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Mini-review

Sex-specific nutrition requirements for preterm infants in India

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This narrative review examines the evidence that sex is a vital factor in determining nutritional interventions for preterm infants. The biological disparities between the sexes are obvious from the initial phase of pregnancy. The female and male foetuses exhibit different responses to maternal nutrition. Female newborns have a natural survival advantage over male. Further, the composition of a mother's breast milk varies depending on the foetal sex and the early neonatal nutritional interventions affect girls and boys differently. The preterm formulas and donors' milk does not vary with infant sex, which might be one reason for better growth and developmental outcomes favoured by mother's own milk. However, preterm neonates have high nutritional requirements that cannot be met by breast milk alone and manifest a need for fortification with human milk fortifiers which are not sex-specific. Thus, optimising early nutrition for preterm girls and boys may improve the outcomes of both sexes as they have distinct and conflicting nutritional needs.

Keywords: Low birth weight, Mother's milk, Preemie feeding, Premature babies, Preterm formulas

Introduction

The 'preterm babies or premature babies' or 'preemies' or 'premmies' are babies born less than 37 weeks of gestation in contrast to full-term baby born at 40 weeks (Fig. 1 & 2)[1,2]. An 'extreme preemie' is born at less than 28 weeks, 'very early preemie' between 28 to 32 weeks, 'early preemie' between 32 to 36 weeks, 'late preemie' between 34 to 36 weeks of gestation[3]. The symptoms of preterm labour include uterine contractions that occur more than once in every ten minutes and leakage of fluid from vagina before 37 weeks[4].

Premature birth is associated with risk factors such as multiple pregnancies, obesity, underweight, gestational diabetes, gestational hypertension, cervical incompetence, vaginal infections, psychological stress and tobacco smoking[5]. The contribution of risk factors to preterm birth is depicted in Fig. 3[2]. Preterm birth is a global concern, especially Africa and South Asia accounting for more than 60%. Every year, around 15 million babies are born premature (5-18% of total deliveries). However, late preterm births accounts for 75% of total preterm births. This rate differs across the nations. India accounted for three million preterm births as portrayed in Fig. 4[1]. Lower-income countries tend to have a higher average rate of premature births, with an average of 12% versus 9% in higher-income countries[3].

Premature birth is one of the major causes for incidence of babies with low birth weight (<2.5 Kg)[6]. Further, it is the world′s leading cause of infant deaths. The preterm birth complications contributed for 0.81 million deaths in 2015[7]. Premature babies are

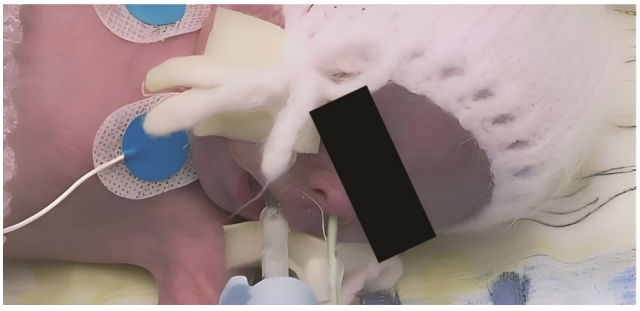

Fig. 1 — Extreme preemie born at 26 weeks gestation (birth weight: 990 g).

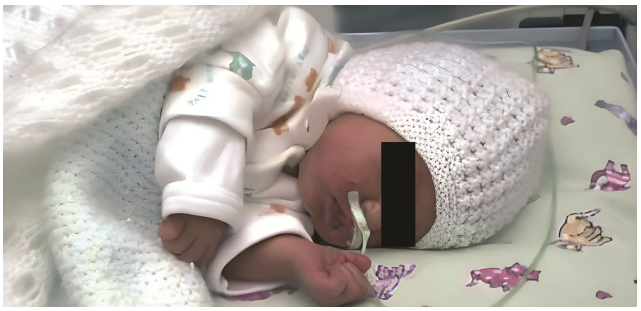

Fig. 2 — Preemie born at 35 weeks gestation.

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more likely to have cerebral palsy, developmental delays, hearing impairments and visual problems[8]. Preterm birth also increases the baby's risk of dying from other causes such as neonatal infections as presented in Fig. 5[1]. Sooner the baby is born, the greater these risks will be. The survival rates are around 6% at 22 weeks, 26% at 23 weeks, 55% at 24 weeks and 72% at 25 weeks. The chance of survival without long-term complications is very low (Table 1)[3].

