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CONSUMPTION OF UNMODIFIED COW'S MILK AND THE RISK OF IRON DEFICIENCY ANEMIA IN INFANTS AND TODDLERS AND ITS MANAGEMENT

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ABSTRACT: Early introduction of complementary foods (weaning) before 4 to 6 months of age and unmodified cow's milk before age 12 months are associated with several health risks in children. Too early introduction of unmodified cow's milk and milk products to infants and toddlers has adverse effects on their iron stores. Children can develop iron-deficiency anemia from chronic enteric blood loss even when occult blood is not found in stools on random testing. Several mechanisms have been identified that may contribute to iron deficiency anemia in young population group. The most important of these is probably the low iron content of Cow's Milk. Other risks in association to the consumption of unmodified cow's milk in infants include increased renal solute load; increased blood loss from the gastrointestinal tract, chronic constipation, and anal fissures; and an increased risk for subsequent type 1 and type 2 diabetes. Evidence is now also growing to show that iron deficiency anemia is associated with developmental delay, and that the association is causal. Breastfed infants may also be still at particular risk for iron deficiency anemia because breast milk by itself has low iron content. *Conclusion:* iron deficiency anemia is readily preventable, even in a profoundly socially disadvantaged population, by the provision of an iron supplemented formula in place of unmodified cow's milk. Regular provision of medicinal iron or iron-fortified cereal improves the iron status of breastfed infants.

INTRODUCTION: A major controversy over the role of unmodified cow's milk (UCM) in the diet of children first arose in September of 1992.

Basically, Cow's milk (CM) and its products are healthful and exceptionally nutritious foods that play an important role in human diet¹.

That is because CM represents a major source of high nutritional quality protein as well as calcium. Moreover, it has a growth-promoting effects independent of specific compounds².

However, there have been clear indications that *introduction of UCM before age 12 months, has association with several health risks in children*³. This is because the too early introduction of UCM and whole milk products to infants and toddlers has adverse effects primarily on their iron stores and result in *Iron deficiency anemia (IDA)*⁴⁶. The most vulnerable age for iron deficiency anemia in children is six months to age three.

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Basically, Iron deficiency anemia occurs because of a lack of the mineral iron in the body⁷. One of the mechanisms for this is chronic blood loss through the Gastro Intestinal tract (GIT) in stool. However, this problem is also difficult to monitor since Children can develop IDA from chronic enteric blood loss even when occult blood is not found in stools on random testing^{5,8}.

Timing of the introduction of complementary foods (weaning) and UCM is particularly important, given the immaturity of the gastrointestinal, renal, and neurophysiological systems in infants younger than age 4 to 6 months and the health risks associated with early weaning³.

The early introduction of UCM as the major milk source at around 6 months of age is the most common dietary characteristic of infants found to have IDA at 1 year⁹. Since IDA in infants and young children is widespread and has serious consequences, *prevention of Iron deficiency (ID)* should therefore be given high priority^{4,10}.

Intake of iron-supplements in infants and toddlers formula is more effective in maintaining iron nutritional status than using UCM¹¹. This is because, by 4 months of age, neonatal iron stores will be reduced by half due to exogenous iron requirement to maintain hemoglobin concentration during the rapid phase of growth between 4 and 12 months⁹.

The World Health Organization's global public health recommendations on infant feeding state that infant should be exclusively breastfed for the first 6 months of life, and thereafter should receive nutritionally adequate and safe complementary foods to meet their evolving nutritional requirements while breastfeeding continues up to or beyond 2 years of age³.

The associations between IDA and children's health have not only been observed in developing countries, with high prevalence of malnutrition, but also in westernized countries where better socioeconomic and living status is expected¹². The objective of this review is to summarize the current state of knowledge concerning the consumption of UCM by infants and toddlers and to present associated risk of IDA in this population. This review will also discuss on other associated

risks consumption of UCM and also forwards the pharmacotherapeutic approaches to prevent these risks.

