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Nutritional and immunological factors in breast milk: a role in the intergenerational transmission from maternal psychopathology to child development

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Abstract

Perinatal psychopathologies affect more than 25% of women during and after their gestational period. These psychiatric disorders can potentially determine important biological variations in their organisms, affecting many different physiological and metabolic pathways. Of relevance, any of these changes occurring in the mother can alter the normal composition of breast milk, particularly the concentration of nutritional and inflammatory components, which play a role in child brain functioning and development. Indeed, there is evidence showing that changes in milk composition can contribute to cognitive impairments and alterations in mental abilities in children. This review aims to shed light on the unique intergenerational role played by breast milk composition, from maternal psychopathologies to child development.

Key words: breast milk composition; perinatal depression; perinatal anxiety; child neurodevelopment; child behavior.

1. Introduction

There is evidence suggesting that stress exposure during the perinatal period may affect the quality of milk (Kawano et al., 2009),which is fundamental not only to sustain child growth and development (Butte and King, 2005; Hair et al., 2013), but also to support the normal brain functioning of the child (Horta et al., 2018). Indeed, maternal milk is an important physiological fluid for nutrient transfer and immune signalling, which potentially shapes infant growth at a cognitive, behavioral and motor level. Therefore, any changes in maternal psychopathology that could severely impact milk composition can also in turn predispose the child to developmental difficulties (Figure 1).

Although many psychological and physiological changes are normal during the perinatal period, if exacerbated, they could potentially make women more susceptible to the development of clinically significant psychiatric conditions, particularly mood and anxiety disorders (Bobo and Yawn, 2014; Paschetta et al., 2014). Perinatal depression is a common disorder that affects women during and after pregnancy (Evans et al., 2001; Thompson and Ajayi, 2016), and it is characterized by a wide spectrum of symptoms, ranging from apathy, appetite and sleep disruption, to cognitive problems and suicidal thoughts (Kazemi, 2016; Pearlstein et al., 2009). Indeed, the perinatal period can be a window of susceptibility, as the mother is more vulnerable to psychological and psychosocial changes that might predispose her to the onset of the depressive psychopathology.

Similarly to depression, also perinatal anxiety and psychosocial stress present a prevalence as high as 10-25% in pregnant women (Fairbrother et al., 2016; Loomans et al., 2012), even though less attention has been given to these perinatal psychopathologies (Reck et al., 2008). These conditions are thought to share common underlying mechanisms, including hormonal dysregulation, such as elevated glucocorticoids levels, immune aberrancies, as well as genetic and epigenetic alterations (Meltzer-brody, 2011).

Of relevance, there is a great deal of research reporting an association between perinatal maternal psychopathologies and child impaired brain development (Stein et al., 2014), and, although few mechanisms have been identified, it is still not clear how psychological and biological alterations present in the mother can be transmitted intergenerationally and ultimately affect child development (Sawyer et al., 2018). In the recent years increasing attention has been given to the role of breast milk composition, which offers a unique nutritional support to the child development. Indeed, the lactation process is characterized by a continuous demand on mothers to provide all necessary nutrients to the infant. Therefore, due to the multiple biological changes that characterize perinatal mental disorders, including alterations in hormonal levels, immune response, vitamins and nutrients, a compromised maternal health might lead to insufficient or abnormal amounts of nutrients and other biological factors in breast milk, ultimately affecting child development. In addition, it is worth of note that the potential alterations in the biology of breast milk expressed by affected women might otherwise be a consequence of unhealthy behaviors that usually characterize the life-style adopted in the context of psychiatric conditions. Indeed, it is common in mental disorders to assume detrimental habits, such as inadequate nutrition, which often leads to gain weight, increased alcohol consumption, substance abuse, smoking and lack of physical activity (Cabello et al., 2017). These unhealthy traits have largely been associated with alterations in the physiology of patients and might consequently induce changes also in the levels of milk components and ultimately affect child growth.

In this review, we will start by summarising the main components of milk, including nutritional and immunological factors, and their importance for child development. We will then examine all studies that have looked at changes in breast milk composition in mothers with mental disorders, and the potential association with child development. We will conclude by discussing the putative role of breast milk in the intergenerational transmission of mental health problems.