Sex differences in neonatal outcomes: Male disadvantage

The large observational studies based on the data from international neonatal networks showed that the overall mortality and morbidity rates of preterm infants have improved (Table 2)[7]. However, preterm boys are at a greater risk of mortality and morbidities including neurodevelopmental impairment in later stages compared to preterm girls. Further, in the individuals born with very low birth weight, the male sex remained a major predictor of metabolic syndrome[9]. A retrospective cohort study was conducted by researchers[10] to examine the differences and trends in the outcomes of preterm boys and girls born before 29 weeks of gestation. Between 2007 and 2016, the rates of mortality and major morbidities were decreased. During this time, the gap between boys and girls was decreased for mortality but not for any other outcomes. Although progress has been

Table 1 — Global survival rates of preterm infants

Gestation	Survival rate
23 weeks	29%
24 weeks	46%
25 weeks	69%
26 weeks	78%
27 weeks	90%
28-31 weeks	90-95%
32-33 weeks	95%
≥34 weeks	Same as term infant

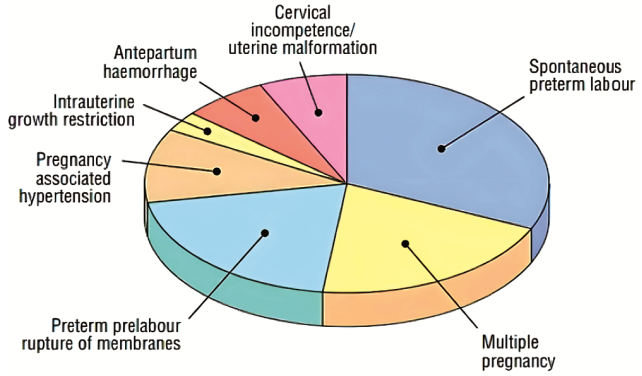


Fig. 3 — Contribution of risk factors to preterm birth.

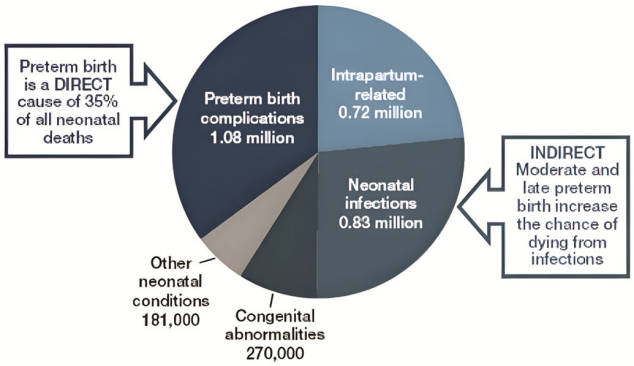


Fig. 5 — Neonatal deaths due to preterm births.

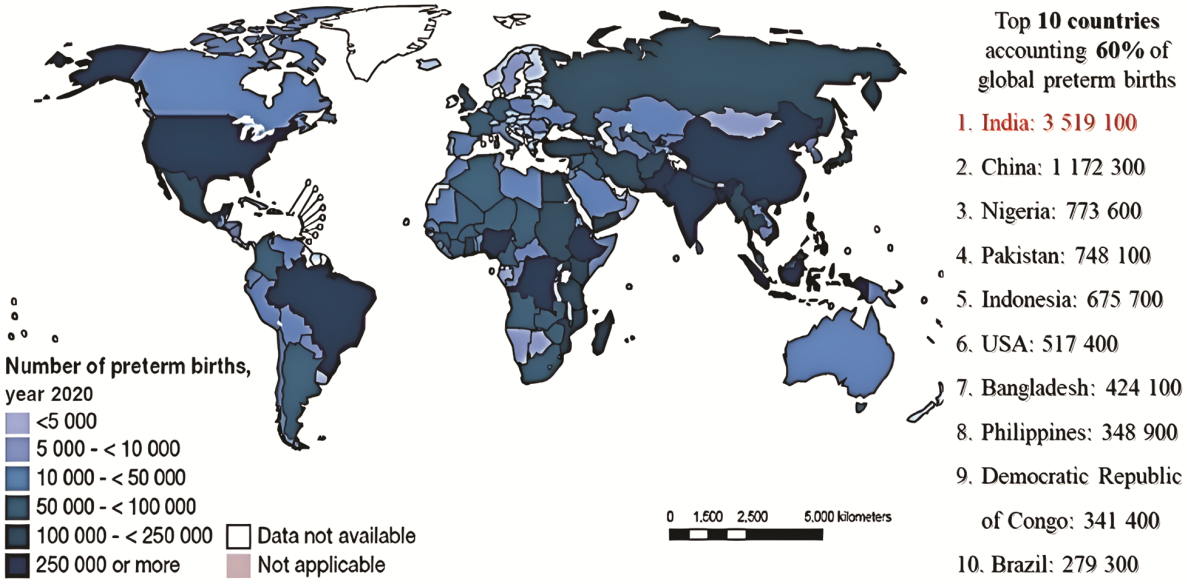


Fig. 4 — Global epidemiology of preterm births.

