Human Milk: The Preferred First Food for Premature Infants

Pinkal Patel and Jatinder Bhatia*
Division of Neonatology, Medical College of Georgia, Georgia

ABSTRACT

Human milk offers many short term and long term health benefits to infants and mothers. Immune protective components including oligosaccharides protect premature infants from infections and necrotizing enterocolitis. It also enhances gut maturity and has shown better tolerance and rapid feeding advancement in premature infants. Human milk is the best initial feeding for the preterm infant; however it does not provide sufficient calories and macronutrients for infant growth and bone health. Human milk must be fortified with commercially available liquid fortifier to increase calorie and macronutrient contents especially calcium and phosphorus. Fortification practice of the human milk has shown improved extra uterine growth in premature infants. This article reviews various components of premature human milk, its benefits and fortification practice.

ABBREVIATIONS

Iga: Immunoglobulin A; WHO: World Health Organization; Mom: Mother Own Milk; HIV: Human Immunodeficiency Virus; HTLV: Human T - Lymphotropic Virus; Igg: Immunoglobulin G; Igm: Immunoglobulin M; ESPGHAN: European Society for Pediatric Gastroenterology Hepatology and Nutrition; IQ: Intelligent Quotient; FDA: Food and Drug Administration; CMV: Cytomegalovirus

INTRODUCTION

Human milk is a complex body fluid. The concentration of its constituents changes over the course of lactation, during a single feed, over a 24-hour period, and among women [1]. The American Academy of Pediatrics (AAP) recommends human milk as the sole nutrient for healthy term infants for approximately the first 6 months of life and supports continued breastfeeding for at least 12 months. It also recommends that all preterm infants should receive human milk, with pasteurized donor milk rather than premature infant formula, if the mother is unable to provide an adequate volume of breast milk or has conditions that preclude provision of breast milk [2,3].

Production

Breast milk is produced by mammary glands of the breast after child birth. During pregnancy, several hormones (especially progesterone) play a key role in differentiation of breast glandular tissue and proliferation of alveolar epithelium. Lactogenesis (ability to secrete milk) takes place in two stages, stage I and stage II. Stage I occurs in the later part of pregnancy and is marked by secretion of small amounts of milk containing secretory IgA, leukocytes and lactose. Actual milk production does not happen during this stage because of high levels of circulating progesterone. Stage II occurs after delivery of the infant, usually day 2 to 8 and marked by onset of copious secretion of milk. This stage is triggered by the drop in progesterone associated with placental removal and support of circulating prolactin and cortisol. Galactopoesis (maintenance of milk secretion) starts approximately, 9 days postpartum. This stage is triggered by continued breast feedings or hand expression of the breast milk and continues until weaning. Galactokinases (milk ejection) depends on oxytocin which is a posterior pituitary hormone. Oxytocin secretion is stimulated by infant suckling and other inputs like infant's cry, smell or touch.

Prematurity and breast milk

Approximately 12% of infants are born premature (<37 weeks gestation) in the United States [4]. This is a highly vulnerable population in terms of risk of nutritional deficiencies and associated morbidities. Most of the nutrients and minerals accretion occurs in the third trimester, making this population of infants vulnerable to nutrient and minerals deficiency. The birth of a premature infant should be viewed as a nutritional emergency, and studies have shown that an early balanced nutritional approach in preterm infants reduces postnatal growth failure, neonatal morbidities and improves long-term neurological outcomes [5].

The composition of term breast milk differs from that of preterm breast milk. Preterm milk contains higher amount of nitrogen, total protein, lipids, medium-chain fatty acids, total energy. Preterm milk also has higher amounts of growth factors, hormones, immunoglobulin's like secretory IgA and anti-
inflammatory factors [6-8]. Breast milk is considered the “ideal” feeding for the premature infants, as it empties faster from the stomach, results in less gastric residuals, reduces intestinal permeability and faster attainment of full enteral feedings [9-13]. Various factors in breast milk stimulate gastrointestinal growth, motility and maturation [14]. Enzymes in breast milk help premature infants absorb and utilize nutrients more efficiently [15]. In addition to nutritional benefits, breast milk has numerous other advantages including decreased rate of sepsis, necrotizing enterocolitis, retinopathy of prematurity and improved neurocognitive outcome. Studies also suggest that breast milk has long term benefits such as lower rate of metabolic syndrome, and in adolescents, it is associated with lowered blood pressure and low density lipoprotein levels, improved leptin and insulin metabolism [16-19]. Table (1) presents comparison of nutrients and calories of preterm, term and donor human milk.

