the activation of the oxytocinergic system is inhibited during pregnancy by the above mentioned mechanisms, its activation is necessary for parturition and for the onset of lactation and maternal behavior. Consistently with the essential role of oxytocin release by magnocellular neurons for parturition and lactation, functional and anatomical plastic changes in oxytocin neurons and associated glial cells are manifested around parturition and the onset of lactation in rodents (Leng et al., 1999; Theodosis and Poulain, 2001; Tasker et al., 2002; Kokasma et al., 2005; Theodosis et al., 2006). These neuroplastic events include changes in oxytocin immunoreactivity (Jirikowski et al., 1989), in neuronal firing (Lincoln and Wakerley, 1974; Leng et al., 1999), in the number of glutamatergic and GABAergic synaptic inputs (Theodosis and Poulain, 2001), in the release of glutamate and GABA (Stern et al.,
Modified from neuroendocrine regulation at perinatal period are likely to increase susceptibility to problems in the newborn in life. Several epistatic-driven scenarios during labor and the postpartum period can be envisaged. These include interventions during labor, such as cesarean section, administration of synthetic oxytocin, oxytocin receptor antagonists or opioids, preterm delivery, mother–infant separation after delivery or the substitution of breastfeeding by bottle-feeding. All these conditions and circumstances result in modifications in the physiological levels of some key hormones, such as oxytocin, which are involved in the process of mother–infant attachment. These peripartal neuroendocrine disruptions may contribute to alterations in maternal care and be a risk factor for the development of affective disorders in the mother, such as postpartum depression (PPD) or posttraumatic stress disorder (PTSD). Hormonal alterations and the disruption of attachment may also affect the development of some regions in the brain in the newborn, such as the hippocampus and may represent a risk factor for the development of autism, attention deficit hyperactive disorder (ADHD), anxiety, feeding disorders, learning disabilities or other mental disorders.

**2.1. Cortisol**

Another hormone that changes during labor and that may affect the interaction of the mother with baby is cortisol. In women, the levels of cortisol are increased during labor (Wilcox et al., 1985; Campbell et al., 1987; Ohana et al., 1996). This increase in cortisol levels may also contribute to the development of mother–child attachment, since circulating or salivary cortisol levels in human mothers have been positively correlated with several aspects of maternal behavior (Fleming et al., 1987, 1997; Stallings et al., 2001; Kranz et al., 2005), including the recognition and attraction for baby odors (Fleming et al., 1997). Corticosterone also increases maternal behavior in postpartum rats (Graham et al., 2006) (see Section 3.1).
2.2. Neuroendocrine events in the fetus at parturition

An investigation of the mechanism of labor using real time MRI confirmed that human fetuses must negotiate a curve to be born. An MRI video from that study shows clearly the strong physical compression that the fetal brain undergoes during labor (Bamberg et al., 2012). This intrapartum mechanical compression of the fetal brain probably leads to a massive neurohumoral release and to electrophysiological changes that have not yet been thoroughly studied. In rats, a dramatic surge of neurotransmitters, neurosteroids, neuropeptides, and neuromodulators occurs during the birth process and shortly thereafter, facilitating physiological processes such as respiration (Ronca and Alberts, 1995) and suckling (Abel et al., 1998). In humans, the passage of the baby head through the birth canal is accompanied by a substantial activation of the sympathetic axis and the enhanced release of noradrenaline, cortisol and vasopressin (Gennser et al., 1977; Puolakka et al., 1983; Costa et al., 1988; Wellmann et al., 2010). This situation has been called by some authors "the stress of labor", which is both beneficial and necessary for newborns (Lagercrantz and Slotkin, 1986). It has been hypothesized that this eustressor acts to prime the fetal genome to trigger optimal responses to extra uterine life (Dahlen et al., 2013). The massive sympathetic activation stimulates lung fluid reabsorption and facilitates newborn physiological adaptation after delivery. It promotes lung maturity, increases blood flow, regulates circulating cytokine levels, mobilizes fuel and activates the central nervous system (Chen et al., 1998; Malamitsi-Puchner et al., 2005; Miller et al., 2005; Yektaei-Karin et al., 2007). The alterations produced by vaginal birth are resolved after birth by vagal stimulation produced by skin to skin contact and early suckling (Bystrova et al., 2003; Ferber and Makboul, 2004).

The increase in noradrenaline levels in the newborn at parturition (Puolakka et al., 1983; Costa et al., 1988) may facilitate mother–child attachment, since noradrenaline levels in the newborn are positively correlated with olfactory learning shortly after birth (Varendi et al., 2002). During a natural childbirth the odor of the mother is supposed to be the first biologically relevant odor that the newborn confronts. Therefore, the increase in noradrenaline levels caused by vaginal delivery may contribute to the identification of the odor of the newborn, and to the establishment of the attachment of the newborns with their mothers. This is suggested by the findings of Varendi et al. (2002), who exposed babies born by Cesarean section to an odor for 30 min shortly after birth. Babies from births with uterine labor contractions before Cesarean delivery showed increased preference for the exposed odor when exposed to a new odor, compared to babies from births without uterine contractions. These findings suggest that labor-induced noradrenaline release facilitates olfactory learning in the newborns shortly after birth and therefore may facilitate mother–child attachment.