Table 2 — Incidence and mortality of global pre-term births[7]

Preterm births	1990		2019		Relative change 1990-2019	
	Incident cases No.×10^5	Deaths No.×10^3	Incident cases No.×10^5	Deaths No.×10^3	Incident cases %	Deaths %
Overall	160.62	1269.04	152.17	663.52	−5.26	−47.71
Female	73.42	560.11	69.75	279.57	−5.00	−50.09
Male	87.19	708.93	82.42	383.95	−5.47	−45.84
Relative change,M-F	↑18.76%	↑20.99%	↑18.16%	↑37.34%		

achieved in implementing good care practices and improving neonatal outcomes, more attention to the 'natural barriers' (*i.e.,* biological differences) between the sexes is required to progress towards precision nutrition and reduce the 'male disadvantage'.

Sexual dimorphism in foetal growth

The biological factors associated with male vulnerability are yet to be elucidated. The sex differences in body size are evident from first trimester of pregnancy and in metabolism begin at the blastocyst stage of embryonic development as portrayed in Table 3[11]. These findings imply that males are more sensitive to growth factors, making them more vulnerable to inadequate nutrient supply[12,13]. Further, pregnancies with male foetus are at greater risk of metabolic complications and shorter gestation periods[14].

Sex-specific placental function

The placentas of female and male foetuses express different proteins and genes[15]. The female foetuses experience mild growth reduction due to expression of multiple placental genes and protein modifications. These adaptations in placental function and growth prepare the female foetuses for adverse events which may further compromise oxygen or nutrient supply[16]. On the other hand, male foetuses generally respond with modest gene and protein modifications in placenta with continued growth in sub-optimal intrauterine environment that puts them at a greater risk for intrauterine growth retardation (IUGR), preterm birth and even death in adverse conditions[17]. The aforementioned foetal observations support the anthropological observations that female foetuses survive adversity better than male foetuses[11].

Sex-specific influence of maternal conditions

Maternal nutrition can affect the foetal growth to a greater extent. A balanced diet during pregnancy may have long-term health benefits[18]. It is argued that male neonates are at greater risk of malnutrition due to rapid growth and brain development compared to female neonates[11]. It is also proposed that male foetuses are more responsive to their mothers' current diet than female foetuses, who are more responsive to their mothers' lifetime nutrition and metabolism[19]. There is growing evidence that maternal pre-pregnancy overweight and obesity are associated with a higher risk of obesity in male infants compared to female infants[20]. Further, gestational diabetes is found to be a risk factor for childhood overweight in boys rather than girls.

Table 3 — Sexual dimorphism in foetal growth[11]

	Male	Female
1st trimester		
Crown-rump length	Larger	Smaller
2nd trimester		
Head circumference	Larger	Smaller
Abdominal circumference	Larger	Smaller
3rd trimester		
Fat mass at birth	9.9%	11%
Lean body mass	Higher	Lower

Table 4 — Variation in birth weight of preterm babies with sex

Gestation	Boys	Girls
24 weeks	0.55–0.87 Kg	0.50–0.80 Kg
26 weeks	0.70–1.13 Kg	0.64–1.08 Kg
28 weeks	0.89–1.42 Kg	0.80–1.37 Kg
30 weeks	1.09–1.79 Kg	1.00–1.70 Kg
32 weeks	1.37–2.20 Kg	1.29–2.14 Kg
34 weeks	1.73–2.77 Kg	1.63–2.62 Kg
36 weeks	2.11–3.30 Kg	2.04–3.16 Kg

Study revealed that the growth of female foetuses was slowed down during pregnancy when the mothers have mild asthma, but not to the point where it resulted in IUGR. On the other hand, male foetuses exhibited IUGR or preterm delivery when there is acute asthma[21]. According to another study[22], mild pre-eclampsia was associated with growth reduction in female foetuses but not in male foetuses. This was consistent with other observations, which depicted female foetuses restricted their growth rate as a survival tactic in preparation for future multiple insults[11]. The intriguing difference in response of a male and female foetus to the same intrauterine environment points to a fundamental biological difference that most likely occurs at the cellular and molecular level[23].