**Energy**

The energy content of term and preterm breast milk is approximately 70-78 kcal/dL, preterm milk with some higher calorie content. Energy content in breast milk varies between mothers, time of day, and by fraction of milk pumped (foremilk vs hind milk) [20-22]. Lipids accounts for ~50% calories of breast milk, and the remaining comes from protein and carbohydrates. Protein composition of human milk is unique, contains 70% whey and 30% casein (contrast to bovine milk-80% casein and 20% whey). Higher concentration of whey makes breast milk easily digestible and it promotes rapid gastric emptying. Alpha-lactalbumin constitutes the major whey protein in breast milk, as compared to beta-lactalbumin in bovine milk, which is associated with milk protein allergy. Lactoferrin, lysozyme, and secretory immunoglobulin A are specific whey proteins which serve as a first line of defense by lining the GI tract [23]. Preterm milk has a higher concentration of protein, fat, lactose and total energy than term milk and its content gradually decreases over time (4-6 weeks) [24,25]. As AAP and WHO recommend to use donor human milk as the first alternative, when MoM is not available for premature infants, it is important to note that most often donors milk provided by mothers of term infants beyond 1month and is low in protein, fat and total energy compared to preterm milk [26]. Donor milk should be obtained from human milk bank (HMB). There are seventeen active milk banks in USA North America (HMBANA). These milk banks screens donors mother for antibodies to HIV-1, HIV-2, HTLV-1, HTLV-2, HBsAg, hepatitis C, and syphilis before collecting their milk. Currently all milk banks of HMBANA use the Holder pasteurization (62.5°C, 30 min) method. Holder pasteurization reliably inactivates cytomegalovirus, HIV and eliminates or significantly decreases titers of most of other viruses [27,28].

Donor milk is released after it is heat-treated and negative from infection. By Holder pasteurization, some of biological components quantity and/or activity gets affected, such as decrease in IgA and secretory IgA, lactoferrin, lysozyme, IgG, cytokines (interleukin-10, tumor necrosis factor-α), and certain growth factors. Major loss occurs in lipase activity, IgM concentration and white blood cells [29-34]. Even with the variable loss of biological components, donor milk is still superior to cow’s milk based prematur formula with decreased NEC rates in premature infants [35-37].

As the preterm infant exhibits a high growth rate and has an increased metabolic need, breast milk (MoM/Donor human milk) is insufficient to provide adequate nutrients. For these reasons, breast milk should be fortified to provide higher energy, protein, calcium and phosphorus to name a few nutrients. Nutrient contents of MoM/Donors milk are variable overtime during lactation, mainly protein contents as it decreases over time. Recent studies have shown that preterm infants fed fortified MoM/Donors milk receive less protein than assumed and grow slowly with standard fortification (as per manufacturer’s instruction) [38]. Therefore an individualized fortification approach should be adapted. Table (2) presents commercially available standard human milk fortifiers. Two of three available fortifiers (Mead Johnson and 'Similac') are cow milk based, one is acidified liquid fortifier (whey protein based) and the other one contains extensively hydrolyzed protein (casein based). Currently only fortifier available based on 100% human milk is Prolact+HMF®. It is available in 24, 26, 28 and 30 cal/oz preparation. Previously used powder fortifier is no longer in use in most neonatal ICUs as there were concerns of invasive infection [as with any powder preparation] and low protein content. There are several approaches of human milk fortification. One approach would be ‘adjustable fortification’, in which increments in fortification should be based on serial measurement blood urea nitrogen [39]. Another approach would be ‘targeted fortification’, which is based on milk analysis [40,41] and adding fortifier to achieve desired fortification, based on protein, fat and carbohydrate content of an alayed milk. As Donor milk protein content is lower than MoM/Preterm formula, infant growth should be followed closely when using standard fortification. If adequate weight gain not achieved with standard fortification, stepwise increase in caloric content (up to 30 cal/oz) should be based on feeding tolerance. Breast