The Possible Mechanisms of Iron Deficiency Anemia:

Several mechanisms have been identified that may contribute to iron deficiency anemia in young population group. The most important of these is probably the low iron content of CM, which makes it difficult for infants to obtain the amounts of iron needed for growth⁴. Unlike breast milk, UCM does not provide a balanced diet for children younger than age 12 months, as it contains excessive levels of protein, sodium, potassium, phosphorus, and calcium for human infant requirements, and insufficient levels of iron, vitamin C, and linoleic acid³. Beside these early exposure to cow's milk proteins increases the risk of developing allergy to milk proteins⁶.

The second mechanism of IDA is that the occult intestinal blood loss associated with CM consumption during infancy, a condition that affects about 40% of otherwise healthy infants. Loss of iron in the form of blood diminishes with age and ceases after the age of 1 year. A third mechanism is the inhibition of non-heme iron absorption by calcium and casein, both of which are present in high amounts in CM⁴.

How Strong is the Association between IDA and UCM?

Iron deficiency anaemia is common in infants living in areas where they are given unmodified cow's milk during their first year of life¹³. Different studies were conducted to associate the prevalence of IDA and consumption of UCM. For example in a randomized double blind intervention trial conducted by J Williams W *et al* of 18 months study, it was found that 33% of the UCM group were anaemic and while only 2% of the iron supplemented group anaemic (P<0.001)¹⁴.

In similar study conducted by F Lehmann *et al*, the prevalence of iron-deficiency anaemia among infants who used to be feed on whole cow's milk before 6 months of age was common (odds ratio [OR] 3.56 [95% CI 1.07 to 11.26])¹⁵. In study done by J Maldonado *et al* for 4 months, the toddler formula group showed significantly higher serum ferritin and lower serum transferrin concentrations than the cow's milk group¹¹, [Table 1].

TABLE 1: AN OVERVIEW OF STUDIES ON TODDLERS FORMULA, COW'S MILK AND BREAST MILK

Authors & year	Participants	Study design	Relevant findings in context of UCM	CONCLUSION
J Maldonado Lozano <i>et al</i> , 2007 ¹¹ .	33 healthy infants and young children	Double blind RCT*	After 4 months, the toddler formula group showed significantly higher serum ferritin and lower serum transferrin concentrations than the cow's milk group.	Intake of iron-supplemented toddler formula for 4 months in 1-3 year-olds is more effective in maintaining iron nutritional status than cow's milk.
Asa V Thorisdottir <i>et al</i> , 2012 ¹⁶ .	254 healthy infants	Prospective cohort	After 9 months, the prevalence of iron deficiency was highest in the cow's milk group and lowest in the follow-on formula group.	cow's milk intake in late infancy associated negatively, and follow-on formula positively, with iron status.
Ekhard E Ziegler <i>et al</i> , 2009 ¹⁷ .	152 healthy breastfed infants	Prospective cohort	The regular provision of iron led to improved iron status during and for some months after the intervention.	Regular provision of medicinal iron or iron-fortified cereal improves the iron status of breastfed infants and may prevent ID.
David Hopkins <i>et al</i> , 2007 ¹⁸ .	928 term infants	an observational study	More breast--than formula-fed infants were anaemic at 8 and 12 months. Cows' milk as the main drink was associated with increased anaemia at 12 months and low ferritin at 8 and 12 months.	Both breast and cows' milk feeding were associated with higher levels of anaemia. Satisfactory iron intake from solids in later infancy is more likely if formula intake is <600 ml per day and breast feeds are limited to <6 feeds per day. Cows' milk should be strongly discouraged as a main drink before 12 months.
Ewa A Szymlek-Gay <i>et al</i> , 2009 ¹⁹ .	225 healthy nonanemic 12-20-month-old children	RCT*	By 20 week, in comparison with the control group, serum ferritin and body iron were significantly higher in the fortified milk group (both P < 0.001) and serum ferritin was significantly higher in the red meat group (P = 0.033).	Consumption of iron-fortified milk can increase iron stores in healthy nonanemic toddlers, whereas increased intakes of red meat can prevent their decline.