Sexual disparities in body composition of neonates

The birth weight of preterm babies varied according to the sex, as shown in Table 4. The female

sex was associated with a higher body fat percentage in neonates indicating that differences in body composition are present from birth[24]. The male preterm babies exhibited more bone area, bone mineral mass and lean mass than the female preterm babies at discharge term, six months and twelve months. Thus, the preterm boys require more nutritional intake than the preterm girls for optimum linear growth and body composition[14]. The sex-specific growth charts are developed for preterm infants as the growth outcomes differ between the sexes as presented in Fig. 6[25]. The male preterm infants exhibited greater weight, length and head circumference at all gestational ages as male foetuses have faster cell division than females[25].

Researchers[26] have compared the body size and body composition of prematurely born four year old boys and girls with full-term controls. Findings revealed that prematurity was not associated with increased body fatness in four year olds. However, gestational age at the birth of prematurely born children correlated positively and significantly (P<0.05) with height, weight, body mass index, fat mass, fat mass index and fat-free mass in girls but not in boys.

Sexual disparities in immune function of preterm neonates

The preterm neonates produce lesser quantity of complement proteins (C1, C4, and factor B) and mannose-binding lectin for pathogen opsonization than the term newborns due to deficiency of humoral and cellular immunity[27]. Hypogammaglobinaemia is often seen in early preterm infants as the antigen-specific immunoglobulin G (*Ig*G) is acquired transplacentally from maternal circulation after 32 weeks gestation. Also, the production of antimicrobial proteins and peptides increases with increasing gestational age[28]. The preterm neonates exhibit relative monocytopenia and neutropenia compared to term newborns due to reduced granulocyte macrophage colony stimulating factor (GM-CSF) levels and impaired migration of neutrophils, phagocytosis, extracellular killing of pathogens[29]. Several researchers depicted that monocytes from preterms showed decreased tumor necrosis factor-α (TNF-α) production, interleukin-8 (IL-8), IL-12 and reduced major histocompatibility