<p>| Table 1: Macronutrient composition of human milk [1]. |
|----------------------------------|----------------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Protein, g/dL</th>
<th>Fat, g/dL</th>
<th>Lactose, g/dL</th>
<th>Energy, kcal/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term</td>
<td>1.2 (0.9-1.5)</td>
<td>3.6 (2.2-5)</td>
<td>7.4 (7.2-7.7)</td>
<td>70 (57-83)</td>
</tr>
<tr>
<td>Donor milk</td>
<td>0.9 (0.6-1.4)</td>
<td>3.6 (1.8-8.9)</td>
<td>7.2 (6.4-7.6)</td>
<td>67 (50-115)</td>
</tr>
<tr>
<td>Preterm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 29 weeks</td>
<td>2.2 (1.3-3.3)</td>
<td>4.4 (2.6-6.2)</td>
<td>7.6 (6.4-8.8)</td>
<td>78 (61-94)</td>
</tr>
<tr>
<td>32-33 weeks</td>
<td>1.9 (1.3-2.5)</td>
<td>4.8 (2.8-6.8)</td>
<td>7.5 (6.5-8.5)</td>
<td>77 (64-89)</td>
</tr>
<tr>
<td>Donor milk</td>
<td>1.4 (0.8-1.9)</td>
<td>4.2 (2.4-5.9)</td>
<td>6.7 (5.5-7.9)</td>
<td>70 (53-87)</td>
</tr>
</tbody>
</table>

Adapted from Ballard and Morrow [20] and references therein: Michaelson et al. [26], Bauer and Gerss [25], Nommsen et al. [24], Wojcik et al. [90], AAP Committee on Nutrition [91] and Landers and Hartmann [92].
milk fortification, especially individualized fortification approach has shown to improve growth in all three parameters: weight, length and head circumference [39,40,42]. Studies suggest that higher protein intake is beneficial for premature infants [43].

Fat is the highly variable nutrient of breast milk. Fatty acid content of breast milk varies in relation to maternal diet. Breast milk has high concentration of palmitic and oleic acids. It also contains linoleic and linolenic acids (essential fatty acids). Derivatives of these essential fatty acids: arachidonic acid (C20:4w6) and docosahexaenoic acid (C22:6w3) are found in breast milk (not present in bovine milk), and have been shown to improve visual function (retinal development) and neurodevelopment outcome [44-46]. Pancreatic lipase is not fully developed in preterm infants and they have to rely on lingual and gastric lipases for fat digestion. Breast milk contains lipases especially bile salt-stimulated lipase (BSSL) which help in fat digestion and its level is similar in preterm and term milk [47]. BSSL also protects infants from viral infections including Norwalk and HIV [48].

The main carbohydrate of breast milk is lactose. The lactose concentration is the least variable component in breast milk. Highest concentrations of lactose are found in breast milk of the mother producing large quantities of it [24]. The second most abundant carbohydrate in breast milk are oligosaccharides, approximately 1 g/dL, depending on stage of lactation and maternal genetic factors [49,50]. They are non-nutritive and mainly function as host defense. Oligosaccharides work as “prebiotic” agents which selectively enhance the growth of beneficial organisms in the gut [“Probiotics”]. In addition, they are recognized as pathogen-binding inhibitors that function as soluble “decoy” receptors on enterocytes, so they can bind competitively to the pathogens [49].

