



## Effectiveness of Starting Weaning at 4 Months Compared to 6 Months Old to Reduce Anemia Among Infants: An Evidence-Based Case Report

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### Abstract

**Introduction** This article aims to compare the effectiveness of introducing complementary foods at four months compared to six months of age to reduce the incidence of iron-deficiency anemia among healthy full-term infants. **Methods** A systematic search was conducted on PubMed, EBSCO, and Cochrane on 28<sup>th</sup> September 2017. The selection of title and abstract was done using the predefined inclusion and exclusion criteria. Twelve original articles were found, however, after full-text assessment, only two studies were considered relevant. These two studies were further critically appraised for their validity, importance, and applicability to measure their usability degree in this study. **Results** These two included studies showed no significant difference of iron-deficiency anemia incidence between the two complementary feeding groups. This can be shown by the absolute risk reduction which varied from -3.1% to 13.4%, relative risk reduction which varied from -22.8% to 18.4%, and number needed to treat which varied from -33 to 8. Both studies found that the ferritin was significantly different between both groups. However, the hemoglobin concentration was significantly higher in the complementary fed group in only one study. **Conclusion** The introduction of complementary feeding at 4 months of age is not effective to reduce the incidence of iron-deficiency anemia.

**Keywords** infant, complementary feeding, iron-deficiency anemia, hemoglobin, ferritin

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## Introduction

Worldwide, anemia affects up to one of every two children younger than five years old.<sup>1</sup> According to World Health Organization (WHO), anemia is defined as a hemoglobin level at two standard deviations below the mean for a normal population of the same gender and age range.<sup>2</sup> In 2002, iron-deficiency anemia (IDA) was deemed to be among the most important contributing factors to the global burden of disease.<sup>3</sup> Anemia causes potentially irreversible negative consequences on cognitive and physical development of children, also physical performance – particularly work productivity in adults – are of major concern.<sup>4</sup>

WHO stated that the best source of nutrition for infants is breast milk. Therefore, WHO recommends infants to be exclusively breastfed (EBF) up to six months of age and be introduced to complementary feeding (CF) thereafter.<sup>5</sup> However, the iron content in breast milk is very low and even full-term infants usually only have sufficient iron stores until four to six months of age. A cohort study in Brazil revealed that 5.7% and 3.4% of healthy full-term infants age four months old presented with iron deficiency and iron deficiency anemia, respectively.<sup>6</sup> For current practice, in settings where IDA is frequent, WHO recommends the provision of iron supplements to infants and young children. Food-based approaches through food fortification and dietary diversification are also encouraged.<sup>1</sup> Therefore, the introduction of CF should start at age four months to accompany the critical window of vulnerability.

Many studies show the effectiveness of complementary feeding in improving iron status among healthy full-term infants.<sup>8</sup> Normal iron status will reduce the occurrence of IDA and prevent its negative effects on infant eventually. This article is made to identify whether the introduction of CF at four months compared to six months is effective as a primary prevention of IDA among healthy full-term infants.

## Case Illustration

A 22 years old woman brought her son (four months old) to the primary health center for a routine vaccination. The doctor said that at the age

of four months old, the iron stores of infants start to deplete. Therefore, he suggested that her son should consume an oral iron supplement daily to prevent him from getting anemia. However, the mother asked whether it can be prevented by starting the complementary food at the age of four months old. Her son was born full term with a good APGAR (appearance, pulse, grimace, activity and respiration) score.

## Clinical Question

Among healthy full-term infants, does the introduction of complementary feeding at four months old reduce the incidence of iron-deficiency anemia compared to its introduction at six months old?

## Methods

### Search Strategy

The search was conducted on *PubMed*<sup>®</sup>, *Cochrane*<sup>®</sup>, and *EBSCO*<sup>®</sup> on 28<sup>th</sup> September 2017 with the Medical Subject Headings (MeSH) and text words listed in Table 1. Search strategy, results, inclusion, and exclusion criteria are shown in a flowchart (Figure 1). Additional searching by checking the reference lists of some relevant articles (snowballing) was also done.

