

# High Osmolality of Fortifier Human Milk Adding with Vitamin (ADEC)

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## Abstract

**Background:** In order to reach nutritional purposes, human milk has to reach 2 g/dL. In his publication Lefebvre et al. 2013, journal of pharmacology and clinical research, the authors stated that, when women's milk is fortified up to 2 g/dL, it may increase its osmolality up to 500 mosm/kg. He also argued that caution should be taken when adding a drug or vitamins into the milk.

**Aim :** We studied for the first time the impact on a women's fortified milk osmolality, when adding multi vitamins (ADEC).

**Method:** The osmolality of 36 pasteurized fortified human milk samples was measured. The amount of milk required as a solvent to maintain osmolality below 500 mosm/Kg was then determined.

**Results:** The 2mL fortified human's milk reached up to 750mosl/kg when the multi vitamins ADEC was added. The osmolality decreased proportionately with the solution dilution. It is only with 20 mL of milk that the osmolality comes down to its initial rate 430mosm/kg. Stronger the milk's fortification is, the bigger impact it has on the milk osmolality.

**Conclusion:** New nutritional recommendations for premature infants are needed. In the meantime, when the fortified milk intake is under 20 mL, it is preferable to extend parenteral intakes with fat-soluble vitamins. Also, we should use enriched women's milk as fortifier and be cautious with fortification « à la carte » or when adding drugs and electrolyte solutions.

**Keywords:** Human milk osmolality ; Human milk fortifier ; Vitamin D ; Preterm ; Nutrition

## Introduction

Human milk is an unequalled way of providing ideal food for the healthy growth and development of infants, especially for premature infants who are born before 32 weeks of gestation and weigh 1,500 kilograms or less [1-3]. Fortifying human milk with energy, protein, mineral, vitamins AEDC and iron is essential in order to improve the infant's growth and its neurological development. It helps also to prevent infants from hyponatremia, hypophosphoremia, anemia and osteomalacia [4,5]. By addition of vitamin D in particular is crucial to the infant development. It reduces the risk of sepsis and atopic symptoms, but also prevents from cancers, diabetes mellitus, cardiovascular and some order inflammatory diseases [6-8]. However, the vitamin D concentration in human milk is low (6UI/100ml). According

to the EPSGHAN, the infant's needs of vitamin D is 800-1000 UI/kg/j, a factor of 150. As an effect, human milk supplementation with vitamin D is essential. Indeed, Curtis et al. showed that human milk fortification may increases osmolality.

## Material and methods

### Milk samples

Human milk samples were collected and treated according to the "Milk Bank Guidelines". A batch of frozen-pasteurized human milk from our human milk bank was used. All donors received information about this study. They gave their written informed consent to the "Lactarium d'Ile de France" in order to participate. This study was approved by the Human Research Ethic Committee-Protection of Person Committee, Hotel Dieu,

Paris, France. A batch of frozen-pasteurized human milk from our human milk bank (Lactarium Regional d'Ile de France) has been used for our study. A bottle (200mL) of unfortified milk (HMF 0) was thaw. We used 2 different methods to fortify human milk. 200 mL bottles of FHM1 and FHM2 were fortified. In the first time, we have used a multi-component human milk fortifier at 4% (HMF) containing whole protein, dextrin and mineral (Suppletine, Milupa, France) and 0.5% of an exclusive whole protein fortified (Nutriprem, Gallia, France) (FHM 1). The second one contained the same multi component HMF at 4% but added with a 1% of an exclusive whole protein fortified (FHM 2). Milk sample were kept 24 hours at +4 °C.

### Supplemented with vitamin ADEC

As recommended in the NICU practice guidelines. We then added 0,3mL of vitamin ADEC (Uvesterol ADEC, Crinex, France). This vitamin is a concentrate of vitamin A (oil formula), Ergocalciferol (vitamin D2), alpha tocopherol acetate (vitamin E), and ascorbic acid (vitamin C). One dose of 0.3 mL contains: 1000 UI of vitamin D was add to milk samples of 2, 6, 12 and 20mL out of each type of milk (HFM 0, HMF 1 and FHM 2).

### Osmolality determination

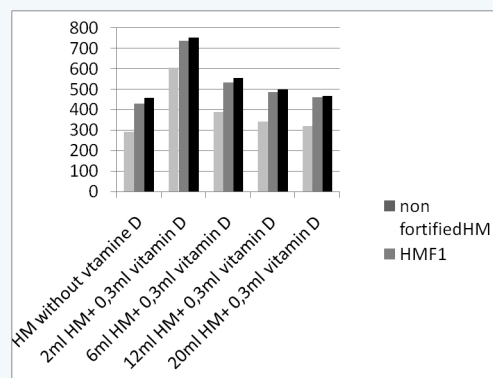
The milk osmolality was measured with an advanced micro-osmometer model, Fiske® Modèle 210 (FISKE® associates, Norwood, Massachusetts, USA) in Hospital Cochin, Paris, France. The method used was the freezing point measurement with a precision of 1 mosm/kg. Measures were made in triplicates.

### Statistical analysis

Data are expressed as means (SD). Student's paired t test was used for statistical evaluation. A p value of < 0.01 was taken as level of significance.

### Results

The osmolality of our unfortified and fortified milk was respectively 292mosm/kg and 432mosm/kg. The same data was found in another study, multi-component fortifier increase significantly the osmolality of human milk. We also demonstrated that fortified human milk (HMF) containing whole protein, dextrin and mineral, increases significantly more the osmolality compare to exclusive whole protein fortified (Figure 1). When vitamin ADEC is added in 2ml of unfortified human milk, the osmolality increases at 600mosm/kg. It can even reach 738 up to 750 mosm/kg if the milk is fortified with standard multi-component added with 0.5 and 1% of exclusive whole protein respectively (Figure 1). When vitamin ADEC is diluted in a higher milk volume, the milk osmolality decreases proportionality, until it reaches the initial osmolality at a volume of 20mL of human milk (Figure 1).