Minerals and vitamins

Some minerals and vitamins in breast milk such as Vitamin A, B complex, D and iodine are dependent on maternal diet and body storage, and therefore multivitamin supplementation to the mother is important during the pregnancy and lactation [51]. Vitamin K is extremely low in breast milk, and intestinal flora of the infant on breast milk synthesizes less vitamin K, so breastfed infants are at risk of vitamin K deficiency and as a result hemorrhagic disease of the newborn. The AAP recommends an intramuscular dose of vitamin K at birth to prevent this deficiency [1]. In addition to vitamin deficiency, premature infants are at risk of developing mineral deficiency especially calcium and phosphorus if not adequately supplemented postnatally. Majority (up to 80%) of the mineral accretion (calcium, phosphorus and magnesium) occurs in the last trimester of pregnancy. The Fetus accrues calcium at a rate of 100-120mg/kg/day and phosphorus at a rate of 50-65 mg/kg/day in last trimester [52,53]. Among other co morbidities of prematurity, metabolic bone disease is fairly common in extremely premature infants and deserves attention. It occurs in up to 55% of infants born with birth weight less than 1000 g and 23% of infants whose birth weight < 1500 g [54,55]. The prevalence is higher in breast fed premature infants (up to 40%) compared to preterm formula fed infants (up to 16%) [56,57]. Metabolic bone disease is characterized by a reduction in bone mineral content (osteopenia), with or without rachitic changes, and is caused by several nutritional and biochemical factors. Major etiological factors are inadequate supply of minerals, vitamin D, prolonged need of total parenteral nutrition and certain drugs like diuretics and steroid. Inadequate mineral accretion, inability to provide optimal calcium and phosphorus in TPN and low level of calcium and phosphorus in breast milk are the major factors placing premature infants further at risk of osteopenia of prematurity. Clinical presentation varies from a totally silent condition to overt rickets with multiple bone fractures and radiographic features of bone under mineralization. It is usually seen between the 10th and 16 week of life. It is imperative to follow biological markers of the disease (calcium, phosphorus, alkaline phosphatase level and appropriate radiological studies) in premature infants fed on human milk (MoM/DBM) and initiate treatment accordingly. Detail review of diagnostic and treatment strategies is beyond the scope of this review. Recommended requirements of calcium, phosphorus and vitamin D in preterm infants varies from different sources. AAP [58] recommended calcium intake of 150-220 mg/kg/day, phosphorus 75-140 mg/kg/day and vitamin D 200-400 IU/day for preterm infants < 1500 g [58] while ESPGHAN [59] recommends Ca intake of 120-140 mg/kg/day, phos 60-90mg/kg/day and vitamin D 800-1000 IU/day. Preterm human milk has lower content of calcium and phosphorus compared to preterm formula (31 mg/100kcal and 20mg/100kcal vs 123-185 mg/100kcal and 80-110 mg/100kcal)

Table 2: Commercially available human milk fortifiers in the United States.

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Nutrient intake guidelines</th>
<th>Mead Johnson acidified liquid human milk fortifier*</th>
<th>Similac Human milk Fortifier extensively hydrolyzed protein concentration</th>
<th>Prolacta +4 human milk fortifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kcal/Oz</td>
<td>115-130 kcal/kg</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Protein, g/100 cal</td>
<td>4-4.5 g/kg</td>
<td>4</td>
<td>3.53</td>
<td>2.8</td>
</tr>
<tr>
<td>Calcium, mg/100 cal</td>
<td>120-200 mg/kg</td>
<td>145(174)</td>
<td>152(182)</td>
<td>150(180)</td>
</tr>
<tr>
<td>Phosphorus, mg/100 cal</td>
<td>60-140 mg/kg</td>
<td>80(96)</td>
<td>85(102)</td>
<td>78(94)</td>
</tr>
<tr>
<td>Iron, mg/100 cal</td>
<td>4-6 mg/kg</td>
<td>1.9(2.3)</td>
<td>0.6(0.7)</td>
<td>0.2(0.3)</td>
</tr>
<tr>
<td>Vitamin D, IU/100 cal</td>
<td>800-1000 IU/day</td>
<td>210(126-453)</td>
<td>130(90-270)</td>
<td>34(20-61)</td>
</tr>
<tr>
<td>mOsm/kg H2O</td>
<td>450</td>
<td>326</td>
<td>450</td>
<td>N/A</td>
</tr>
</tbody>
</table>

(Acidified liquid HMF. *Extensively hydrolyzed protein concentration liquid.) (Amount in parenthesis is what is provided with goal feeds of 150 mL/kg/day) Courtesy Amy Gates, RD and Dr. Jatinder Bhatia-2015
Substance abuse such as PCP (phencyclidine) and cocaine. On the breast, HIV+ mother in industrialized nations, maternal galactosemia, active maternal tuberculosis, active herpes lesions are fed at high volumes (180-200 ml/kg) of breast milk, this would provide only one third of in utero mineral accretion. So it is essential to fortify the breast milk (MoM/DBM) for preterm infants in order to provide extra minerals. Role of vitamin D in causing osteopenia of prematurity is certain and is a subject of a considerable discussion. Vitamin D level in breast milk depends on maternal vitamin D stores. Breast fed infants especially those with dark skin pigmentation and little sun exposure are at risk for vitamin D deficiency which may manifest as rickets. American Academy of Pediatrics and Institute of Medicine (IOM) recommends supplementation of vitamin D (400-600 IU/day) to the breast fed infant [62], while ESPGHAN recommends 800 to 1000 IU/day [59,63].