Vaginal birth is also associated with an extremely steep rise of circulating vasopressin in the newborn (Schubert et al., 1981), higher than that observed in critically ill adult patients with shock or brain injury (Wellmann et al., 2010). The consequences of this massive increase in vasopressin in human newborns have not been studied, although it has been proposed that the vasopressin rise may be involved in the analgesic effects caused by vaginal delivery in human newborns (Wellmann and Buhrer, 2012).

3. Immediate postpartum: Sensitive period

3.1. Mother–child synchrony: Importance of skin-to-skin contact

Humans are born biologically prepared to establish coordinated interactions from the first hours of life. Right after delivery occurs the so-called sensitive period, a quiet alertness state that lasts for about two hours (Bystrova et al., 2009). The neonatal sensitive period includes the spontaneous onset of breastfeeding in the first two hours of life. The first hours after birth are also a critical period for the development of attachment behavior (Mehler et al., 2011).

In humans, randomized controlled studies suggest that the body of the mother is the natural habitat for the naked infant (Winberg, 2005). Skin-to-skin contact immediately after delivery helps the baby to conserve energy, adjust acid–base balance and breathing and has a calming effect (Uvnäs-Moberg, 1996; Winberg, 2005). It also increases maternal attention to her baby (Winberg, 2005) and reduces cortisol levels in the mother (Handlin et al., 2009). Skin-to-skin contact with both mothers and fathers reduces infants’ crying (Christessonn et al., 1995; Erlandsson et al., 2007) and promotes vocal communication between parents and newborns (Velandia et al., 2010). It is likely that oxytocin released during the skin-to-skin contact also increases the parental responsiveness to infant cues (Velandia et al., 2010). As a consequence of early skin-to-skin contact, infant regulation of emotions, stress reactivity, metabolic adaptation, social and cognitive development and future interaction between mother and infant are promoted (Bystrova et al., 2009; Velandia et al., 2010). It is the beginning of the continuous development of mother–child synchrony (Winberg, 2005), facilitated mostly by lactation and oxytocin. Indeed, salivary oxytocin levels between mothers and infants are significantly correlated, being high oxytocin levels associated with greater degree of mother–infant affect synchrony (Feldman et al., 2010a).

Increased oxytocin levels in the newborn caused by skin-to-skin contact probably play an important role in the initiation of breastfeeding. The smell of the breast helps the baby to initiate breastfeeding. Natural maternal breast odors reduce crying (Doucet et al., 2007) and elicit approach behavior in newborns whereas unpleasant odors induce avoidant behavior (Varendi and Porter, 2001). Newborns guided by smell spontaneously seek the nipple and usually initiate breastfeeding in the first hour of life (Porter and Winberg, 1999; Varendi et al., 2002) if they are placed in skin-to-skin contact with their mothers (Widstrom et al., 1987). In rats, maternal skin-to-skin contact increases central oxytocin in the pups, facilitating the induction of preference for maternal odor and the establishment of social affiliation (Kojima and Alberts, 2011; Kojima et al., 2012). Furthermore, higher levels of noradrenaline immediately after birth may support better odor learning in rat pups (Miller and Spear, 2008). Thus, odor exposure after birth likely occurs under a different internal neurochemical milieu for the pup odor exposure later in life (Ronca et al., 2006). Indeed, the neonatal surge of noradrenaline may induce an olfactory imprinting-like occurrence in mammals without the need for an explicit reinforcer to form a lasting odor preference (Sullivan et al., 1991). This is also probably the case in humans, in which noradrenaline released in the newborn during labor facilitates learning and recognition of the mother odor (Varendi et al., 2002).

In most mammals, pup odors elicit maternal behavior in the mother (Kinsley and Amory-Meyer, 2011; Levy et al., 2004). Human mothers also show changes in olfaction and recognize the odors of their babies as pleasant. Interestingly, human mothers have increased oxytocin levels during the first hour after delivery (Nissen et al., 1995), corresponding to the sensitive period. Oxytocin plays a key role in the processing of olfactory information by mothers and the infusion of oxytocin in the olfactory bulb produces a rapid onset of maternal behavior in rats. This, in turn, modulates the release of noradrenaline, which is involved in olfactory learning not only in the newborn but also in the mother (Levy et al., 2004; Kinsley and Amory-Meyer, 2011). In rats corticosterone enhances maternal behavior and maternal memory (Graham et al., 2006). In women, cortisol plays an important role in the attraction to the body odor of their infants in human mothers.
Indeed, postpartum cortisol levels in women are positively correlated with attraction for the odor of their own babies and with the ability to recognize their own baby’s odor (Fleming et al., 1997).

Vasopressin is also involved in maternal behavior, regulating maternal care and maternal aggression (Bosch and Neumann, 2008). In rats, the vasopressin system in the mother is activated around parturition and in lactation, with increased expression of vasopressin in the paraventricular nucleus of the hypothalamus and increased release in different structures, such as the bed nucleus of the stria terminalis and the medial preoptic area (Landgraf et al., 1991; Bosch and Neumann, 2008; Bosch, 2011). This increased release of vasopressin is necessary for the maintenance of maternal care (Bosch, 2011). In addition, vasopressin release in the central amygdala correlates with the amount of maternal aggression, which may be in part mediated by the regulation of the central amygdala correlates with the amount of maternal anxiety (aggression, which may be in part mediated by the regulation of the central amygdala). Therefore, the interaction of the mother with her pups seems to be necessary for the generation of specific neuroplastic changes in the mother brain during the postpartum period. It is unknown if similar neuroplastic changes occur in the brain of human mothers, although the limited fMRI studies available suggest the existence of functional modifications in the hypothalamus, amygdala and cerebral cortex in the brain of women during the postpartum period (Kim et al., 2010; Lord et al., 2012; Rupp et al., 2014). In addition, these functional modifications in the brain of postpartum women are influenced by the interaction with their infants (Kim et al., 2010; Musser et al., 2012).