**Figure 1:** Osmolality (mosm/kg H<sub>2</sub>O) of human milk with or without different process of fortification. Unfortified milk (HM), HM with a 4% human milk fortified (HMF) containing whole protein, dextrin and mineral (suppletine, milupafrench) and 0.5% of a exclusively whole protein fortified (HMF 1) and another one with 4% HMF and 0.5% of a exclusively whole protein fortified (HMF 2). Different volume (2, 6, 12 and 20) of each HM was added with vitamin D (0,3ml).

### Discussion

The osmolality of unfortified milk is similar to amniotic fluid 275mosm/kg. High milk osmolality reflects a high concentration of solute particles. In 2010 EPSGHAN published new recommendations for preterm's enteral nutrition [1]. Especially the increase of protein and caloric intake for immature infants. In order to reach nutritional purposes, human milk has to reach 2 g/dL. In 2013, Lafeber and al states that when women's milk is fortified up to 2 g/dL, it may increase its osmolality up to 500 mosm/kg [10]. Even though the link with necrotizing entero colitis is not yet well established, digestives disorders can be found. He will forbidden the use of multi-vitamin. The author also said to be careful when adding hyper osmoler drugs or vitamins into the human's milk. The results on the milk's osmolality after adding multi component fortifiers such as 4% of Supplétine and protein (0.5% to1% of Nutriprem) were comforting. However, no study has yet evaluated the impact of multivitamins addition on fortified human milk's osmolality. As proven by de Curtis and et al. [9] osmolality is similar after storage 24h at +4°C thus we use 24h +4°C storage milk for more facility to prepare our milk samples. When the milk is being pasteurized the amylase rate remains stable so this could explain an increase of osmolality in pasteurized human milk. In fact Kreisll and et al. [11] found a decrease of osmolality from 20 to 30 mosm/L after pasteurization and they had the same value that we have found for our unfortified pasteurized human milk. Like Curtis we also found an increase of human milk osmolality (292 mosm/kg) with standard fortification (431 mosm/kg). Adding fortified human milk with only whole protein increases less significantly osmolality (471mosm/kg) as demonstrated by Curtis and et al. [9]. But we found a dose response effect for

different concentrations of fortifiers so it need to be controlled. Agarwal and et al. [12] suggest that fat has no effect on milk's osmolality and that it may be preferable to use a predominantly fat based HMF. Pearson and al suggest that the addition of mineral and vitamin into human milk, can increase osmolality. Srinivasan and et al. [13] demonstrated an increase of the raw milk's osmolality, with increasing dose of all additives (sodium, iron, dalavit-vitamin ABCD, folic acid) until 951 mosm/kg excepted for cafein. They did not find a significant increase of the milk's osmolality when adding fortifier, their osmolality was not more than 400mosm/kg. Consequently they did not test the effect of both fortifiers and vitamins. Our results have proved by adding vitamin ADEC to human milk, will increased the milk's osmolality (Figure 1). We have demonstrated for the first time that this increase was larger when the milk contained human milk fortifier. This could be responsible for slowing down gastric emptying, causing intestinal distension, frequent stools and more rarely diarrhea. Some authors have showed that there might be a correlation between osmolality superior to 400mosm/kg and necrotizing enterocolitis [12,14]. But for others there is no evidence of mucosal injury. However the safety cut offs to prevent enterocolitis are unclear [2]. Current lipo solubles vitamins are used by NICU with an osmolality as high as 3200 mosm/ml. The addition of vitamins into a small volume of milk, increases significantly osmolality (up to 700 mosm/l for 2ml milk sample). Osmolality decreases proportionally to the increase of milk volume used for administration (Figure 1). When the volume of dilution reaches 20ml, the osmolality of unfortified and fortified milk remains unchanged. Hyperosmolar drug like retrovir have been responsible of netrotizing enterocolitis for preterm baby will it is well tolerate for term baby and special recommendations of dilution have been written [15,16]. Kreissl and et al. [11] concludes that adding therapeutic additives such as iron, multivitamin supplement and calcium-phosphorus capsules may increase osmolality up to 868 mosm/l. Liposoluble oral suspension of vitamin could have the same impact on human milk osmolality. A certain amount of milk (20ml) is required as a solvent to maintain osmolality below 400 mosm/kg. It is not possible for very small premature babies to receive such a volume of dilution, when enteral nutrition has been initiated, in order to administrate orally these vitamins. It may be safer to start this type of oral vitamin when preterm tolerates 20ml of milk. As 800 to 100UI/kg/day of vitamin D is recommended we could suggest to pursue as late as possible intravenous fat-soluble vitamins. We could also prefer to use human milk fortifier with high concentration of vitamin D. The ultimate question could be is this osmolality reflect the one measured in gastric contents in very low-birth-weight infants after gavages feeding. Thatrimontrichai and et al. [17] found no significantly change in osmolality, so we could expect than our results are representative of the effective osmolality of gastric content with fortified milk and vitamins.

## Conclusion

The use of human milk fortifiers with an additive therapy, like fat-soluble vitamins, increases significantly osmolality of human milk. This increase is significantly more important than the one expected with human milk fortified alone. Like fortification, vitamins are necessary in order to optimize the infant's growth and development. Rational policies for the use of additives with human milk will allow safety administrations in neonatal units unfortunately with fortification "à la carte" or with additive in human milk [18].

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