Another crucial mineral which deserves attention in preterm infants fed breast milk, is iron. The iron concentration of human milk varies from day to day and mother to mother. Its concentration in breast milk (0.5 to 1 mg/L) is significantly lower than in currently available premature infant formulas (12-14mg/L) [64]. Preterm infants are at risk of developing iron deficiency anemia, frequently because of blood loss from phlebotomy. The estimated iron requirement for preterm infants is 1.4-2mg/kg/day assuming 20-27% absorption [65] and this requirement does not consider blood loss and blood transfusion which is frequent in premature infants. Doyle et al. [66], showed early iron supplementation does not improve early anemia of prematurity (mostly happens before 2 months) which is likely from ineffective erythropoiesis. Two recent studies have shown that iron supplementation or fortification at 2 weeks age leads to reduced need for blood transfusion in VLBW infants compared to supplementation from 6-8 weeks [67,68]. AAP recommends that term infants receiving more than 50% of their feedings as breast milk and who are not receiving iron-containing complementary foods should receive 1 mg/kg per day of supplement of iron, beginning at 4 months of age [28,69,70]. ESPGHAN recommends 2-4 mg/kg/day for infants with a birth weight of < 1800 g [59] while World Health Organization recommends 2.4 mg/kg/day for all LBW infants aged 2-24 months [71]. Studies have shown that breastfed infants who receive iron supplementation before 6 months of age have higher hemoglobin concentrations at 6 months of age compared with those who did not and it also resulted in improved visual acuity and higher Bayley psychomotor developmental indices by 13 months of age [69].

Immunologic/bioactive compounds

Bioactive factors in human milk are important components of the innate immune system. Colostrum is the first fluid produced by mothers after delivery, and it is distinct in appearance and composition. It is rich in immunologic factors such as secretory IgA, lactoferrin, leukocytes, and developmental factors such as epidermal growth factor [72,73]. Differences in cytokines, growth factors and lactoferrin between preterm and term milk are most noticeable in colostrum and early milk. Stage II lactogenesis follows colostrum production which is marked by copious milk production. Detailed description of each bioactive factor function is beyond scope of this article. Reduction in bioactive factors has been demonstrated by pasteurization (especially Holder's pasteurization method), while freezing does not affect their levels.

Fortifiers

As the fetus accrues a major portion of nutrients in the last trimester especially fat (highest percentage), protein, calcium and phosphorus, preterm infants miss out on this opportunity. Growth is the major concern in preterm infants receiving human milk (MoM/Donors milk) as it's content especially protein and energy changes over time. Postnatal growth restriction has been associated with, impaired long term neurodevelopment, and lower IQ scores [74]. For this rationale, preterm infants fed on MoM/Donors milk must receive fortified milk to enhance its protein, energy and mineral content to meet the need of the growing preterm infant. Currently in the US, three human milk fortifiers are available. There have been reports of an increased incidence of metabolic acidosis in infants receiving feeds fortified with the acidified fortifier. These studies used 18 and 18.5 mEq/dL of CO2 as a marker of acidosis. Since metabolic acidosis is recognized in premature infants both in early and late postnatal period, the study of Sernard et al. [75], using 17 meq/dL, did not find sustained metabolic acidosis with the use of acidified fortifier both in MoM and donor human milk-fed infants. Most of acidosis was observed during the provision of parenteral nutrition and the early stages of fortification.