3.2. Lactation

In most mammals, the stimulation of the teats by her pups elicits a modification in the activity of oxytocin magnocellular neurons, resulting in a pulsatile release of oxytocin in the hypothalamus that leads to periodic milk ejections (Poulain and Wakerley, 1982). In humans, nipple stimulation also increases oxytocin levels in breastfeeding mothers (Dawood et al., 1981; Amico and Finley, 1986; Uvnäs-Moberg et al., 1990; Uvnäs-Moberg, 1996; Matthiasen et al., 2001; White-Traut et al., 2009). In a parallel increased intracerebral release of oxytocin during lactation, together with an increased expression of oxytocin receptors, in specific brain regions (Kendrick et al., 1988; Moos et al., 1989; Neumann et al., 1993a,b; Bealer and Crowley, 2001; Veenema and Neumann, 2008). This increase in intracerebral oxytocinergic signaling may mediate the association between breastfeeding and mother–child attachment, since central oxytocin promotes maternal care in rodents (Bosch and Neumann, 2012). Although the relation of peripheral and central oxytocin is not well understood (Neumann et al., 2013), in women there is a positive correlation between salivary oxytocin levels and affectionate maternal behavior during mother–child interactions (Feldman et al., 2010b). Furthermore, the interaction with their infants causes higher circulating oxytocin levels and increased activation of mesocorticolimbic reward regions in women with secure attachment than in women with insecure/dismissing attachment (Strathern et al., 2009a; Strathern, 2011). Higher circulating oxytocin in fathers is also correlated with more affectionate and stimulatory behaviors when interacting with their children (Feldman et al., 2010a,b; Gordon et al., 2010).

Breastfeeding has additional affective consequences for mothers that may also facilitate their interactions with their infants. Lactation in humans and other mammals reduces physiological reactivity to various stressors (Stern et al., 1973; Neumann et al., 1998; Johnstone et al., 2000; Walker et al., 2001; Heinrichs et al., 2001, 2002; Slattery and Neumann, 2008; Bosch and Neumann, 2012). In rats, lactation reduces corticotropin-releasing factor mRNA expression in the parvocellular paraventricular hypothalamic neurons (Johnstone et al., 2000; Walker et al., 2001; Klampfl et al., 2013) and reduced expression of corticotropin-releasing factor receptors in the pituitary corticortrophs (Neumann et al., 1998). In women, breastfeeding decreases adrenocorticotropic hormone, total plasma cortisol and salivary free cortisol and the HPA axis response to physical and psychosocial stress (Altemus et al., 1995; Heinrichs et al., 2001, 2002). Nursing mothers often describe a state of decreased anxiety (Carter and Altemus, 1997) and interact more positively with their babies, touching and directing more smiles towards them, than those using artificial feeding (Duna and Richards, 1977). Similarly, there is a reduction of the autonomic responses, such as modifications in heart rate and skin conductance, to the cries of babies in lactating versus non-lactating mothers (Wiesenfeld et al., 1985). This reduction in stress response associated with breastfeeding, could be seen as an adaptive response that protects mothers from an exaggerated response to stressful stimuli ensuring successful breastfeeding (Carter and Altemus, 1997).
It is also important to consider that breastfeeding may have long-term consequences for the infants. Some studies suggest that early exclusive breastfeeding may be associated with better cognitive skills latter in life (Isaacs et al., 2010; Hallowell and Spatz, 2012; Deoni et al., 2013; Kafouri et al., 2013). In a study using MRI, infant breastfeeding was associated with improved developmental growth in late maturing white matter association regions involved in higher-order cognition, such as executive functioning, planning, social-emotional functioning and language, domains in which breastfed infants were also found to have improved performance (Deoni et al., 2013; Julevat et al., 2014). In the same study breastfeeding duration beyond 15 months was associated with improved white matter structure and cognitive performance (Deoni et al., 2013). In this regard it is important to consider that the duration of breastfeeding in humans is estimated to range physiologically from two and a half to seven years of life (Dettwyler, 1995) and that the World Health Organization (WHO) recommends breastfeeding continuation for up to two years of age or beyond (WHO, 2003). Breastfeeding statistics indicate that most women breast their baby soon after birth (95% in Norway, 92% in Australia, (WHO, 2003). Breastfeeding statistics indicate that most women breast their baby soon after birth (95% in Norway, 92% in Australia, 89% in Canada and 76.5% in the United States). In the United States, infants born in 2010, 49% were breastfeeding at 6 months and 27% at 12 months (Gionet, 2013; National Center for Chronic Disease Prevention and Health Promotion, 2013).