*Randomized controlled trial

Adequate iron status in infancy is extremely important as ID during the first months of life can negatively affect the child's development and health with persistent effects into adulthood²⁰. Prolonged partial breast-feeding does not seem to be of important for iron status. Fortified food seems to improve iron status in late infancy²¹. In the UK, ID is more common in those children consuming over one liter of CM and in those in whom UCM was introduced before 8 months⁹.

Generally, Infants and toddlers are particularly vulnerable to developing IDA²², which can cause irreversible deficits in neurodevelopment. Children at highest risk include premature and low birth weight infants, those who are fed cow's milk rather than breast milk or formula prior to age one, and those who drink large

amounts of whole cow's milk as toddlers²³, [Table 1].

Comparison of Nutritional Breast Milk & Toddler formula to Cow's Milk: Cow's Milk is low in iron, but the existing evidence suggests that factors other than low iron concentration are at least as important in causing IDA⁹.

Breast-fed babies are less likely to suffer from diarrhea, pneumonia, ear infection, meningitis, and urinary infection. These benefits are mostly due to the nutrition superiority of human milk compared with animal milk such as cow milk [Table 2]. However, breastfed infants may be still at particular risk for iron deficiency because breast milk is low in iron²⁴.

TABLE 2: OVERVIEW OF NUTRITIONAL COMPOSITION OF BREAST MILK, TODDLER FORMULA & COW'S MILK*

Nutritional Composition	Breast milk	Iron-Fortified Infant Formula	Whole Cow's milk
Energy (kcal/oz)	21.6 (balanced)	20.0 (balanced)	20.0 (balanced)
Fat (g/l)	4.2% (balanced)	balanced	Excessive
Carbohydrate (g/l)	72.0 Primarily lactose (balanced)	69.0–72.3 (balanced)	48.0 (Excessive)
Proteins (g/l)	10.5 (balanced) <ul style="list-style-type: none"> ❖ Contains far less protein than cow milk. However, the proteins in human milk are balanced and easier to digest. ❖ Human milk is less allergenic due to the lack of beta-lactoglobulin, an offending protein for babies who are intolerant of cow milk. ❖ Human milk also contains enzymes, growth factors, and immunoglobulins. ❖ In addition, breakdown of the human milk protein casein in the baby's gut produces an opioid-like substance called casomorphin that can influence baby's mood and behavior. 	15.0 (Balanced) <ul style="list-style-type: none"> ❖ May be allergenic ❖ May be intolerant to babies ❖ Contains no enzymes, growth factors, and immunoglobulins. 	34.0 (Excessive) <ul style="list-style-type: none"> ❖ May be allergenic ❖ May be intolerant to babies
Vitamins and minerals	<ul style="list-style-type: none"> ❖ Has all the necessary vitamins and minerals that are required for the baby's growth and development, with the exception of vitamin D. 	Not sufficient <ul style="list-style-type: none"> ❖ Vitamins sufficient ❖ Iron Excessive ❖ Calcium ❖ Phosphorus ❖ Potassium 	Not sufficient <ul style="list-style-type: none"> ❖ Relatively low in iron and copper. Excessive <ul style="list-style-type: none"> ❖ Too much casein, calcium, Potassium and phosphorus for the baby's kidneys to handle.
Calcium (mg/l)	280.0	400.0–510.0	1,291.0
Phosphorus (mg/l)	140.0	300.0–390.0	959.0
Sodium (mg/l)	179.0	161.0–230.0	506.0
Potassium (mg/l)	524.0	547.0–821.0	1,486.0
Chloride (mg/l)	419.0	390.0–497.0	959.0
Iron (mg/l)	0.3**	12.0–12.7	0.4
Variations	Both breast Milk and Cow's milks show variation in nutrients with diet, season, lactation stage, and genetics. For example, the fatty acids and the water-soluble B and C vitamins in human milk vary with the maternal diet.	Cannot replace breast milk but relatively tolerable than cow's milk	Shows significant Variation

*Adapted from references ^{17, 25-27}.