2. The importance of breast milk

2.1 Lactation stages

To best adapt to the child's metabolic and nutritional necessities, breast milk composition changes constantly throughout the entire lactation period. It is commonly classified into: colostrum, transitional milk and mature milk, with reference to a gradual adjustment process (Ballard and Morrow, 2013). Colostrum is the secretion produced during the first few days after delivery, containing a wide array of proteins and growth factors, and it is rich in immunological components, such as immunoglobulins and leukocytes, which play a major role in building up the immune system in newborns (Gephart and Weller, 2014; Neville et al., 1988; Neville and Morton, 2018; Pang and Hartmann, 2007; Pribylova et al., 2012). Transitional milk is produced after colostrum and lasts for approximately two weeks. The content of transitional milk includes high levels of fat, lactose and water-soluble vitamins, and it contains a higher abundance of calories than colostrum (Gidrewicz and Fenton, 2014). Finally, mature milk is produced from about day 15. It consists of 90% water and 10% of carbohydrates, proteins and fats, and therefore results in a more watery milk (Jenness, 1979)**.**

2.2. Components of human milk

As it changes throughout the different periods of lactation, finely attuning to every requirement of the new baby, breast milk constitutes a comprehensive source of macronutrients, micronutrients as well as bioactive factors, which are essential for the growth of the child (Picciano, 2001). The volume and composition of human milk varies between individuals, and even in the same woman it can be altered by her nutritional status (Gidrewicz and Fenton, 2014; Pauline M. Emmett et al., 1997).

Human milk oligosaccharides

More than 150 different forms of oligosaccharides can be found in breast milk (Thurl et al., 2017) and are delivered to the infant intestine, where they exert their multiple actions. Indeed, human milk oligosaccharides (HMOs) cannot be digested by the still immature intestine of the infant, therefore they act locally, stimulating the maturation of the intestinal epithelial cells and protecting the lumen from external pathogens infections, via improvement of the gut barrier permeability (Akbari et al., 2017; Holscher et al., 2014). However, the most recognized action of HMOs is the prebiotic effect they exert on the gut microbiota of the infant, that is firstly modelled during birth, depending on the mode of delivery (Francino, 2018). In particular, HMOs have a fundamental role on the intestinal flora by promoting the heterogeneity and survival of beneficial commensal bacteria (Jantscher-krenn and Bode, 2012), which confer benefits on different aspects of the host health, including the child neurodevelopment. Indeed, a great deal of research confirmed the role of the gut microbiome in supporting the brain development and normal functioning (Sudo et al., 2004; Tognini, 2017). From this perspective, more recently, a few forms of HMOs have been added to infant formula, in order to reduce the difference between composition of breast milk and formula, and improve cognitive outcomes in formula-fed children (Einerhand, 2016).

Lipids

The total lipid content, milk’s main source of energy, is extremely variable depending on timing or physical condition of the mother, showing a gradual increase from the beginning of feeding, defined as foremilk, to the end of a feed, known as hindmilk (Picciano, 2001; Saarela et al., 2005). Almost all of the lipids in breast milk are triglycerides with polyunsaturated fatty acids (PUFAs), which are essential for the nutritional and developmental needs of the child (Picciano, 2001). Indeed, PUFAs have a fundamental role in governing both structural and functional development of brain architectures (Birch et al., 2005; Hadley et al., 2016; Makrides et al., 1994). Long-chain PUFAs (L-PUFAs) arachidonic acid (ARA) and docosahexaenoic acid (DHA), should be present in a 2:1 ratio in colostrum to best benefit the infant from the very first days after delivery (Kelishadi et al., 2012). Indeed, during these early stages of life, 90% of milk lipids are absorbed in the gastrointestinal tract, therefore being a fundamental source for early life brain development. Whereas, the unabsorbed amount of L-PUFAs remains in the colon until excretion, although it is still unknown its potential regulatory effect on the infant gut microbiota (Abrahamse et al., 2012).

Vitamins, ions and metals

Along with macronutrients, human milk provides necessary micronutrients, such as vitamins, which are primarily absorbed in the infant intestine, through carrier-mediated systems, and transferred in the systemic circulation, to act as essential bioregulators for metabolic activities (Boudry et al., 2010). In addition, vitamins, and especially those from the group B, play a fundamental role in supporting brain plasticity, including regulation of neuronal differentiation and repair, as well as the synthesis of different neurotransmitters, and their deficiency has been extensively associated with neurological and psychiatric symptoms (Kennedy, 2016). Although, the concentration of some water-soluble vitamins, such as vitamin B-1, vitamin B-6 and B-7, increases during the lactation period, the content of the vitamin B-2 remains constant. Vitamins A and E are present in high concentrations in colostrum compared to mature milk, while vitamins D and K remain in low quantity in human milk (Coryell et al., 1945; Dror and Allen, 2018). Maternal diet seems to notably influence the vitamin profile in breast milk, resulting, in some instances, in the necessity of dietary supplementation for the mother during the lactation period (Valentine and Wagner, 2013), as it might be the case for vegetarian and vegan women, who majorly risk to be lacking an adequate intake of vitamin B-12 (Dror and Allen, 2008). In contrast, other micronutrients, such as ions and mineral salts, show a constant bioavailability during the course of lactation, with the exception of zinc, copper and iron, which are present in high concentration immediately after childbirth, but decrease in the following months, and seem to be less influenced by maternal diet (Dror and Allen, 2018).