### Critical Appraisal

After the selection, the included articles were appraised using appraisal tools for randomized controlled trial from Centre of Evidence-based Medicine, University of Oxford ([www.cebm.net](http://www.cebm.net)), every text was appraised individually by a reviewer. However, any confusion was discussed and decided based on the agreement of all authors. The critical appraisal results are showed in Table 2.

## Results

This evidence-based case report reviews the effectiveness of the introduction of complementary feeding at four months (CF) compared to six months – or exclusively breastfed for the first six months (EBF) – in reducing the risk of anemia among healthy full-term infants. The primary

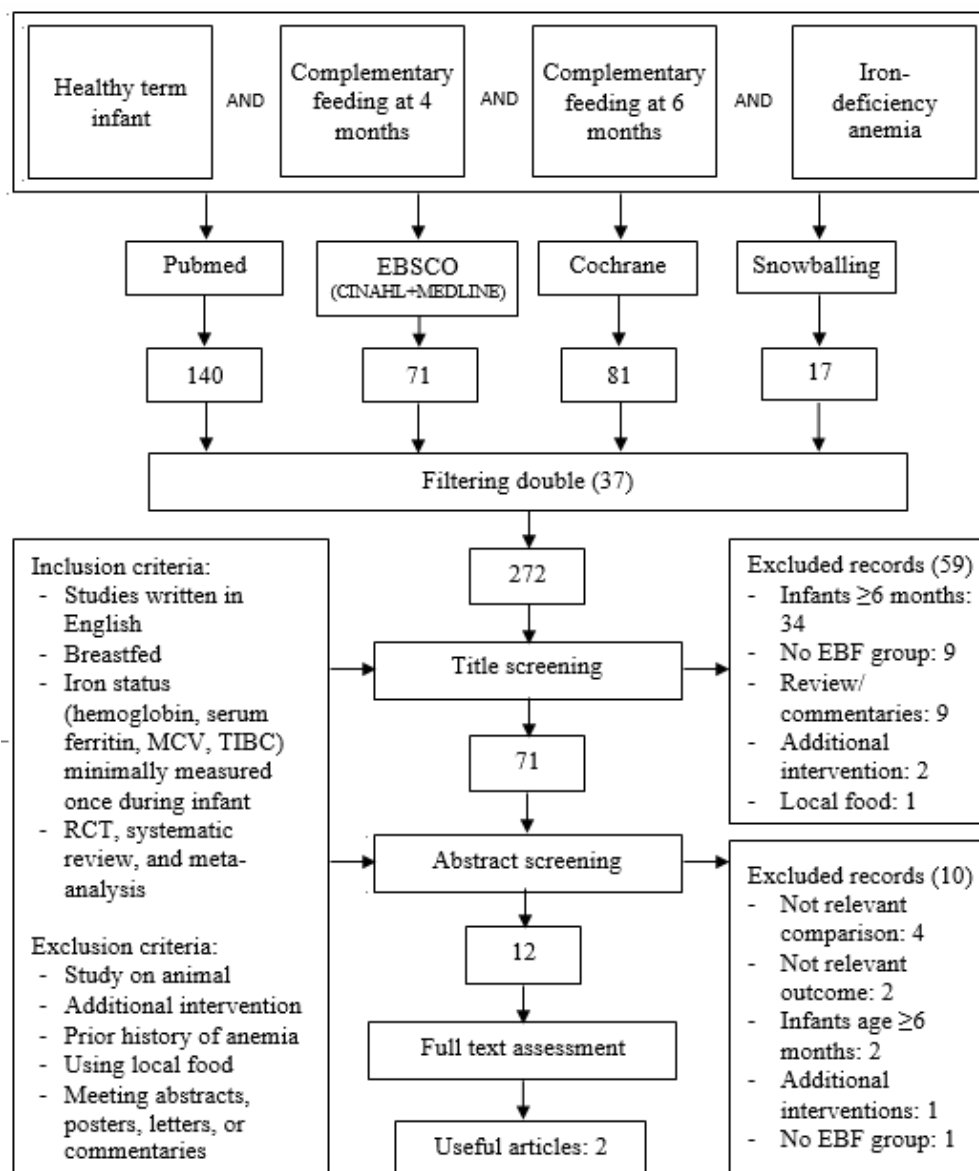


Figure 1. Flowchart of search strategy

Note: MCV: mean corpuscular volume; TIBC: total iron binding capacity; EBF: exclusive breastfeeding, RCT: randomized controlled trial

outcome was the reduction of incidence of IDA among infants.