** The iron content of breast milk should not be directly compared with that of cows' milk or infant formula because the iron in breast milk is present in a different form which may be better absorbed from the gastrointestinal tract into the bloodstream.

Secondary complications associated with consumption of UCM: Introduction of CM before age 12 months can lead to increased renal solute load; increased blood loss from the gastrointestinal tract, chronic constipation, and anal fissures; and an increased risk for subsequent type 1 and type 2 diabetes^{3-4, 28}. The high protein intake from CM may also place infants at increased risk of obesity in later childhood⁴.

Systemic abnormalities including blue sclerae, koilonychia, impaired exercise capacity, urinary discoloration, increased lead absorption, and an increased susceptibility to infection can result secondary to IDA⁹.

Evidence is now also growing to show that IDA is associated with developmental delay, and that the association is causal⁹. Two double blind randomised trials showed that there is a clear causal link between developmental delay and IDA⁹. The mechanism of delay may be due to specific effects on the central nervous system because rat model study showed similar effects⁹, because adequate stores are essential for optimum brain function²⁹.

Furthermore, Iron deficiency may have effects on neurologic and intellectual function. A number of reports suggest that iron-deficiency anemia, and even iron deficiency without significant anemia, affects attention span, alertness, and learning of both infants and adolescents⁵.

Research has shown that iron deficient infants are at increased risk for modest declines in psychomotor and mental development³⁰⁻³¹. In clinical trials, infants at high risk for iron deficiency, when fed iron-fortified formulas, had significantly fewer declines in measures of psychomotor skills, when compared to infants who were not on fortified formula³¹. IDA is also associated with an increased morbidity from fever, respiratory tract infections, and diarrhea⁹.

Monoamine oxidase (MAO), an iron-dependent enzyme, has a crucial role in neurochemical reactions in the central nervous system. Iron deficiency states produces decreases in the activities of enzymes such as catalase and cytochromes⁵.

Clinical Manifestations of Iron Deficiency Anemia: Pallor is the most important sign of IDA^{5, 32}. In mild to moderate IDA (hemoglobin levels of 6-10mg/dL), the following clinical manifestations may be common, compensatory mechanisms, including increased levels of 2,3-diphosphoglycerate (2,3-DPG) and a shift of the oxygen dissociation curve, pagophagia, the desire to ingest unusual substances such as ice or dirt, ingestion of lead-containing substances may lead to concomitant plumbism^{5, 32-33}.

In severe anemia, a hemoglobin (Hgb) <8 mg/dL, heart rate, and stroke volume often increase in an attempt to improve oxygen delivery to tissues. These changes in heart rate and stroke volume can result in systolic murmurs, angina pectoris, high output congestive heart failure, pulmonary congestion, ascites, and edema³⁴.

When the hemoglobin level falls below 5mg/dL, the following clinical manifestations are common: Irritability and anorexia are prominent, tachycardia and cardiac dilation occur, and Systolic murmurs are often present^{5, 32}.

Laboratory Investigations: In progressive iron deficiency, a sequence of biochemical and hematologic events occurs. Initially, the tissue iron stores represented by bone marrow hemosiderin disappear⁵. Serum ferritin is the single best laboratory test for the diagnosis of iron deficiency in the absence of inflammatory disease³³. However, normal ranges are age dependent, and decreased levels accompany iron deficiency^{5, 35}.

Then, serum iron level decreases (also age dependent), the iron-binding capacity of the serum (serum transferrin) increases, and the percent saturation (transferrin saturation) falls below normal. When the availability of iron becomes rate limiting for hemoglobin synthesis, free erythrocyte protoporphyrins (FEP) accumulates^{5, 32}.