4. Potential etiopathogenic neurohormonal scenarios during labor and the early postpartum period

4.1. The intrapartum period

4.1.1. Omission of all the stages of labor: elective Cesarean section

4.1.1.1. Consequences for the newborn. Several circumstances may potentially disrupt the neuroendocrine mechanisms of mother–child attachment during the peripartal period in humans (Fig. 2). One of these is the elimination of labor in planned Cesarean sections. The use of Cesarean section for delivery is continuously rising worldwide, often for non medical reasons. Cesarean rates were of 32.8% in the US in 2011 (Hamilton et al., 2013), 48% in China in 2010 (Lumbiganon et al., 2010; Souza et al., 2010) and 45.9% in Brazil and 41.9% in Iran in 2008 (Gibbons et al., 2012). In some cultural groups Cesarean can be perceived as a preferred way to deliver (Nuttall, 2000) or even as a safer option, without a medical reason for it. Although there is a growing concern about the effects of Cesarean section on brain maturation of infants (Kapellou, 2011), the potential long term consequences of elective Cesarean sections in both the maternal and the newborn brain have received little attention. The studies that assess the effects of Cesareans typically consider only short term health outcomes and physical morbidity (Chirossi et al., 2013).

In planned Cesarean sections the neurohormonal transition is quite sharp, very different to the neuroendocrine cascade that happens in a physiological vaginal delivery. As mentioned before, with vaginal delivery there is a dramatic surge of circulating vasopressin (approximately 100-fold) in the newborn that does not occur after programmed Cesarean section (Wellmann et al., 2010; Wellmann and Buhrer, 2012). The consequences that for the neonate born by Cesarean section may have the abolition of this increase in vasopressin levels are unknown (see Section 2.2). In addition, catecholamines and cortisol levels are relatively low in babies born by Cesarean section compared to babies born by vaginal delivery (Gitau et al., 2001; Mears et al., 2004; Miller et al., 2005). These differences in catecholamines and cortisol levels may be related with the reported differences in respiratory distress, a complication that is more frequent after elective Cesarean sections than after normal vaginal deliveries (Wankaew et al., 2013). Cesarean section delivery may also alter gut colonization and immunological development (Malamitsi-Puchner et al., 2005; Vogt et al., 2006) and may cause epigenetic changes in the neonate (Dahlen et al., 2013). Indeed, an increased DNA-methylation in leucocytes has been detected in infants delivered by Cesarean section compared to infants vaginally born (Schlizzig et al., 2009), although another study did not detect an effect of the type of delivery on global methylation of DNA from blood isolated from umbilical venous cord at birth (Virani et al., 2012).

A crucial event that occurs in the newborn brain at parturition is the shift of GABA neurotransmission from being excitatory before birth to be inhibitory after birth (Cherubini et al., 1991). This is because during embryonic development the intracellular chloride concentration [Cl−]i in neurons is higher than in postnatal neurons. Thus, when GABA opens the GABA_A channel, there is a chloride efflux and depolarization in prenatal neurons and a chloride influx and hyperpolarization in postnatal neurons (Cherubini et al., 1991). Oxytocin plays an essential role in the reduction of [Cl−]i in neurons during parturition (Tyzio et al., 2006; Khazipov et al., 2008). This action of oxytocin protects the newborn brain from delivery hypoxia and also exerts analgesic actions in the newborn (Tyzio et al., 2006; Mazzuca et al., 2011). In addition, the action of oxytocin on GABAergic neurons during delivery may also decrease the risk of long-term deleterious consequences on an enhanced neuronal activity and may contribute to prevent the development of autism (Tyzio et al., 2014). The origin of oxytocin in the offspring brain during parturition is under debate. In rodents, the synthesis of brain oxytocin increase progressively during fetal development (Altstein and Gainer, 1988). However, the amide mature oxytocin is not produced after term (Altstein and Gainer, 1988). Thus, it has been proposed that maternal oxytocin, which is known to cross the placenta (Malek et al., 1996), is the main source of oxytocin for the fetal brain in rodents (Tyzio et al., 2006). However, there is evidence of production of oxytocin by the human fetal brain (Tyzio et al., 2007). With independence of the origin of oxytocin, an important question that remains to be determined is whether the reduction of [Cl−]i in neurons during parturition, and the consequent shift of GABA neurotransmission from excitatory to inhibitory, is altered in absence of labor.

Experiments in mice suggest that the omission of the stages of labor in elective Cesarean sections may affect brain development of the offspring. Vaginal delivery, but not Cesarean section, induces the expression of mitochondrial uncoupling protein 2 (UCP2) in the newborn hippocampus (Simon-Areces et al., 2012). UCP2 is involved in synaptogenesis, fuel utilization, and mitochondrial bioenergetics and proliferation. Therefore, the induction of UCP2 by vaginal delivery may have important consequences for the developing brain. Indeed, the relevance of the induction of UCP2 in the newborn hippocampus is suggested by the fact that the pharmacological inhibition or the genetic ablation of UCP2 lead to diminished neuronal number, neuronal size, dendritic growth and synaptogenesis in vitro and impaired spatial memory in adulthood (Simon-Areces et al., 2012).