From the selection and filtration mentioned above, seventy one articles were obtained, out of which only two full-text articles were deemed eligible and relevant to this searching. The validity, importance, and applicability of each paper is appraised by Oxford Randomized Controlled Trials Appraisal Sheet as depicted at in Table 1. The summary of those two RCTs is depicted in Table 2.

The occurrence of IDA and iron deficiency were not significantly different between CF and

EBF group, according to both studies.<sup>9</sup> However, in Dewey et al,<sup>10</sup> the hemoglobin (Hb), hematocrit (Ht), and serum ferritin (SF) values were significantly higher in CF group than in EBF group at six months of age.<sup>10</sup> In Jonsdottir et al,<sup>9</sup> even though SF level was significantly higher in the CF group, but there was no significant difference in hemoglobin concentration.

The anemia status was determined by hemoglobin level measured at six months of age in both studies. The cut off for anemia determination in Dewey et al<sup>10</sup> and Jonsdottir et al<sup>9</sup> was 11.0 g/dL

and 10.5 g/dL, respectively. In Jonsdottir et al,<sup>9</sup> hemoglobin, mean corpuscular volume, serum ferritin values were measured using an automated hematology analyzer. Meanwhile, in Dewey et al,<sup>10</sup> hemoglobin and hematocrit values were also measured using an automated analyzer, while the serum ferritin was analyzed by radioimmunoassay.

## Discussion

There were only two eligible RCT articles obtained, which were Jonsdottir et al.<sup>9</sup> and Dewey et al.<sup>10</sup> Both Jonsdottir et al<sup>9</sup> and Dewey et al<sup>10</sup> showed similar results that introduction of complementary feeding four months is not effective to reduce the risk of IDA compared to its

Table 1. Search strategy in PubMed, EBSCO, and Cochrane (conducted on 28<sup>th</sup> September 2017)

Database	Search Strategy	Hits	Selected articles
PubMed®	((healthy[All Fields] AND ("infant"[MeSH Terms] OR "infant"[All Fields])) OR ("infant"[MeSH Terms] OR "infant"[All Fields]) OR ("term birth"[MeSH Terms] OR ("term"[All Fields] AND "birth"[All Fields]) OR "term birth"[All Fields] OR "term"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields])) AND (("infant nutritional physiological phenomena"[MeSH Terms] OR ("infant"[All Fields] AND "nutritional"[All Fields] AND "physiological"[All Fields] AND "phenomena"[All Fields]) OR "infant nutritional physiological phenomena"[All Fields] OR ("complementary"[All Fields] AND "feeding"[All Fields]) OR "complementary feeding"[All Fields]) OR ("infant nutritional physiological phenomena"[MeSH Terms] OR ("infant"[All Fields] AND "nutritional"[All Fields] AND "physiological"[All Fields] AND "phenomena"[All Fields]) OR "infant nutritional physiological phenomena"[All Fields] OR ("supplementary"[All Fields] AND "feeding"[All Fields]) OR "supplementary feeding"[All Fields]) OR ("weaning"[MeSH Terms] OR "weaning"[All Fields])) AND (("Age"[Journal] OR "age"[All Fields] OR "Age (Omaha)"[Journal] OR "age"[All Fields] OR "Age (Dordr)"[Journal] OR "age"[All Fields] OR "Adv Genet Eng"[Journal] OR "age"[All Fields]) OR (4[All Fields] AND months[All Fields])) AND (("Age"[Journal] OR "age"[All Fields] OR "Age (Omaha)"[Journal] OR "age"[All Fields] OR "Age (Dordr)"[Journal] OR "age"[All Fields] OR "Adv Genet Eng"[Journal] OR "age"[All Fields]) OR (6[All Fields] AND months[All Fields])) AND (("anaemia"[All Fields] OR "anemia"[MeSH Terms] OR "anemia"[All Fields]) OR "haemoglobin"[All Fields] OR "hemoglobins"[MeSH Terms] OR "hemoglobins"[All Fields] OR "hemoglobin"[All Fields]) OR ("ferritins"[MeSH Terms] OR "ferritins"[All Fields] OR "ferritin"[All Fields])) AND ((Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb]) AND "humans"[MeSH Terms])	140	12
Cochrane®	((full-term infant) OR (healthy infant) OR infant) AND ((complementary feeding) OR (supplementary feeding) OR weaning) AND (Age OR 4 months) AND (age OR 6 months) AND (((((((anemia) OR iron status) OR hemoglobin) OR ferritin) OR mean corpuscular volume) OR Total iron-binding capacity) OR transferrin iron-binding capacity)	81	25
EBSCO®	infant AND ((complementary feeding) OR (supplementary feeding)) AND (age OR (4 months)) AND (Age OR (6 months)) AND (anemia OR hemoglobin OR ferritin) NOT (prenatal)	71	19