As the deficiency progresses, the red blood cells (RBCs) become smaller than normal (microcytic anemia) and their hemoglobin content decreases. The morphologic characteristics of RBCs are best quantified by the determination of mean corpuscular hemoglobin (MCH) and mean corpuscular volume (MCV)^{5, 33, 35}.

Developmental changes in MCV require the use of age-related standards for diagnosis of microcytosis. With increasing deficiency, the RBCs become deformed and misshapen and present characteristic microcytosis, hypochromia, poikilocytosis, and increased RBC distribution width (RDW). The reticulocyte percentage may be normal or moderately elevated, but absolute reticulocyte counts indicate an insufficient response to anemia^{5, 32}.

Nucleated RBCs occasionally are seen in the peripheral blood if the anemia is severe. White blood cell counts are normal. Sometimes there is a striking thrombocytosis (600,000–1 million/mm³). Just as in the case of transient erythroblastopenia of childhood, thrombocytosis presumably is caused by increased erythropoietin, which is known to have some structural homology with thrombopoietin^{5, 35}. However, it should also be noted that very severe iron-deficiency anemia occasionally may be associated with thrombocytopenia, and this can confuse the diagnosis with other bone marrow failure disorders^{5, 32}.

The bone marrow is hypercellular, with erythroid hyperplasia. The normoblasts may have scanty, fragmented cytoplasm with poor hemoglobination. Leukocytes and megakaryocytes are normal. There is no stainable iron in marrow reticulum cells. In about one third of the cases, occult blood can be detected in the stools^{5, 32}.

Approaches to prevent the risks: IDA is readily preventable, even in a profoundly socially disadvantaged population, by the provision of an iron supplemented formula in place of unmodified cows' milk⁹. Prevention is the best treatment for iron deficiency³¹. Prevention can be accomplished with appropriate diet and occasionally with the addition of modest supplementation^{5, 31}.

The incidence of IDA among infants in the United States for example has declined to about 3% before the millennium. This decline has been attributed to increased breastfeeding and increased use of iron-fortified infant formulae and cereals³⁶.

Primary Prevention: Sufficient dietary iron must be available from 4 months of age and throughout the weaning period.

Primary prevention can be achieved by giving supplementary iron, by the fortification of foods, and by dietary education changing feeding practice⁹. In term, exclusively breastfed infants, begin iron supplement drops at 4 months of age³¹.

Accordingly, several authorities, including the American Academy of Pediatrics, recommend that UCM should not become part of an infant's diet before age 12 months^{3, 30-31}. Fortification of CM with iron, as practiced in some countries, can protect infants and toddlers against CM's negative effects on iron status⁴. CM-induced intestinal bleeding... in all cases, resolved completely after instituting a cow's milk-free diet³⁷. Iron fortified cereals diet can be started at 6 months child's of age³⁰⁻³¹.

Secondary Prevention:

- **Screen and Treat (Pharmacotherapy):** A test is available (measurement of hemoglobin by haemoglobinometer) which is simple and relatively cheap, and effective treatment is available^{5, 29}. However, screening has been criticized on several counts. First, the accuracy of the results obtained by haemoglobinometer (Hemocue) will vary, and are dependent on good sampling technique.

Second, the use of hemoglobin alone will underestimate the frequency of iron deficiency, and the addition of other, more sensitive parameters is more costly and complex to organize, nor does it provide an instant result. Third, the timing of the test is a problem. Some children found not to be anemic at 12–18 months will become so later, while others found to be anemic may improve spontaneously, or if treated, relapse. There is no clear evidence about the optimal age^{9, 30, 32}.

Choosing the right infant and toddler formula is very important. Formula milks are made from cow's milk which has been modified. They are produced either in dried, powdered or ready-to-feed form. There are different types of infant milk formula³⁸.

The iron content of the milk protein based-infant formulas currently on the market varies from 0.4 mg per 100 mL to 1.2 mg per 100 mL.