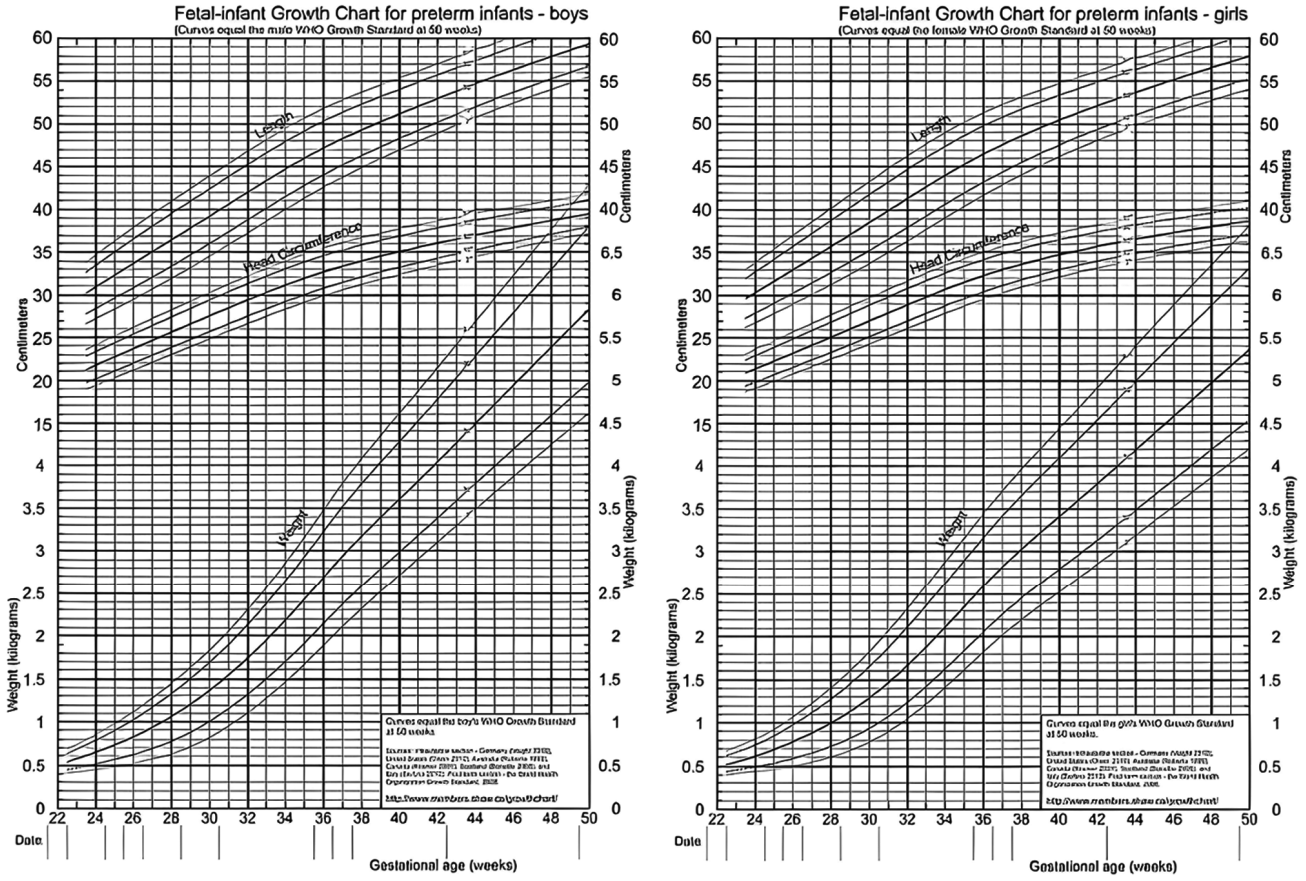


Fig. 6 — Sex-specific growth charts.

complex class II expression[30-32]. Further, preterm infants have lower toll-like receptor (TLR) responses that are essential for innate immune function and pathogen clearance compared to term neonates[33]. Fig. 7 summarizes the sex-specific immune responses and dysregulation in immune function of neonates born preterm. In utero, foetus can suppress potentially harmful immune responses to avoid self-injury which is crucial for antenatal events and subsequent postnatal inflammatory reactions. Female preterms possess significantly higher circulating catecholamine levels associated with regulation of immune function and hypoxic defence mechanisms, which may partially explain the better neurological outcomes in females[28]. The deficiency of amino acids in male newborns is associated with impaired immune function and increased susceptibility to infectious diseases. However, the female neonates possess higher basal levels of amino acids such as alanine, glycine, methionine, valine and tyrosine, exhibiting better immune function[34]. Excessive free iron is linked with infections and oxidative tissue damage. According to researchers[35] the preterm males were more prone to serum iron overload despite a similar number of blood transfusions as the preterm females. Further, the XX chromosome of females is immunologically beneficial in some cases than the XY of males[36].

Nutritional management of preterm infants

The intrauterine accretion of nutrients occurs mainly in the later part of the third trimester. Hence, preterm infants have low body stores of macro- and micro-nutrients at birth and high requirements to support growth and development[37]. Extra uterine growth restriction (EUGR) is common among preterm infants, occurring in more than 50% of very low birth weight (<1.5 Kg) babies. Inadequate postnatal nutrition is a significant factor contributing to growth failure. Around 90% of extremely low birth weight (<1.0 Kg) infants are small for gestational age (SGA) babies displaying growth failure at 36 weeks of gestational age[38]. The higher nutritional requirements for preterm infants compared to term infants are depicted in Table 5[39]. Infants born prematurely lack adequate feeding skills including sucking and swallowing difficulties and may experience feeding intolerance due to gut immaturity. The appropriate nutritional care of preterm infants can positively influence their early growth, development and long-term outcomes. The initial feeding method depends on the feeding skill of baby. The decision tool for initiation and advancement of preterm infant feeding is given in Table 6[39]. There is an ever-growing evidence depicting that prompt provision of parenteral nutrition to preterm infants can improve survival and