Immune components

Alongside its nutritional role, breast milk contributes also to the development of the infant immune system. Indeed, it contains a plethora of immunological factors, which includes immune cells, such as macrophages, neutrophils, T cells, stem cells and lymphocytes, proteins, like the lysoenzyme, an aspecific antimicrobial factor, different cytokines and many immunoglobulins (Ig): IgM, IgG, secretory IgG and secretory IgA (sIgA) (Palmeira and Carneiro-Sampaio, 2016; Prentice et al., 1987). During pregnancy, the mother transmits her antibodies to the foetus through the placenta; then, in the postnatal period, the newborn receives these antibodies from breast milk, establishing a defence mechanism for the first months of life (Berg et al., 2014; Hanson and Söderström, 1981). Among milk conveyed antibodies, the most prevalent one is sIgA, an oligomeric Ig that neutralizes pathogenic intestinal microorganisms, hence favouring a healthy gut microbiota composition and intestinal mucosal immunity (Mantis et al., 2013).

Hormones

In addition to nutrients and immune components, human milk contains a substantial number of hormones, that act on many different physiological and metabolic pathways in the organism of the infant, allowing a healthy growth. Among the array of hormones, glucocorticoids are transferred from plasma to milk (Kato et al., 1985; van der Voorn et al., 2016) where they reflect the circadian rhythm of maternal hypothalamic-pituitary-adrenal (HPA) axis (van der Voorn et al., 2016). After milk ingestion, these hormones readily cross the infant epithelial gut barrier, to be transferred in the systemic circulation (Angelucci et al., 1983; Neelon et al., 2015). Similarly, prolactin, the hormone that stimulates milk production, can also be detected in human milk, with higher concentration in foremilk compared to hindmilk (Cox et al., 1996). Prolactin release is stimulated by the baby's nipple suckling, therefore creating a positive loop mechanism for increasing milk availability (Crowley, 2015). Likewise, oxytocin is also implicated in the milk ejection reflex and it can be measured in breast milk, although in very small amounts (Moberg and Prime, 2013; Takeda, 1986). Due to its low presence, it seems unlikely that low traces of oxytocin in breast milk would significantly impact the infant physiological status (Moberg and Prime, 2013). Instead, babies seem to be able to produce autonomously this hormone in response to the oral suckling stimulus or via skin to skin contact, which takes place during breastfeeding sessions (Moberg and Prime, 2013).

Milk microbiota

Along with nutritional, hormonal and immunological components, more recent findings assessed the presence of a wide array of different non-pathogenic bacteria populating human milk, which can shape the initial intestinal microbiome. This community of bacteria, which includes Lactobacilli, Staphylococci, Streptococci and Bifidobacteria derives from the mammary skin, the oral cavity of the suckling child, and the maternal gut microbiota (Hunt et al., 2011; Moossavi et al., 2019), and therefore it constitutes an important link between maternal and infant health. In addition, milk microbiome composition is characterized by a high variability in the quantity of the aforementioned bacteria, which depends on many factors, including the physiopathological state of the mother, the mode of delivery and the breastfeeding practice (Moossavi et al., 2019), and can differently impact various aspects of the infant development (Cerdò et al., 2016). In particular, exposure to Bifidobacteria was shown to exert beneficial effects in preventing the development of several intestinal diseases, including inflammatory bowel disease and colorectal cancer, as well as neuropsychatric conditions, such as depression and anxiety (Callaghan and Sinderen, 2016; Savignac et al., 2014).

2.3The role of milk on child development

Although the research literature has provided evidence for the composition of human milk, as well as observations for changes in milk components during the whole period of lactation, it is still not fully understood how milk and its constituents can affect child growth, from infancy to late development. There is evidence showing that breast milk contributes to physical and cognitive neurodevelopment in the child (Agostoni et al., 2009; Quigley et al., 2012). In many studies children who receive breast milk, compared with those who are nourished with formula, have higher intelligence quotient (IQ), better school performance and higher income in adulthood (Horta et al., 2018). Moreover, the developmental benefits of breastfeeding appear to be associated not only to the type of feeding (either breast milk or formula) but also on the duration of lactation. Indeed, being exclusively breastfed over a period of at least 6 months is positively associated with better brain functions during both childhood and adulthood (Horta et al., 2018).

These evidences seem to outline a clear association between breastfeeding and better developmental outcomes in children, however other aspects need to be taken into consideration to make an unbiased judgement on the role of breastfeeding on child development(Kramer et al., 2011). Indeed, mothers from difficult social backgrounds, characterized by low social support, unhealthy dietary patterns and low education level, are more likely to discontinue breastfeeding and choose formula-feeding (Taveras et al., 2003). As a consequence, children living in such adverse environment are more likely to be exposed to elevated risks of developing emotional and behavioural dysregulations (Garratt et al., 2017).Therefore, this suggests that although the beneficial effect of breast milk on child development has been established, further investigations are needed to distinguish the negative influence that disadvantaged socio-economic conditions have on children’s growth, in addition to lack of breastfeeding.