introduction at six months, in accordance with current global recommendations, because the incidence of IDA between groups was not significantly different.

Dewey et al<sup>10</sup> showed that introducing CF at 4 months reduced the occurrence of anemia by 13.4% using Intention to Treat analysis (ITT). Meanwhile, with the same intervention, in Jonsdottir et al's<sup>9</sup> study, the occurrence of anemia was increased by 3.1% (ITT). No specific type of food given to the infants in Jonsdottir et al<sup>9</sup> study might contribute to this discrepancy because the average energy and iron intake that the infants received was small, only 59% of the mean energy intake (451 kJ/ day) and 15% of the mean iron intake (4.1 mg/ day) taken by infants in Dewey et al's<sup>10</sup> study. Moreover, vitamin C supplementation in Jonsdottir et al's<sup>9</sup> study may also affect the iron absorption, even though there is no association between vitamin C intake and measures of iron status in both group. A randomized cross-over study proved that ascorbic acid or vitamin C enhanced iron absorption by 1.5%.<sup>10</sup> Poor intake of complementary food might cause low intake of both iron and vitamin C among CF infants which lead to poor iron status in spite of complementary food consumption.

In addition to the low intake of CF, early introduction of complementary food was shown to increase infant morbidity and mortality, as a result of reduced ingestion of protective factors present in breast milk, in addition to the early introduction of contaminant from complementary food.<sup>12</sup> Introduction of weaning process may also cause several difficulties such as often refusal to eat followed by vomiting, colic, allergic reactions, and diarrhea.<sup>14</sup>

For current practices, WHO recommends infants to start weaning at six months of age in addition to breastfeeding, starting from 2–3 times a day between age 6–8 months, increasing to 3–4 times daily between 9–11 months, and 1–2 times additional nutritious snacks per day on 12–24 months, as desired. Food should be given in appropriate way, meaning that foods are of appropriate texture for the age of the child and apply the responsive feeding technique following the principles of psycho-social care.<sup>13</sup> WHO also suggests daily supplementation of 10–12.5 mg

elemental iron for 6–23 months old infants who live in high anemia prevalent population. It is given daily for 3 consecutive months in a year.<sup>15</sup>

In general, the nutritional needs of infants less than six months can still be met by breastfeeding. After six months of age, infants start to be more active and tend to eat more to fulfill their daily energy requirement. Moreover, by this time, baby's gastrointestinal system should be already developed and ready to process the solid foods.<sup>12</sup>

In conclusion, the two studies gave same results that the introduction of CF at age four months compared to six months is not an effective way to reduce IDA. Infants should be exclusively breastfed for six months and start weaning thereafter to prevent IDA and fulfill the increasing daily energy requirement. Current WHO recommendation regarding the introduction of complementary food at six months of age is still valid and should be encouraged more.

### **Conflict of Interest**

None of the other authors have conflict of interest. No educational grant is provided to the rest of authors.