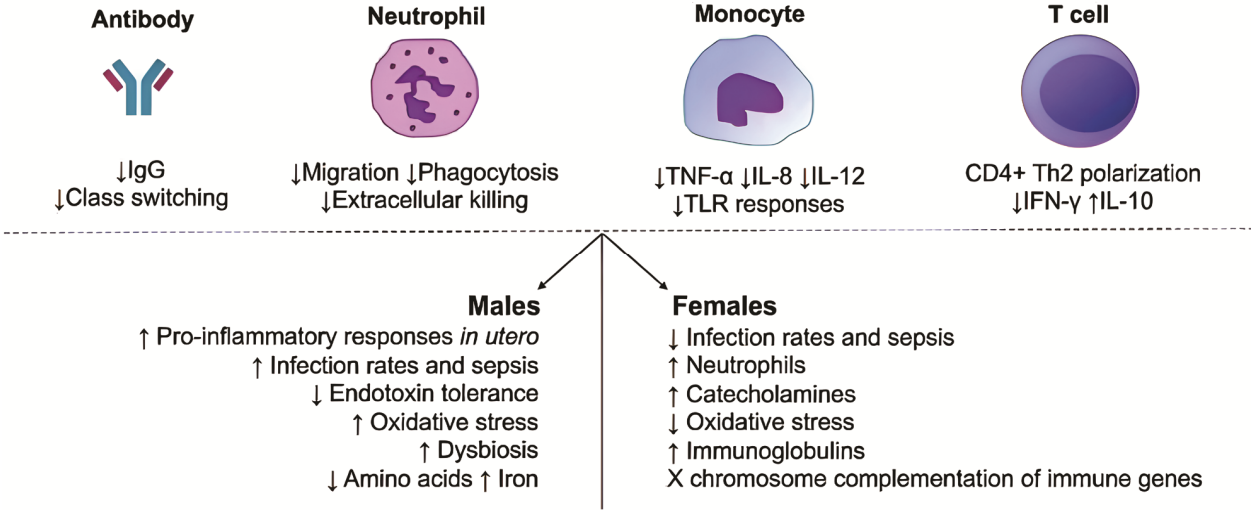


Fig. 7 — Preterm neonatal sex disparities in immune function.

Table 5 — Nutritional requirements of preterm and term infants[39]

Nutrient (per Kg/day)	Preterm infants (GA < 28 weeks)	Term infants (GA 39-41 weeks)	Higher needs (Preterm *vs* Term)
Energy, Kcal/Kg	125	110	>10%
Protein, g/Kg	4	1.5	>2.5-fold
Calcium, mg/Kg	120-140	55-120	>2-fold
Phosphorus, mg/ Kg	60-90	30-75	2-fold more

[GA; Gestational age]

Table 6 — Decision tool for initiation and advancement of feeding for preterm infants[39]

Gestational age	Feeding skills	Initial feeding method
<28 weeks	Inadequate sucking skills; propulsive gut motility	Intravenous fluids
28-31 weeks	Developing sucking bursts; poor coordination of suck/swallow and breathing	Nasogastric tube feeding can be coupled with spoon/ paladai feeding
32-34 weeks	Slightly mature sucking; beginning of breath and swallow coordination	Spoon/ paladai feeding
>34 weeks	Mature sucking; coordinated breathing and swallowing	Breastfeeding

Table 7 — Feeding volume and frequency of feed as per birth weight of preterm infants[39]

Birth weight (g)	Starting volume (mL/Kg/d)	Volume increment (mL/Kg/d)	Feed frequency
<1200	10-20	20	2 h
1200-1600	60	30	2 h
>1600	60	30	3 h

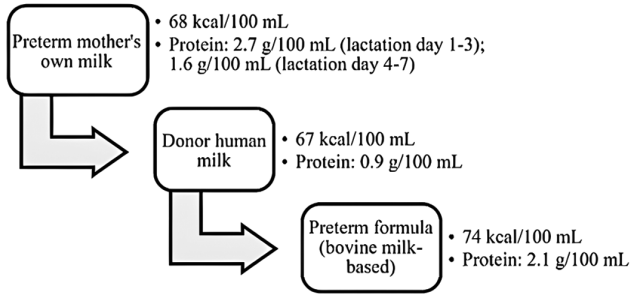


Fig. 8 — Preference for type of enteral preterm nutrition.

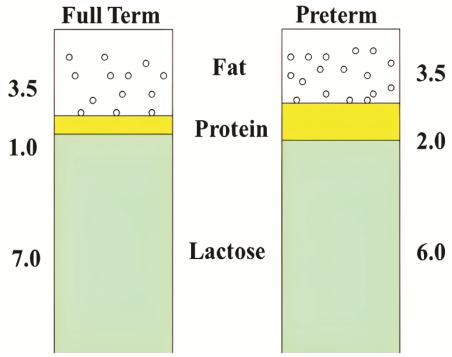


Fig. 9 — Composition of preterm and full-term milk (g/dL).

early outcomes such as growth, pulmonary function, neurodevelopment and bone maturation[39]. Likewise, early enteral feeding (small volume trophic feeds) with gradual progression to full enteral feeding (tube or oral) showed well-evidenced benefits such as improved maturation of gastrointestinal tract, immune function, feeding tolerance, growth (weight and length) and decreased risk of infections, sepsis, cholestasis and necrotizing enterocolitis. The preference for type of enteral preterm nutrition is given in Fig. 8[40]. The feeding frequency is decided based on the birth weight, gestational age and clinical condition of infant (Table 7)[40]. The feeds are given through nasogastric or orogastric tubes as bolus over 10 to 20 min[39].