3. Maternal mental health, milk composition, and child development

This is the first review summarising evidence collected from the available literature investigating either1) an association between maternal perinatal depression, anxiety and stress, and breast milk composition, or 2) an association between breast milk composition and child development during three main developmental stages: infancy, toddlerhood and childhood.

We performed a search via PubMed of the literature published up to January 2019, considering cohort studies and case control studies, without any exclusion in terms of age and gender. Relevant key words included: “perinatal depression”, “postpartum depression”, “stress”, “anxiety”, “breast milk”, “brain development”, “motor development”, “neurodevelopment”. No study characteristics or publication date restriction were imposed. Papers employing animal models were excluded. In addition, the search was limited to English-language studies. We included papers from studies where analyses of milk composition and psychological maternal assessment or child neurodevelopment were assessed. The following measurements were used to assess both cognitive and motor tasks, in the developing child:

- **The Brazelton Neonatal Behavioral Assessment Scale (NBAS):** it investigates habituation, orientation, motor, range of state, regulation of state and autonomic stability in infants between the ages of 3 days and 4 weeks (Als et al., 1977).
- **The Fagan Test of Infant Intelligence:** it assesses visual recognition memory (Fagan and Shepherd, 1991).
- **The Bayley Scales of Infants and Toddlers Development:** it assesses language and visual-motor problem solving (Mental Development index (MDI)) and both fine and gross motor development (Psychomotor Development Index (PDI)) in children of 1-42 months of age (Bayley, 1993).

- **The Clinical Adaptive Test/Clinical Linguistic and Auditory Milestone Scale (CAT/CLAMS):**it assesses visual-motor functioning and expressive and receptive language abilities in children aged 0 to 36 months (Wachtel et al., 1994).
- **The Gesell Developmental Inventory:** it assessesdifferent outcomes of development in young children, including gross motor functions (Ball, 1977).
- **The Ages and Stages Questionnaire (ASQ):** it assesses fine and gross motor development, communication skills and personal and social skills (Squires and Bricker, 2009).
- **Videotaped free-play sessions:** it assesses child's attention to the play activity (Goldman et al., 2004).
- **Kaufman Assessment Battery for Children (K-ABC):** it assesses cognitive development and intelligence in children aged 2.5 to 12.5 years(Kaufman and Kaufman, 1985).
- **Wechsler Intelligence Scale for Children – Third edition (WISC-III):**it assesses IQ in children aged 6 to 16 years old (Wechsler, 1939).
- **The Dutch CITO-elementary (CITO) Test:** it measures school performance in children aged 11-12 years in Netherlands (Bartels et al., 2002).

This section of the review is organised into three subsections: the first one describing the influence of maternal psychological state on milk composition, the second one focussing on the influence of breast milk composition on child neurodevelopment, and finally a third one describing the intergenerational mother-milk-child link. In each subsection, we first describe the studies that assessed the respective associations and, secondly, we discuss the results comparing them to findings from the literature. A total of twenty-eight studies have been included in this review, among them fifteen investigate how maternal psychological state influences milk composition (Table 1), whereas fifteen studies investigate how breast milk composition affects child neurodevelopment and cognition

(Table 2); two studies were included in both categories, as they reported both psychological assessment in mothers, as well as neurocognitive, behavioral and brain-motor assessment in children.

3.1 Influence of maternal psychological state on milk composition

3.1.1Perinatal depression

Eleven studies assessed symptoms of perinatal depression: one study assessed prenatal depression (Keim et al., 2012), and ten studies conducted postnatal evaluation. Several breast milk components were investigated, including lipids, vitamins, immune proteins and hormones.

Lipids

One study only described measures of L-PUFAs levels in breast milk (Keim et al., 2012). Prenatal depressive symptoms measured at 20 weeks of pregnancy, but not at 24 to 29 weeks, predicted low levels of DHA and total ω-3L-PUFAs in milk at 4 months. However, after adjusting for variables such as education, smoking, maternal age and income, only the association between depressive symptoms at 20 weeks and DHA levels remained significant (Keim et al., 2012). This is in line with results from a cross-national ecological study that merged together data collected from 16 different countries, in which prevalence of maternal depression and milk L-PUFAs levels were independently investigated (Hibbeln, 2002). In particular, they found low levels of milk DHA in those countries where the prevalence of maternal depression was high. In addition, they found a higher seafood consumption in those countries where the prevalence of perinatal depression was low. This last finding, however, is in contrast with the observational study from our review, conducted on 287 women living in USA (Keim et al., 2012), where quantity of ω-3 L-PUFAs intake did not correlate with either maternal depression or L-PUFAs milk content. This perhaps suggests that maternal psychological state, rather than food consumption, when investigated at individual level, plays a major role in determining L-PUFAs milk composition.

Vitamins, ions and metals

One study investigated the association between postpartum depression and milk content of theB-6 vitamin and results were not significant. However, the study reported a positive correlation between maternal vitamin B-6 intake and milk B-6 levels (Boylan et al., 2002). This last result is in line with findings from another older study (Thomas et al., 1979), therefore suggesting that vitamin B-6 consumption, rather than maternal psychopathology, could be the strongest predictor of changes in milk vitamin composition.