Human studies also suggest that the omission of labor may affect brain development in the newborn. The limited available data indicate that children born from Cesarean delivery at maternal request, i.e. from Cesarean sections performed when labor is not initiated, may face more emotional disturbances and sleep problems at preschool age. In one study, preschool children born by Cesarean deliveries at maternal request presented significantly more anxiety/depression, withdrawal and sleep problems. In addition, they had statistically significantly higher values on internalization problems at preschool age. In one study, preschool children born by Cesarean deliveries at maternal request presented significantly more anxiety/depression, withdrawal and sleep problems. In addition, they had statistically significantly higher values on internalization problems at preschool age.
may increase the risk of autism (Glasson et al., 2004). Autism cases were more likely to have experienced fetal distress, been delivered by an elective or emergency Cesarean section, and had an Apgar score of less than 6 at 1 min (Glasson et al., 2004). Preterm birth and planned Cesarean section have been also identified as risk factors for autism and other Pervasive Developmental Disorders in another study (Guinchat et al., 2012). In a meta-analysis, Cesarean delivery was associated with a 26% increased risk of autism that did not reach statistical significance (Gardener et al., 2011). Birth by Cesarean section is also a risk factor for attention deficit hyperactivity disorder (ADHD) in children (Amiri et al., 2012). Unfortunately most studies that review risk for autism or ADHD in children do not differentiate between elective and urgent Cesareans.

Concerning the potential consequences that elective Cesarean section may have for brain development in the newborn it is also relevant to mention that Cesarean sections may be programmed earlier than in the due date. This is because the length of human gestation shows a considerable variation (Jukic et al., 2013), which can reach even one month. This is a relevant issue, since there is increasing evidence that birth at 39–41 weeks provides developmental advantages compared to birth at 37–38 weeks. Indeed, greater gestational age is associated with greater maturity of movement, better regulation, less excitability and less educational needs (MacKay et al., 2010; Fink et al., 2012).

A central issue for the main subject of the present paper is the impact that the omission of labor may have on the process of mother–child attachment. The lack of the labor-associated noradrenaline peak in the babies born by elective Cesarean section could hinder the olfactory orientation for the initiation of breastfeeding. Indeed, as mentioned in Section 2.2, babies born by Cesarean section performed during labor showed a better olfactory learning during the first hour after birth compared to babies born by elective Cesarean section without labor (Varendi et al., 2002). Thus, the omission of labor may potentially affect one of the first steps in the generation of mother–child attachment. More recent studies have shown that, depending on the type of delivery, there are differences in the behavioral responses of the newborns to maternal separation. A pilot study by our group revealed that neonatal crying following brief maternal separation was reduced in the neonates born by a planned Cesarean section compared to vaginally delivered neonates (Olza Fernandez et al., 2013). In addition, when proximity to the mother was restored, most neonates born by planned Cesarean section did not cry at all or cried less than vaginally delivered neonates, which in addition continued crying for longer time. These different responses could reflect modifications in early infant attachment behavior (Olza Fernandez et al., 2013). This different newborn behavior in response to maternal separation should be understood within the attachment theory paradigm: lack of response to maternal separation is an early symptom of un-attachment, which could mean that the generation of attachment is more difficult for babies born after a planned Cesarean. Also, the altered response to maternal separation could indicate an alteration of the stress response, which could be related to later difficulties with attention or spatial memory processes similar to the findings in rats described by Simon-Areces et al. (2012).

The potential negative effects of Cesarean section in children may be in part due to the impact of Cesarean section on maternal attitudes and behaviors in relation to their children. Therefore, in the next section we will review the potential consequences of Cesarean section for the mother.

4.1.2. Consequences for the mother. Cesarean section is associated with significantly lower maternal levels of catecholamines, adrenocorticotrophic hormone, cortisol, prolactin, corticotropin-releasing factor, beta-endorphin and oxytocin in plasma (Takagi et al., 1985; Takeda et al., 1985; Nissen et al., 1996; Vogel et al., 2006). It might be hypothesized that, in mothers who give birth by planned Cesarean section, the absence of the neuroendocrine changes associated with physiological labor may produce difficulties in the bonding process and in the recognition by the mother of her child as her own. This may explain the feeling of estrangement and bonding difficulties that some mothers have described after Cesarean section (Beck, 2004).

The reduced levels of oxytocin in the cerebrospinal fluid of mothers in absence of labor (Takagi et al., 1985; Takeda et al., 1985) may impair maternal adaptations normally induced during labor and may influence her interactive ability to calm the infant (Nissen et al., 1998). Although one study found that the mode of delivery does not affect maternal interaction with the newborn (Carlander et al., 2010), functional neuroimaging studies have shown that mothers who give birth by Cesarean have a significantly less response in the brain to the cries of their babies than those who had a vaginal birth (Swain et al., 2008). Lower levels of brain oxytocin in the mother in absence of labor may also reduce breastfeeding, which in turn may further affect the process of mother–child attachment, since breastfeeding increases the intracerebral release of oxytocin in the brain (see Section 3.2). Indeed, it has been reported that risk of breastfeeding failure is higher after Cesarean delivery, particularly if primary and scheduled before 39 weeks of gestation (Zanardo et al., 2012, 2013). Several studies have also investigated the association between type of delivery and risk of developing postpartum depression. It has been suggested that Cesarean section may increase the risk of depression (Ryding et al., 1998). A recent prospective longitudinal study, that recruited 1100 women, reported that those who underwent Cesarean section, urgent or elective, had higher scores in the Edinburgh Postnatal Depression Scale (EPDS), although six months after birth these differences were no longer detectable (Rauh et al., 2012). This possible effect of Cesarean section on maternal depression is also relevant for mother–child attachment, since postpartum depression causes alterations in the relation of the mother with her baby (Kingston et al., 2012).