Numerous studies have demonstrated better weight gain of preterm infants receiving fortified human milk. A Cochrane review cited one study where weight, length, and head circumference were statically significantly greater in infants fed fortified human milk for 12 weeks compared to control [76]. Studies have found better outcomes in terms of weight gain and improved length in preterm infants receiving fortified human milk [77-79]. The current approach of human milk fortification is by assuming its calorlic content (20 cal/oz) and adding fixed dose of the fortifier, does not take into account the variability among the population and change of caloric and protein content over time of lactation. Recent studies have shown that up to 58% of very low birth weight infants fed with fortified breast milk have postnatal growth restriction [80]. An alternate approach is analysis of human milk for its macronutrient (protein, fat and lactose) content by using mid-infrared spectroscopy and then base fortification on the analyses [81]. Rochow et al. [82], have shown better weight gain and improved growth in very low birth weight infants by target fortification of human milk [83]. Though labor intensive and time consuming, target fortification of preterm human milk is promising, but at present, is a research tool and human milk analyzers are not FDA approved to use in the United States. Till human milk analyzers are approved for clinical, one should adapt individualized fortification approach based on variability of MoM and low energy contents of donor milk while closely follow infant’s growth.

Contraindication to breast feeding

Even though breast feeding or provision of human milk is the preferred feeding for infants, contraindications include, galactosemia, active maternal tuberculosis, active herpes lesions on the breast, HIV + mother in industrialized nations, maternal substance abuse such as PCP (phencyclidine) and cocaine.
Maternal substance abuse and breast feeding is a broad topic and difficult to cover each substance use and breastfeeding in a review article. Authors suggest readers should refer to LactMed (https://toxnet.nlm.nih.gov/newtoxnet/lactmed.html) for detail review of substance use and breast feeding. LactMed includes up-to-date information on drug levels in human milk and infant serum, possible adverse effects on breast feeding infants, potential effects on lactation, and recommendations for possible alternative drugs to consider. The extent of drug excretion in human milk is depends on chemical properties such as size of the drug molecule, bioavailability and half-life, ionization and fat solubility [84]. The effect of a drug may be more severe in a premature infant, because of immature metabolizing enzymes and larger volume of distribution. According to ABM (The Academy of breastfeeding Medicine) protocol, 2015 [85] - mother on commonly used opioids such as methadone and buprenorphine should maintain breast feeding regardless of the dose if they are in an enrolled program and weaning can occur both in the mother and the infant. In general, per ABM protocol 2015 [85], contraindication of breast feeding besides active maternal use of PCP and cocaine is as follows: (i) Mothers not engaged in substance abuse treatment (ii) Not engaged in prenatal care (iii) Positive maternal urine toxicology screen for substances other than marijuana at delivery (iv) No plan for postpartum substance abuse treatment or pediatric care (v) mothers relapsing to illicit drug use or legal substance misuse in the 30-day period prior to delivery (vi) Any behavioral or other indicators that the mother is actively abusing substance (vii) Chronic alcohol use. Mothers with untreated brucellosis and human T-cell lymphotropic virus type I or II should not breast feed [83]. Maternal CMV infection and breast feeding is much debatable topic, as post-natal transmission of cytomegalovirus through breast milk occurs. A meta-analysis has found wide variation among studies on overall mean rate of CMV transmission via breast milk 23%, mean risk of symptomatic CMV infection 3.7%, and mean risk of sepsis-like symptoms of 0.7% with most in premature infants [86,87]. Pasteurization inactivates CMV while freezing decreases, but does not eliminate transmission of CMV. Currently there is no consensus among neonatologists regarding benefits of human milk and the risks of CMV infection.

CONCLUSION

In summary, breast milk is uniquely suited to human infants and is the preferred feeding for all infants, term and preterm. The content of various nutrients in breast milk of preterm infants is different from that of mothers delivering at term. In the absence of mother own milk, use of human donors milk from milk bank (HMBANA) should be prioritized while adapting appropriate fortification practice. Nonetheless, small preterm infants benefit from reduced medical complications with the use of human milk-based diet, but, the milk must be fortified. With newer devices available to quantify nutrients in breast milk, though at present it is a research tool, fortification of breast milk can become targeted rather than the current strategy based on assumptions of nutrient content based on stage of lactation and postmenstrual age. Future studies should focus on changes in fortification strategies based on growth and biochemical responses (Targeted fortification). Every mother should be motivated to provide breast milk or feed breast milk regardless of infant’s gestation, as feeding human milk practice has shown multiple medical benefits both in the infant and mother. Furthermore it also decreases health care related cost, which is huge for a premature infant.

Strongly advice mothers found with a positive urine screen for THC (Cannabis) to discontinue exposure while breast feeding and counsel them as to it may have long-term adverse neurobehavioral effects [87-89].

REFERENCES


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