Two more studies, performed 10 years apart, investigated the association between postpartum depression and milk sodium levels. The first study did not report any association (Ozbek et al., 2008). On the contrary, in the second study, mothers with postpartum depression had higher sodium levels and sodium/potassium ratio (Serim Demirgoren et al., 2017). Interestingly, these two parameters are biological indicators of mammary gland permeability, which is generally increased due to a prolonged milk stasis in the mammary gland, suggesting a not efficient milk extraction (Filteau et al., 1999). Therefore, this condition can be considered a parameter of decreased lactation success (Flores-quijano et al., 2008), a common complication for perinatally depressed women. Finally, one study examined the association between postpartum depression and concentration of metals in breast milk. The study did not find any correlation between maternal depression and milk mercury levels at 2 months postpartum (Örün et al., 2012).

Immune components

Two studies investigated the association between postpartum depression and milk levels of the transforming growth factor beta 2 (TGFβ2), an immune regulator involved in the programming of infant immune cells system (Penttila, 2010). Both studies showed that women with postpartum depression had increased levels of TGFβ2 in milk (Kondo et al., 2011; Shariat et al., 2017). Interestingly, a recent meta-analysis did not report any significant association between depressive status in general population and TGFβ2 levels in blood (Kohler et al., 2017). A possible explanation for these discrepancies might be due to the fact that milk levels of TGFβ2 are primarily regulated by local production of the cytokine from the mammary glands, rather than from peripheral immune cells (Hawkes et al., 2002), therefore, proposing maternal depression as a fundamental contributing factor in the regulation of the biological mechanisms involved in the production of milk TGFβ2 cytokine. Indeed, milk TGFβ2 levels have been associated with increased mammary gland permeability caused by local inflammation (Chockalingam et al., 2005; Filteau et al., 1999), which results in breastfeeding difficulties and pain, which is associated with the development postpartum depression (Brown et al., 2015).

In addition to TGFβ2, three studies investigated the association between postpartum depression and milk sIgA levels, with one study reporting an increase of sIgA levels in depressed mothers (Hart et al., 2004), one study reporting no correlation (Groër et al., 1994) and one reporting a significant decrease of sIgA levels in depressed mothers (Kawano and Emori, 2015). Results from the last study are in line with previous evidence, showing a decrease in sIgA levels in faecal samples of children who were breastfed by depressed mothers (Kang et al., 2017). Although in this study sIgA levels were not measured in breast milk, faecal sIgA levels represents a good indicator of milk sIgA levels(Bridgman et al., 2016). Indeed, once ingested through milk, sIgA does not get absorbed and its concentration remains constantly available until it gets expelled in the faeces (Roux et al., 1977).

Hormones

To our knowledge, only one study examined the association between postpartum depression and milk cortisol levels, however the authors did not find any significant results (Groër et al., 1994). A more recent paper investigated the concentration of two other hormones, melatonin and prolactin, in breast milk. The authors found a trend towards an association between postpartum depression, and lower prolactin, and higher melatonin concentration in milk samples (Groër et al., 2005), although both results were not significant. With respect to melatonin, these findings are partially in contrast with previous research, showing a decrease in melatonin levels in plasma samples of postpartum depressed women (Parry et al., 2008). Although both milk and plasma melatonin follow the same circadian rhythm (Illnerova et al., 1993), the opposite findings suggest that melatonin levels in milk might be regulated by distinct pathophysiological patterns that are different from those involved in plasma.

3.1.2 Perinatal anxiety

Ions

Two studies investigated the correlation between postpartum maternal anxiety and ions concentration in breast milk. In both studies the authors found a positive association between postpartum state anxiety, but not trait anxiety, and milk sodium levels (Ozbek et al., 2008; Serim Demirgoren et al., 2017). Although both state and trait anxiety are common in the postpartum period (Giakoumaki et al., 2009), findings from the two above studies might suggest that the transient anxiety symptoms occurring postnatally in a specific moment (“state anxiety”) might affect more prominently the composition of breast milk, compared to the individual’s personality and proneness to anxiety (“trait anxiety”). Indeed, maternal milk is constantly subjected to short-term changes, which are primarily influenced by the maternal physiological state (Khan, 2012; Khan et al., 2013).

Therefore, addressing state rather than trait anxiety levels in the perinatal period might be a more useful indicator to investigate the influence of maternal anxiety on milk composition.