4.1.2. Intrapartum neurohormonal manipulations

4.1.2.1. Synthetic oxytocin. Intrapartum neurohormonal manipulations happen when birth is induced or stimulated with synthetic oxytocin (Pitocin) or when anesthetic drugs with a central effect are administered to mothers during childbirth. Other subtle manipulations happen when birth is disturbed by obstetric interventions such as amniotomy, lithotomy or unsupportive care but this have rarely taken into account. Mothers may receive Pitocin before delivery to induce labor or after delivery to prevent postpartum hemorrhage. In several cases the use of Pitocin is needed for the health and wellbeing of the mother and child. However, the use of intrapartum exogenous oxytocin has increased considerably in recent years (Clark et al., 2009). Possible long-term consequences of the manipulation with synthetic oxytocin in humans at the time of birth have not been extensively studied, although some studies suggest that the administration of Pitocin is associated with an increased number of women abandoning breastfeeding (Ounsted et al., 1978a;b; Wiklund et al., 2009).

The intrapartum administration of oxytocin results in altered postpartum oxytocin levels in the mother. Thus, higher amount of exogenous intrapartum oxytocin predicts higher plasma oxytocin levels at 2 months postpartum (Prevost et al., 2014). However, mothers who receive intrapartum Pitocin, present lower levels of endogenous oxytocin and increased levels of prolactin two days after delivery. These changes may be the consequence of a dose-dependent alteration of the feedback mechanism of both hormones by Pitocin (Jonas et al., 2009). Thus, it has been proposed that the
systemic administration of Pitocin, to induce or enhance uterine contractions, may alter the recycling of oxytocin receptors in the brain, reducing their availability in the postsynaptic membrane and therefore decreasing the response to new oxytocin stimuli (Wahl, 2004). Such a mechanism in the uterus may explain the increased risk of severe maternal bleeding observed when synthetic oxytocin is administered at birth (Belghiti et al., 2011). Pitocin use also increases the risk of operative delivery and emergency Cesarean (Buchanan et al., 2012) which in turn may increase the risk of maternal posttraumatic stress disorder (PTSD) following childbirth (Beck et al., 2011). The high prevalence of complete or partial PTSD after childbirth observed in different studies (Rydning et al., 1997; Wijma et al., 1997; Creedy et al., 2000; Soderquist et al., 2002; Ayers et al., 2008) raises the question of whether peripartal hormonal manipulation alters the maternal neurohormonal milieu at a time primed for lasting memories.

In addition to the possible effects in the mother, it is also important to determine whether intrapartum Pitocin may affect the newborn. The increase in autism spectrum disorders in the recent decades and the observation that perinatal factors play a role in their etiology has led to the hypothesis that oxytocin administration at birth for labor induction could contribute to the development of these diseases (Gardener et al., 2011). Indeed, induction/augmentation of labor may result in an increased risk of autism, being this probability increased in male children (Gregory et al., 2013). Recent studies suggest that Pitocin may interfere with the initiation of breastfeeding by the newborn (Olza Fernandez et al., 2012). In a pilot study, we observed a negative association between oxytocin dose and newborn sucking (Olza Fernandez et al., 2012). Similar findings have been recently reported in the hour following birth: fewer prefeeding cues were observed in infants exposed versus unexposed to Pitocin (Bell et al., 2013). The mechanisms involved in these effects of Pitocin are unknown.

4.1.2.2. Oxytocin receptor antagonists. Oxytocin receptor antagonists are frequently used to prevent preterm labor. Atosiban is a mixed oxytocin/vasopressin V1a receptor antagonist that provides an effective and more safety therapy than other tocolytic drugs to delay delivery, being more effective as gestation progresses and the expression of oxytocin receptor increases (Haas et al., 2012). The possible long-term consequences of the treatment with Atosiban for the brain of the mother and the fetus have not been studied. However, treatment of pregnant rats from days 15 to 20 of gestation (Neumann et al., 2000) and whether these drugs may act directly on the neonatal brain region in which the oxytocin receptor antagonist reduced suckling-evoked activity in different brain regions related with olfaction, such as the insular cortex, the piriform cortex, the anterior olfactory nucleus and the olfactory tubercle. Other brain regions in which the oxytocin receptor antagonist reduced suckling-evoked activity include the prefrontal cortex, the dentate gyrus and the hippocampal CA1 and CA3 (Febo et al., 2005). Therefore, this suggests that the antagonism of brain oxytocin receptors may impair olfactory and cognitive responses elicited by suckling in the mother brain, which in turn may alter the process of bonding with the newborn.

Concerning the fetus, since oxytocin is protective for fetal neurons, the antagonism of its receptors may increase the susceptibility for hypoxic-ischemic insults (Ceanga et al., 2010). Furthermore, in agreement with the analgesic effect of oxytocin, Atosiban administration increases pain in rat newborns (Mazzuca et al., 2011). However, it is unclear whether Atosiban administrated to the mother may directly affect the newborn. A minimal placental transfer of Atosiban was detected in a study with eight women undergoing Cesarean section at term (Valenzuela et al., 1995). However, the antagonism of oxytocin receptors in the mother may influence the fetus by indirect mechanisms. Therefore, future studies are necessary to determine the possible long-term consequences in the infant (Papatsonis et al., 2013).