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Table 2. Critical appraisal of the 2 studies based on criteria by center of evidence medicine University of Oxford

Article	Year	Number of samples	Validity					Importance					Relevance			
			Randomization	Similarity treatment and control	Blinding	Equal treatment	ITT	Control event rate	Experimental event rate	Relative risk reduction	Absolute risk reduction	Number needed to treat	Domain	Determinant	Measurement of outcome	Level of evidence
Jonsdottir et al. <sup>9</sup>	2012	100	+	+	NA	+	+	0.136 <sup>a</sup>	0.167 <sup>a</sup>	0.228 <sup>a</sup>	-0.031 (-0.088 – 0.150) <sup>a</sup>	-33 <sup>a</sup>	+	+	+	1B
								0.017 <sup>b</sup>	0.016 <sup>b</sup>	0.063 <sup>b</sup>	0.001 (-0.045 – 0.047) <sup>b</sup>	1000 <sup>b</sup>				
Dewey et al. <sup>10</sup>	1998	164	+	+	NA	+	-	0.730 <sup>a</sup>	0.596 <sup>a</sup>	0.184 <sup>a</sup>	0.134 (-0.012 – 0.28) <sup>a</sup>	8 <sup>a</sup>	+	+	+	1B
								0.660 <sup>b</sup>	0.551 <sup>b</sup>	0.165 <sup>b</sup>	0.109 (-0.058 – 0.276) <sup>b</sup>	10 <sup>b</sup>				

Legend: + stated clearly in the article; - not being done. ITT: Intention to Treat analysis

\* Levels of evidence based on the Oxford Centre of Evidence-based Medicine

a Analyzed using Intention to Treat method

b Analyzed using Per Protocol method

Table 3. Results of the two included studies

Author	Study design	Result
Jonsdottir et al. <sup>9</sup>	Masked RCT in seven health care centers in Iceland with 119 samples. Both groups receive vitamin D supplements and the mothers received counseling. EBF means no additional liquid or solid foods other than vitamins and medications. The food types for CF group were not regulated. Hb, mean corpuscular (MCV), red cell distribution width (RDW), SF, and total iron binding capacity (TIBC) value were obtained at age six months ( $\pm$ seven days). The criteria for IDA was: Hb < 105 g/L, MCV < 74 fl, and SF < 12 mg/L.	At six months of age, one infant in EBF group and one infant in CF group had IDA ( $p = 1.00$ ). Infant in CF group had significantly higher SF levels than those in EBF group ( $p = 0.02$ ). Excluding 16 infants who might have any problem affecting the ferritin level, SF level remained significantly higher in CF group ( $67.0 \pm 61.0$ mg/L vs $34.0 \pm 44.5$ mg/L in the EBF group; $P = .003$ ). For Hb, MCV, TIBC, and RDW, no significant differences were found between groups.
Dewey et al. <sup>10</sup>	RCT in two public maternity hospitals in Honduras, Brazil with 164 samples. Lactation guidance was provided to all mothers throughout the study. EBF means no additional liquid (water, milk, or formula) or solids. CF included iron-fortified rice cereal (16-18 weeks), iron-fortified rice cereal with egg yolk (18-26 weeks), non-iron-fortified fruit (banana, papaya, and pineapple, 17-26 week), and vegetables (17-26 weeks). Hb, Hct, and ferritin data were obtained at the age of 26 weeks. The criteria for anemia is Hb < 11.0 g/dL.	At six months of age, there were 49 and 33 anemic infants in CF and EBF group, respectively. CF group had significantly higher iron intake than EBF group ( $4.32-4.76$ mg/day vs $0.16-0.17$ mg/day). Mean Hb and Ht value were also higher in CF group (for Hb cutoff of 10.3 g/dL and 11.0 g/dL). Anemia incidence did not differ significantly between groups, but CF group had fewer infants with low Ht ( $< 0.33$ ) than EBF group ( $21.4\%$ vs $32\%$ , $p = .17$ ). Moreover, CF group had significantly more infants with SF < 12mg/L than EBF group ( $17\%$ vs $7\%$ ; $67.3 \pm 64.5$ vs $48.4 \pm 44.2$ )

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