Immune components

Four papers investigated the association between maternal postpartum anxiety and concentrations of distinct immune components in breast milk. Among these, one paper found a significant positive correlation between milk TGFβ2 concentration and both postpartum state and trait anxiety (Shariat et al., 2017). Finally, three studies investigated the association between postnatal anxiety and milk sIgA concentration. Two studies did not find any significant correlation between maternal state or trait anxiety and sIgA (Groër et al., 1994), and state anxiety and sIgA milk levels (Hart et al., 2004). However, one study found a negative association between postpartum state and trait anxiety scores, and sIgA milk levels (Kawano and Emori, 2015). This is in contrast with results previously described where only state anxiety, but not trait anxiety, was associated with high ions levels in milk (Ozbek et al., 2008; Serim Demirgoren et al., 2017). Overall, this potentially suggests that maternal personality trait anxiety, which is stable and long-lasting, can exert effect over time on milk immune components.

Hormones

To our knowledge, only one paper examined the correlation between maternal postpartum state or trait anxiety and cortisol levels in breast milk, however results did not show any significant association (Groër et al., 1994). In addition, one study investigated the association between postpartum anxiety and opioids concentration in breast milk. The authors found a negative association between postpartum state anxiety and colostral β-endorphin in milk, but only when mothers who underwent caesarean section were excluded from the analysis (Zanardo et al., 2001). This result perhaps suggests that an increase in pain, due to natural birth, might induce a higher production of milk β-endorphin, when compared to the caesarean section, which confound the possible association with state anxiety. In the same paper, no significant association was found between postpartum trait anxiety and β-endorphin milk content (Zanardo et al., 2001). This finding is in accordance with results previously mentioned, where high level of milk sodium correlated with state anxiety only (Ozbek et al., 2008; Serim Demirgoren et al., 2017), and support the hypothesis that state, but not trait anxiety, might be the strongest predictor of milk content of some non-immunological molecules, such as sodium and β-endorphin.

3.1.3 Perinatal stress

Immune components

Three studies investigated the association between postpartum stress and milk immune components. Two of these studies found a positive association between high maternal postpartum stress and an increase in milk sIgA levels (Groër et al., 2004; O'Connor et al., 1998). This is surprising since sIgA is a well-known anti-inflammatory agent (Monteiro, 2014). However, this might represent an example of protective mechanism activated by the mothers, that upon exposure to stressful challenges start to produce higher levels of milk sIgA to protect the infant against maternal stress-related changes.

In contrast, a third study did not find any significant correlation between postpartum stress at day 3 postnatally and milk sIgA, interleukin (IL)-4, IL-6, IL-10 and monocyte chemotactic protein-1levelsat day 3 and 14 (Thibeau et al., 2016). However, the authors found a negative correlation between maternal postpartum stress and milk macrophage inflammatory protein-1-alpha (MIP-1α) and tumor necrosis factor α (TNF-α) levels at day 3 postnatally. Furthermore, a positive association between maternal stress at day 3 postnatally, and milk IL-8 and MIP-1α content at day 14 was found. This last finding is in line with previous literature showing an increased levels of cytokines in plasma of stressed mothers (Coussons-read et al., 2007; Entringer et al., 2008). In addition, mammary gland cells as well as milk immune cells, are also known as potential sources of chemokines and cytokines found in breast milk, therefore suggesting the existence of a complex net of peripheral and local sources regulating the presence of these cytokines in milk and putatively modulated by stress (Garofalo, 2010).

Hormones

To our knowledge only one paper investigated the association between maternal postpartum stress and concentration of hormones in breast milk. Interestingly, they found a trend towards an association between maternal postpartum stress and lower milk prolactin and higher milk melatonin (Groër et al., 2005), however results were not significant. An increase of milk prolactin levels in the stressed mothers is in accordance with previous evidence showing an association between stress and higher incidence of hyperprolactinemia in general population (Levine and Muneyyirci-Delale, 2018; Sonino et al., 2004). However, further investigations are needed to better understand the underlying mechanism through which stress, experienced during the perinatal period, can influence the hormonal milk content.

3.2 Influence of breast milk composition on child neurodevelopment

In this section of the review we summarise and discuss papers investigating the effect of breast milk composition on child neurodevelopmental status, behavior and cognition. Overall, we collected fifteen papers. A variety of assessment tools were used in order to test child performance during the developmental stages of infancy, toddlerhood and childhood; for example, from birth until one year of age, NBAS and the IBQ-R; from one year to three years old, the Bayley and the ASQ, as well as videotaped free-play sessions; and from four years to twelve years old, the K-ABC and the WISC-III.