4.1.2.3. Morphine. In view of the importance of the endogenous opioid system in modulating oxytocin release, it is of interest to consider the consequences of the use of exogenous opioids as analgesics in human parturition. Morphine provides women in latent labor with analgesia and rest and contractions may cease soon after injection. Morphine is not only used for analgesia, but also to differentiate true labor from false (Mackeen et al., 2014). The clinical observation that morphine gives patients rest from contractions and delays childbirth is likely to be due to inhibition of oxytocin release. As the drug wears off, or as opioid receptors are down regulated, oxytocin levels rebound significantly and the patient enters in active labor or return to baseline uterine activity without labor (Wilson et al., 2010).

A Cochrane systematic review (Anim-Somuah et al., 2011) reported that the use of epidural analgesia in women was associated with an increase risk of assisted vaginal birth (RR 1.42, 95% CI 1.28–1.57, 23 trials, 7939 women), longer second stage of labor (MD 13.66 min, 95% CI 6.87–20.66, 13 trials, 4233 women), oxytocin administration (RR 1.19, 95% CI 1.03–1.39, 13 trials, 5815 women) and an increased risk of Cesarean section for fetal distress (RR 1.43, 95% CI 1.03–1.97, 11 trials, 4816 women). However, epidural analgesia did not affect the neonatal status, assessed with the Apgar score. However, further research is needed to evaluate rare but potential severe adverse effects of epidural analgesia on women in labor, long-term neonatal outcomes and the impact of this analgesia on infant–mother attachment and infant neurodevelopment.

Concerning breastfeeding, although many studies have raised the question of whether labor epidural analgesia inclusive of opioids has a negative impact on breastfeeding success, the answer remains uncertain. Studies are both conflicting and fraught with potentially confounding variables such as the mode of delivery, prior breastfeeding success and parity (Wieczorek et al., 2010; Szabo, 2013). In the largest study to date, Wilson et al. randomized 1054 patients to various epidural and non-epidural regimens and did not detect significant differences in breastfeeding success (Wilson et al., 2010). Further research is needed to elucidate the specific relationship between neuraxial opioids and breastfeeding and whether these drugs may act directly on the neonatal brain to attenuate exhibition of breastfeeding behaviors (Dondi et al., 1991).

4.2. Preterm delivery

The main factor that interferes with the attachment process in premature babies is their incomplete brain maturation. Thus, the full response to olfactory stimuli, which allows the newborn to locate the nipple, does not take place until about the 29th gestational week. Also, the response to auditory stimuli, such as the voice of the mother, cannot be appreciated until near the 32nd gestational week (Lagercrantz and Changeux, 2010). The bonding process of the mother and the newborns is also impaired by the separation of the preterm newborns from their mothers, as a result of their need of intensive care (see Section 4.3). In consequence, the neuroendocrine changes that are associated with mother–child synchrony are not elicited in premature babies. This may have consequences not only for the preterm newborn but also for the parents. Preterm birth and hospitalization of the preterm infant
have been associated with a high incidence of parental PTSD that may persist even eighteen months after birth and impair parent–infant interaction (Pierrehumbert et al., 2003; Forcada-Guex et al., 2006; Shaw et al., 2009). Thus it seems crucial to include perinatal specialized psychological care in the entire context of prematurity for these families (Hatters Friedman et al., 2013) and to promote actions to restore contact of the newborn with the mother or father, such as Kangaroo Mother care (KMC) method and the Newborn Individualized Developmental Care and Assessment Program (NIDCAP). The KMC implies continuous skin-to-skin contact between the mother and the infant, exclusive breastfeeding and early home discharge in the kangaroo position (Charpak et al., 2005). It has been reported that KMC enhances bonding and attachment, reduces maternal postpartum depression symptoms, enhances infant physiologic stability, reduces pain, increases parental sensitivity to infant cues, contributes to the establishment and longer duration of breastfeeding and has positive effects on infant development and infant/parent interaction (Nyqvist et al., 2010). The NIDCAP also mimics the intrauterine environment, minimizing environmental stress and promoting physiological individualized care (Als et al., 1996).

### 4.3. Mother–infant postpartum separation

Sometimes, as consequence of maternal or neonatal pathology, or due to practices without scientific evidence, such as limiting access to parents to neonatal units or avoiding the postpartum mother–infant skin-to-skin contact, separation occurs between the mother and the newborn immediately after childbirth. Mother–infant postpartum interaction modifies oxytocin levels in both the mother and the newborn brain (Kendrick, 2000). Therefore, the deprivation of the physical and tactile stimuli provided by the mother may have potential long-term consequences for the newborn. Although this question has not been adequately studied in humans, it is known that the deprivation of contact with the mother results in long-term affective and cognitive alterations in rodents (Meany et al., 2002; Nagasawa et al., 2012; Marco et al., 2013).

Maternal separation in rodents not only affects the newborns but also the behavior of the mother. In rats, maternal separation reduces maternal care (Aguggia et al., 2013). In addition, long periods of mother–infant separation during the postnatal period inhibit subsequent maternal behavior, probably though oxytocin receptor modulation in the brain (Boccia and Pedersen, 2001). In humans, separation and swaddling of the baby at birth impairs the interaction with the mother during breastfeeding and also affects the behavior of the mother with her child (Dumas et al., 2013). The effects of the early maternal separation are durable. A study reported that, regardless of other variables, when newborns spend the first two hours separated from their mothers there was a worse mother–baby interaction one year after birth (Bystrova et al., 2009). The stress of prolonged mother–infant separation is also associated with reduced maternal sensitivity and more negative patterns of mothering throughout the first 3 years of life (NICHD Early Child Care Research Network, 1999).