The lower iron formulas (0.4 mg per 100 mL) provide sufficient iron for the healthy term infant. Higher iron formulas may be recommended for infants at risk of iron deficiency^{32, 38}. The goals of iron therapy are to normalize the Hgb and Hct concentrations and to replete iron stores³⁴. One of the problems of the pharmacotherapy of IDA especially in developing countries is its association with malnutrition and creating difficulties of IDA management. In malnutrition iron treatment usually needs to be postponed and management of malnutrition given priority, so as to prevent binding of iron to already limited stores of transferrin, which, in turn, may interfere with the protein's host defense mechanisms³⁹. The other problem is the association of iron treatment and the risk of infections. During Iron treatment cautions should be taken if infection is already established. The most important thing to note is, treatment with iron, with subsequent complete resolution of the anemia and the iron deficiency, does not correct all of the behavioral effects³⁰.

Iron supplements are best absorbed on an empty stomach³¹ and absorption is improved if it is ingested with a source of vitamin C, such as orange juice³⁰. No evidence shows that addition of any trace metal, vitamin, or other hematinic substance significantly increases the response to simple ferrous salts⁵.

Intolerance to oral iron is uncommon in young children, although older children and adolescents sometimes have gastrointestinal complaints. The therapeutic dose should be calculated in terms of elemental iron; ferrous sulfate is 20% elemental iron by weight.

A daily total of 4–6 mg/kg of elemental iron in three divided doses provides an optimal amount of iron for the stimulated bone marrow to use^{5, 30}. Total length of treatment is three months, including the one-month therapeutic trial of iron³⁰.

Parenteral iron administration can be considered when there is failure to respond to oral iron therapy due to nonadherence, misdiagnosis (e.g., inflammation), malabsorption (e.g., sprue, radiation enteritis, duodenal or upper small intestine resection), and continuing blood loss equal to or greater than the rate of RBC production³⁴.

A parenteral iron preparation (iron dextran) is an effective form of iron and is usually safe when given in a properly calculated dose, but the response to parenteral iron is no more rapid or complete than that obtained with proper oral administration of iron⁵.

While adequate iron medication is given, the family must be educated about the patient's diet, and the consumption of milk should be limited to a reasonable quantity, preferably 500 mL (1 pint)/24hr or less. This reduction has a dual effect: The amount of iron-rich foods is increased, and blood loss from intolerance to cow's milk proteins is reduced^{5, 40}. When the re-education of child and parent is not successful, parenteral iron medication may be indicated. Iron deficiency can be prevented in high-risk populations by providing iron-fortified formula or cereals during infancy^{5, 41}.

Within 72–96 hr after administration of iron to an anemic child, peripheral reticulocytosis is noted^{5, 33}. The height of this response is inversely proportional to the severity of the anemia. Reticulocytosis is followed by a rise in the hemoglobin level, which may increase as much as 0.5g/dL/24hr. Iron medication should be continued for 8 wk after blood values are normal^{5, 30}.

Blood transfusion may be only indicated when the anemia is very severe or when superimposed infection may interfere with the response and as in case of severe malnutrition. But we should be very cautious that, it is a dangerous attempt to correct very severe anemia with rapid transfusion because of the risk of associated hypervolemia and cardiac dilatation. Packed or sedimented RBCs should be administered 2–3mL/kg slowly in an amount sufficient to raise the hemoglobin to a safe level at which the response to iron therapy can be awaited (furosemide may also be administered as a diuretic)⁵.

CONCLUSIONS AND RECOMMENDATIONS:

Iron deficiency anemia is readily preventable, even in a profoundly socially disadvantaged population, by the provision of an iron supplemented formula in place of unmodified cow's milk. Regular provision of medicinal iron or iron-fortified cereal improves the iron status of breastfed infants. Unmodified cow's milk is not recommended for infants under the age of one year.

Families should discuss with their physicians, clinical pharmacists and Nurses on how to ensure that their child is getting adequate dietary sources of iron to allow for optimum development during their growing years.

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