3.2.1 Infancy

Lipids and Vitamins

Using the NBAS, the first study found a positive correlation between high levels of milk L-PUFA DHA and superior arousal in the infant(Hart et al., 2006). In contrast, using the Fagan Test of Infant Intelligence another study did not find any association between concentration of L-PUFAs in milk and infant cognitive function (Helland et al., 2001). In addition to L-PUFAs, two more studies investigated a possible association between milk levels of vitamin B-6 and child behavioral response using the NBAS scale. The first study found a significant correlation between high levels of vitamin B-6and higher consolability of the infant, as well as longer time to build-up distress and irritability when exposing the infant to aversive stimuli (McCullough et al., 1990). Similarly, the second study found a positive association between breast milk levels of B-6 vitamin and increased infant habituation to outer stimuli, as well as infant ability to control involuntary autonomic responses (Boylan et al., 2002). Overall, findings suggest that macronutrients, like L-PUFA DHA, are involved in infant attention, as already reported in previous studies, conducted on infants, investigating the effect of pre- and postnatal DHA exposure (Colombo et al., 2012, 2004). This is supported by findings from preclinical studies in rodents, showing that DHA presence in synaptic membranes of neurons in hippocampal and frontal regions contributes to an improvement in synaptic efficiency and transmission speed, which putatively enhance the efficacy of whole brain information processing (Cheatham et al., 2006).On the other hand, similarly to what has been proposed for adults, micronutrients, like vitamin B-6,might play an important role in dealing with stressful challenges also in infants, via potential regulation of distinct molecular mechanisms, including modulation of central serotoninergic and gabaergic systems (Mccarty, 2000).

Immune components

With respect to milk immune components, one study using the NBAS found a positive association between high milk sIgA content and infant responsiveness to visual and auditory stimuli (Hart et al., 2004). This is interesting, and it might suggest a potential role for sIgA in brain development and neuroplasticity. One hypothesis might be that milk sIgA, although is not absorbed in the intestine of the infant (Roux et al., 1977), can still regulate the composition of the gut microbiome, promoting symbiosis between bacteria (Nakajima et al., 2018), and ultimately reducing the expression of distinct pro-inflammatory cytokines, like TNF-α, both at gut and brain level (Sun et al., 2018). Indeed, a reduced neuroinflammation has been shown to ameliorate both neurogenesis and brain plasticity (Borsini et al., 2018, 2017, 2015; Innes et al., 2019; Zunszain et al., 2012), therefore potentially leading to infant better performances in cognitive tasks.

Hormones

To our knowledge only two studies investigated the association between maternal milk cortisol level and infant neurobehavioral development. The first study, using the IBQ-R, found a significant positive association between milk cortisol levels and negative emotional and behavioral reactions from the infant, and only a trend for a negative association between cortisol milk level and infant reactivity (Grey et al., 2013). As suggested by preclinical studies, this adverse effect of cortisol on the infant emotional attitude might be due to developmental alterations, caused by glucocorticoids exposure in early life, of distinct brain structures, including the amygdala, which is highly involved in the emotional regulation (Kraszpulski et al., 2006; Salm et al., 2004). In contrast, using the NBAS scale the second study found a positive correlation between high levels of milk cortisol and improved ability to control involuntary autonomic responses (Hart et al., 2004). This last evidence is supported by two other studies which reported a positive association between infant cortisol levels in saliva (Magnano et al., 1992) and plasma (Gunnar et al., 1987)and, respectively, infant arousal, measured as the HPA axis activation to a stressor, and NBAS scores. Interestingly, in all of the above studies the concentration of cortisol was around normal levels, roughly 0.4ug/dL in breast milk and saliva (Hart et al., 2004; Magnano et al., 1992), and 9ug/dL in plasma (Gunnar et al., 1987), therefore suggesting that cortisol, within certain ranges, plays a positive role in infant emotional, behavioral and autonomic functions. Indeed, a particular infant congenital disorder, the Smith-Lemli-Opitz syndrome disease, which can induce high plasma cortisol levels, up to 34ug/dL(Kumar et al., 2012), has been associated with cognitive impairments (Diaz-stransky and Tierney, 2012), as well as disorders of the infant autonomic nervous system (Sinclair et al., 1968).

3.2.2 Toddlerhood

Lipids

Six studies investigated a possible association between maternal milk levels of L-PUFAs during child infancy, and child mental development using the MDI of the Bayley, which evaluates several aspects related to toddler cognitive development, including memory, habituation and problem solving, through the assignment of a score directly proportional to the quality of the toddler's performance. Half of the studies did not find a significant association between milk L-PUFAs levels and MDI scores (Hurtado et al., 2015; Jensen et al., 2005; Westerberg et al., 2011). In contrast, three studies found a significant association between high total milk fat content (Agostoni et al., 2001) or DHA milk levels (Makrides et al., 2009) and high MDI scores; and a trend for an association between high levels of ω-3 L-PUFAs and ω-3/ω-6 L-PUFAs ratio and high MDI scores (Guxens et al., 2011). In accordance, these findings are supported by a recent meta-analysis, which reports a trend for a positive correlation between formula L-PUFAs supplementation and increased mental development in toddlers (Qawasmi et al., 2012).

Using the PDI of the Bayley scale, which tests for fine and gross motor development, one study found a positive association between high milk DHA levels, low ARA levels, and higher PDI scores, which indicates better psychomotor coordination(Jensen et al., 2005). In contrast with this finding, three more studies did not find any significant association between L-PUFA milk concentration and PDI scores (Agostoni et al., 2001; Hurtado et al., 2015; Makrides et al., 2009). This is in line with the previously mentioned meta-analysis by Qawasmi et al., which also did not find any significant association between formula L-PUFAs supplementation and toddlers' psychomotor development (Qawasmi et al., 2012), therefore suggesting that milk L-PUFAs content plays a role only on mental development, but not on psychomotor development, at least if measured in toddlers.