Early enteral feedings enriched with calcium and phosphorus significantly increase the bone mineral content during the first three months of growth[41] in babies born prematurely. Breast milk offers benefits to preterm infants. However, studies have shown that the greatest benefits (increased growth and bone mineral content) occur only when human milk is fortified to meet the higher needs of preterm infants[42,43]. The composition of milk of preterm mothers differs from that of term mothers (Fig. 9). The preterm milk has more protein, fat, free amino acids and sodium but these quantities decrease within the first few weeks after birth. It has a comparable mineral composition (including trace minerals) to term milk, with the following exceptions: calcium content in preterm milk is much lower than in term milk and does not appear to increase with time while copper and zinc contents in preterm milk are higher than in term milk and decreases over the time of lactation[44].

The energy and protein intakes in the first week after birth have been shown to influence mental development at age 18 months; specifically, there was a 4.6-point increase in mental development index for every 10 Kcal/Kg body weight/day of energy intake and an 8.2-point increase for every g/Kg body weight/day of protein intake[39]. The daily recommended nutrient intake for preterm infants and the composition of preterm milk with and without fortification is given in Table 8[45-47]. The human milk fortifiers and preterm formulas commonly available in Indian market are depicted in Fig. 10 & 11.

Sex-specific human milk composition

The sex of the infant is one of the crucial factors influencing the composition of mother′s milk (Fig. 12). The variation in the mother′s milk composition reflects the difference in requirement of metabolic substrates for optimum growth and development in male

Table 8 — Recommended nutrient intake and composition of preterm milk[45–47]

Nutrient	Recommended intake* (per Kg/day)	Preterm milk (per 100mL)	Preterm milk+HMF** (4g/100mL)	Preterm milk+ Preterm formula (3g/100mL)
Fluid (mL)	150-180	-	-	-
Energy (Kcal)	115-140	67	78	81
Proteins (g)	3.5-4.0	1.4	1.8	1.5
Carbohydrates (g)	11.0–15.0	6.6	9.4	9.2
Fat (g)	5.0-8.0	3.9	4.1	4.6
LA (mg)	385-1540	1020	1146	1068
ALA (mg)	>55	75	NM	85
AA (mg)	30-100	40	NM	43
EPA (mg)	<20	6	NM	NM
DHA (mg)	30-65	33	NM	34
Calcium (mg)	120–220	40	140	60
Phosphorus (mg)	70-115	20	70	36
Magnesium (mg)	9.0-12.5	3.7	11.7	4.9
Vitamin A (IU)	400-700	250	1650	295
Vitamin D (IU)	1,300–3,300	2.5	500	11.5
Sodium (mmol)	3.0-5.0	0.8	1.6	1.3
Potassium (mmol)	2.3-4.6	1.2	2.1	1.4
Iron (mg)	200–300	121	300	500
Folate (mg)	2-5	5	6	17
Zinc (mg)	2-3	3.4	3.7	3.5
Copper (µg)	130-230	36	106	45

[*ESPGHAN 2021: European Society of Paediatric Gastroenterology, Hepatology and Nutrition; **HMF: Human Milk Fortifier (Lactodex-HMF); Preterm formula: Lactodex Regular; NM: Not mentioned]

Net wt.: 1.0 g
Price: ₹ 16.00

Net wt.: 1.0 g
Price: ₹ 40.00

Net wt.: 1.0 g
Price: ₹ 23.00

Fig. 10 — Human milk fortifiers available in Indian markets

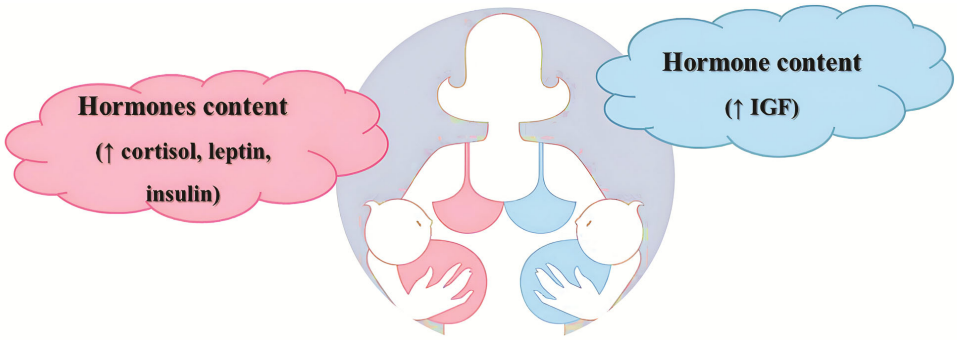
Net wt.: 400 g
Price: ₹ 590

Net wt.: 400 g
Price: ₹ 585

Net wt.: 400 g
Price: ₹ 730

Net wt.: 400 g
Price: ₹ 420

Fig. 11 — Preterm formulas available in Indian markets



Nutrient	Female	Male
Calories	Lower	Higher
Carbohydrate	Lower	Higher
Fat	Lower	Higher
Protein	Lower	Higher
Free amino acids	Higher taurine	Higher glutamine, glycine, cysteine, tyrosine