### 4.4. Bottle-feeding versus breastfeeding

Neuroendocrine setting of bottle-feeding may be very different from lactation. In bottle-feeding, the absence of the increased release of oxytocin and prolactin in the mother induced by breastfeeding may affect the bonding process with her newborn. This has led some authors to hypothesize that, for the maternal brain, not breastfeeding may mean the ‘death’ of the newborn. Therefore, the brain might be involved in a postpartum mourning state that may explain the higher incidence of postpartum depression in the case of bottle-feeding (Gallup et al., 2010). Indeed, a lack of brain activation in response to the crying of the newborn, similar to what it has been described after elective Cesarean sections, has been reported in mothers that use bottle-feeding (Swain et al., 2008; Kim et al., 2011). Long-term consequences of these differences are still unknown. Duration of breastfeeding has been inversely associated with risk of subsequent maternal neglect in a large 15-year longitudinal study of over 7000 mother–infant dyads (Strathern et al., 2009b). In addition, a significant correlation between stress, dysphoric moods and decreased levels of interferon-γ have been detected in formula feeder mothers, an effect consistent with depression of cellular immunity (Groer and Davis, 2006). Furthermore, recent studies suggest that breastfeeding reduces women’s risk of Alzheimer’s disease and that women with shorter breastfeeding duration have increased risk of Alzheimer’s disease (Fox et al., 2013).

### 4.5. Summation of effects

Unfortunately many mother infant dyads suffer not one but many of these peripartum disruptions. For instance, prematurity can be associated to betamethasone and Atosiban exposure in uterus, followed by an emergency Cesarean birth, maternal infant separation, prolonged hospitalization and formula feeding. In some countries maternal infant abandonment may be followed by formula feeding and institutionalization until 10 months of age without a primary caregiver (Gribble, 2006). The consequences of the accumulative effects of these events, which impact on the neuroendocrine homeostasis of the baby, are unknown. However, it has been reported that birth complications and early child rejection increases the risk of violent behavior in adulthood (Raine et al., 1994, 1997). It is unknown if the summation of potential etiopathogenic neurohormonal scenarios during labor and the early postpartum period may represent an increased risk for other neurobiological disorders that affect systems and functions regulated by neurohormones such as attachment disorders, childhood anxiety disorders, early feeding disorders, changes in sexual behavior in adulthood or primary enuresis.

### 5. Conclusions

Childbirth can be considered as a neurohormonal event where both maternal and fetal brains participate and where a specific neurohormonal scenario is settled. The studies reviewed in this paper suggest that hormonal changes in the maternal and the fetal/newborn brains during parturition, the immediate postpartum period and lactation are involved in the generation of mother–child attachment in humans. Several hormones seem to play a key role in the mechanisms of initiation and consolidation of this attachment. However, our knowledge on these mechanisms is still incomplete. Little is known on the neurohormonal changes during intrapartum and we ignore the neurobiological and neuroendocrine changes that may occur in the maternal and the fetal brain as the fetus goes down the birth channel. Also, we need to increase our knowledge on the mechanisms that initiate attachment behavior between the mother and the newborn immediately postpartum. This knowledge will allow the implementation of adequate actions to minimize the negative effects of peripartum disruptions. For this it is essential to obtain a systematic recollection of data regarding any peripartum attachment disruption in the medical records, such as the time, dose and duration of synthetic oxytocin exposure or of maternal infant separation. More investigation is needed to develop scores to assess peripartum disruptions and identify high risk neonates and dyads.
The limited available evidence suggests that the disruption of the neurohormonal process of childbirth in humans may increase the risk of developing mental, learning, attachment and personality disorders later in life. Therefore, several actions to counteract the effects of birth interventions disrupting perinatal neuroendocrine events have been proposed, including strategies that maximize skin-to-skin contact, carrying the child frequently, providing massage, co-sleeping and co-bathing (see also Section 4.2). In general, it would be convenient to educate both professionals and parents on the critical issues that take place in the central nervous system at delivery or during perinatal period as well as to promote physiological care perinatal health disorders seems to be critical to newborns basic biological needs (Bergman and Bergman, 2013), minimizing pharmacological interventions that may disrupt the neuroendocrine cascade involved in mother–child attachment, performing Cesarean sections as physiological as possible (Smith et al., 2008) and promoting strategies to decrease the alarmingly high birth rate by Cesarean sections, many of them unnecessary (Young, 2011). Routine mother infant separation should be avoided. Instead, skin-to-skin contact with the mother for the first 24 h should be provided when possible to keep uninterupted access to the breast. When breastfeeding is not possible, or is not the preferred option, it is recommended to bottle feed mimicking breastfeeding, holding the child in a breastfeeding position with the child skin-to-skin with the mother bare breasts, using a slow-flow bottle teat and changing sides while bottle feeding (Gribble, 2006). If maternal illness causes infant separation, skin to skin contact with the father or other relatives should be provided and intensive breastfeeding should be promoted after reunion with the mother to restore brain oxytocin levels. Finally, screening for perinatal mental health disorders seems to be critical to optimize maternal well-being and attachment. Perinatal and infant mental health services should be provided to all families who experience traumatic childbirth and or prematurity.

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