Finally, two of the above-mentioned studies performed also additional investigations. The first study assessed the association between milk L-PUFAs and mental and motor development, using the ASQ. The authors reported no significant association between milk levels of L-PUFAs and the ASQ scores, however they found a positive association between milk L-PUFAs levels and increased child attention during free-play sessions (Westerberg et al., 2011). Finally, the second study assessed the association between milk L-PUFAs levels and child gross motor development (Gesell Developmental Inventory scale), and language development and visual-motor problem solving abilities (CAT/CLAMS). However, the authors did not find any significant results among any of those associations (Jensen et al., 2005). These findings therefore confirm our previous hypothesis that milk L-PUFAs content is primarily involved in conferring normal mental development in toddlers, via increasing attention performances and alertness, but without no particular influence on toddlers' psychomotor skills.

3.2.3 Childhood

Lipids

To our knowledge three studies investigated the association between maternal milk L-PUFAs concentrations during the first year of life of the child, and child development. The first study assessed

IQ using the K-ABC test, and found an association between high DHA and low ARA milk levels and better performance in problem solving and information processing abilities in children (Helland et al., 2003). Similarly, another study found a positive correlation between colostral content of L-PUFAs and IQ in children. In particular, children who received milk with higher DHA/ARA ratio of levels scored better in the WISC-III. No significant association was found for L-PUFAs contained in mature milk and IQ scores (Gustafsson et al., 2004). Finally, using the CITO test, one study found an association between high milk total ω-3 L-PUFAs, DHA and DHA/ARA ratio, and better school performance in 12 years old girls (Dalmeijer et al., 2016), therefore suggesting the ability for milk L-PUFAs to exert long term effects on child development, up to early adolescence.

3.3 Mother-milk-child link

We found only two studies that investigated *both* the association between maternal psychopathology and milk composition, and between milk composition and child development. The first study did not find any association between postpartum depression and milk vitamin B-6 levels, but only between milk B-6 levels and infant involuntary responses (Boylan et al., 2002). However, the second study identified an association between postpartum depression and high milk sIgA, as well as between high milk sIgA and improved infant alertness (Hart et al., 2004). Although, the authors did not investigate any direct effect between maternal depression and infant performance, indirect analyses seem to propose milk sIgA as a key biological link between mother and child interaction. Of relevance, the finding reported in this study suggests that depressed mothers, who have a high milk sIgA levels, have infants with improved alertness. This is surprising if considering that, in general, infants of depressed mothers show electrophysiological alterations in their frontal lobes (Soe et al., 2016), which play a major role in distinct cognitive functions, including stimuli processing (Paterson et al., 2006). Additionally, these babies receive lower scores on orienting to the live face/voice stimulus and on the alertness items of behavioural assessment, which is usually attributed to the less responsive behavior of the depressed mothers (Field et al., 2010). However, we hypothesise that the results from the study in our review might be explained by the previously discussed anti-inflammatory and, ultimately, neuroprotective role of sIgA (Nakajima et al., 2018; Sun et al., 2018). Indeed, an increase in milk sIgA levels in depressed mothers might represent a form of protective mechanism to defend the infant against any detrimental changes occurring in the depressed mother, and which can be transmitted during the stages of breastfeeding (Goldman et al., 1990).

4. Conclusion

To our knowledge this is the first review summarizing current evidence of the potential role of breast milk composition in mediating the link between maternal psychopathologies and child brain development. Overall, our findings confirm and extend evidence for the contributing role of milk composition on the regulation of child development, from the early stages of infancy until late childhood. Moreover, findings from our review suggest that breast milk composition might also play a role in the proposed association, and it deserves further consideration. Milk factors like L-PUFAs, vitamins, immune components, such as sIgA, and hormones, like cortisol, investigated in this review, have all been identified as regulatory mechanisms in the context of psychiatric disorders, as well as in conditions associated with alteration in both brain development and behavior.

This review is limited in part by the inclusion of only 28 studies, as a consequence of the narrow available literature surrounding this field, and by the heterogeneity of the studies design, and different assessment tools employed when evaluating maternal psychopathology and child development. Despite these limitations this review sheds light on the impact of perinatal psychopathologies on a wide array of breast milk components, which, if altered in their levels, can severely affect infant development. Therefore, we would argue that the molecular mechanisms, by which milk nutritional constituents and bioactive factors may be altered by maternal psychopathological status, should be the focus of future investigations. These would allow a better understanding of the ethiopathology of perinatal disorders and their consequence on the child, leading to the identification of novel therapeutic approaches for the treatment of both the mother and the child.

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