Fig. 12 — Sex differences in human milk composition

Table 9 — Studies depicting sex-specific human milk composition

Country	Sample size	Collection method	Infant age at collection	Findings		
Massachusetts, USA[48]	25 (12 F, 13 M)	Pump expression	2–5 months	per 100mL Energy (Kcal)	Female 60.8	Male 75.6
Singapore[47]	50 (25 F, 25 M)	Pump expression	1 month (completed)	Energy (Kcal) Fat (g) Lactose (g)	64 3.9 6.3	67 4.3 6.2
			2 months (completed)	Energy (Kcal) Fat (g) Lactose (g)	62 3.8 6.5	69 4.4 6.3
			3 months (completed)	Energy (Kcal) Fat (g) Lactose (g)	62 3.6 6.5	77 5.4 6.4
Libya, North Africa[49]	50 (25 F, 25 M)	Pump expression	2 months (completed	Lactose (g) Protein (g) Ca (mg) Mg (mg)	6.3 1.0 24 3	6.3 1.2 31 5
Poland[50]	77 (35 M, 42 F)	Pump expression	4-8 weeks	per 100mL Carbohydrates (g)	Female 6.90	Male 7.13
Canada[51]	428 (218 M, 210 F)	Pump expression	3-4 months	Hormone (per mL) Adiponectin (ng) Insulin (pg) Leptin (pg)	Female 19.2 386.8 595.3	Male 19.7 337.6 582.9

and female infants. The maternal breastmilk supplies more energy, protein and fat to male neonates compared to female neonates (Table 9)[47-51]. The sex-specific differences are not only observed in the macronutrient content of breastmilk but also other components such as immunoglobulin content, glucocorticoid concentration and hormone content (such as insulin-like growth factor (IGF)) impacting the growth of neonates. Further, the composition of the milk microbiome varies according to the sex[14,52]. Earlier researchers[53] have investigated the association of sex-specific variability of key metabolic hormone concentrations in breast milk with growth outcomes in moderate-late preterm infants. Human milk concentrations of IGF-1 and leptin were associated differently with growth and body composition

outcomes in boys and girls from birth to four months age suggesting requirement of sex-specific nutrition for preemies to thrive.

Researchers[54] have carried out a retrospective cohort study to determine sex-specific relationship between early nutrition and neurodevelopmental outcome at two years age in children born preterm. Higher fat, energy and enteral feed intakes during first month of life were associated with improved neurodevelopmental outcomes in girls but not boys. Likewise, other researchers[55,56] have assessed association between increased amino acid and energy intakes in preemies during first week of life with neurodevelopment at 24 months age. Early high protein and energy intakes were associated with different improvements in growth and neurodevelopment in boys and girls highlighting sex-specific nutritional needs in preemies. Also, other researchers[57] have explored the impact of feeding type and sex on day-to-day gut microbial colonization patterns in preemies during first 30 days of their life by a prospective longitudinal study. The results depicted that the infant's postnatal age, sex and feeding type have significantly contributed to the active development of gut microbiome in the preterm neonates.

The variation in the breastmilk composition with offspring sex explained the fact of absence of growth differences between the sexes in studies where the enteral nutrition was predominantly mothers' own milk (MOM) and the presence of growth differences between female and male infants who received same intravenous nutrition or infant formula[14,52,58]. Further, better postnatal growth is favoured with MOM which is sex-specific compared to pasteurized donor breast milk (DBM) that is collected by the human milk banks from several mothers regardless of the sex of their offspring[43,52,59].

Conclusion

Preterm formulas and donors' milk does not vary with the infant sex, which might be one reason for better growth and developmental outcomes favoured by mother′s milk. However, preterm babies have higher nutritional requirements compared to term babies, which cannot be met by breast milk alone, and the need for the fortification of human milk with fortifiers that are not sex-specific is manifested. Optimising the early nutrition for the girls and boys born preterm may improve the outcomes of both sexes as they have different and competing nutritional needs. However, further large-scale cohort studies are required to arrive at sex-specific nutritional recommendations for preemies.

Conflict of interest

The author has no conflict of interest to declare.

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