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# Effectiveness of weekly and daily iron administration for the prevention of iron deficiency anemia in infants

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## ABSTRACT

***Introduction.*** Iron deficiency (ID) is the most prevalent nutritional deficiency and the main cause of anemia in infants. There is consensus on daily iron supplementation as a preventive strategy; and weekly iron supplementation has also been shown to be effective, but evidence in infants is scarce. The objective of this study was to compare the effectiveness of daily versus weekly iron administration for the prevention of ID anemia (IDA) in infants.

***Population and methods.*** Randomized, controlled clinical trial. Infants seen at a public health center, without anemia at 3 months of age, were randomized into 3 groups: daily supplementation (1 mg/kg/day), weekly supplementation (4 mg/kg/week), or no supplementation (control group with exclusive breastfeeding [EB]). Anemia and ID were assessed at 3 and 6 months old. Adherence and adverse events were recorded. Data were analyzed using the R software, version 4.0.3.

***Results.*** A total of 227 infants participated. At 6 months, the group of infants with EB without supplementation (control) had a higher prevalence of ID and IDA than the intervention groups (daily and weekly). ID: 40.5% versus 13.5% and 16.7% ($p$ = 0.002); IDA: 33.3% versus 7.8% and 10% ($p$ < 0.001). There were no differences between the daily and weekly supplementation groups. There were also no differences in the percentage of high adherence to supplementation (50.6% daily versus 57.1% weekly) or adverse events.

***Conclusions.*** No significant differences in effectiveness were observed between daily and weekly administration for the prevention of infant IDA.

***Key words:*** *infant; anemia; iron deficiency; ferrous sulfate; dietary supplements.*

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## INTRODUCTION

Iron deficiency (ID) is the most prevalent nutritional deficiency and the main cause of anemia worldwide. Children under 2 years of age and pregnant women are the most vulnerable groups.[1] The global prevalence of anemia in children younger than 5 years was estimated at 43%.[2] In Latin America, approximately 60% of 6-month-old infants have anemia (71.4% in Bolivia, 63.5% in Honduras, 59.4% in Peru).[3] In Argentina, nutritional anemia is a long-standing problem that continues to be prevalent in young children.[4] According to the National Survey on Nutrition and Health (Encuesta Nacional de Nutrición y Salud, ENNyS), 34.1% of children under 2 years of age and 50.8% of infants aged 6 to 9 months were anemic.[5]

There is an international scientific consensus that universal iron supplementation is a priority strategy when prevalence in a particular population group is high.[6] Locally, until 2017, the Sociedad Argentina de Pediatría (SAP) did not recommend supplementation in exclusively breastfed infants before 6 months of age.[7] As of that year, the recommendation changed to daily preventive supplementation with ferrous sulfate in at-risk groups starting at 2 months of age.[8]

There is evidence that adherence to daily preventive supplementation is low.[9,10] In the 1990s, weekly administration was proposed as an alternative for the prevention of anemia. The rationale for such proposal was that intestinal cells are renewed every 5–6 days and are limited in their ability to absorb iron. In contrast, intermittent iron administration would expose only new epithelial cells to this nutrient and improve absorption efficiency.[11] However, most of these studies were focused on pregnant women and children older than 1 year; the evidence in infants was scant.[12,13]

The objective of this study was to compare the effectiveness of daily and weekly iron administration for 3 months for the prevention of iron deficiency anemia (IDA) in non-anemic infants as of 3 months of age. Our secondary objective was to compare the effectiveness of iron administration (daily and weekly) versus no supplementation at 6 months of age in infants with exclusive breastfeeding (EB).

## POPULATION AND METHODS

This was a randomized, controlled clinical trial. Infants who attended a public health center for their health checkup during the 2017–2019 period participated. Clinically healthy, 3-month-old infants born at term with a birth weight of more than 2500 g and less than 4000 g, with a cord clamping time greater than 30 seconds, normal fetal-neonatal history, whose parents or legal guardians agreed to participate in the study were included. Infants with anemia at study initiation, with chronic conditions or acute infections in the 15 days prior to the study, or receiving antibiotic therapy or iron supplementation were excluded.

At study initiation, infants were divided according to the type of feeding: EB or mixed feeding (breastfeeding and formula) (MF).

Infants with EB were randomly divided into 3 groups: weekly supplementation, daily supplementation, and no intervention (control group). Those receiving MF were divided into 2 groups: weekly supplementation and daily supplementation.

The randomization process was performed by generating a sequence of random numbers with blocks of variable length, stratified by type of feeding.

Due to the characteristics of the intervention, once the envelope was opened, the pediatricians in charge of supplementation were aware of the assigned intervention, unlike the health care providers in charge of performing the laboratory tests, who remained blinded.

### Intervention

All infants, except the control group, received supplementation for 3 months: ferrous sulfate 1 mg/kg/day on a daily basis or 4 mg/kg/week on a weekly basis. The maximum dose was 40 mg/day.[14] An oral solution of ferrous sulfate was used, containing 15 mg elemental iron/0.6 mL (Fer-In-Sol by INVESTI, Argentina).

The dosage and administration of the drug were accompanied by instructions and a dosage recording calendar that was adjusted monthly by the pediatrician.

Before and after the intervention, a blood sample (3 mL) was collected from the infants, and the following hematological variables were measured: hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), using a Coulter counter (Pentra XLR Horiba Medical, France); ferritin, by enzyme immunoassay (Access-Beckman Coulter, Fullerton, USA); and C-reactive protein (CRP), by turbidimetry (BT 3000 Plus Wiener Autoanalyzer). Anemia

was defined as follows: Hb < 9.5 g/dL at 3 months of age and < 11.0 g/dL at 6 months of age, ID: ferritin < 12 ng/mL, and IDA: Hb < 11 g/dL and ferritin < 12 ng/mL.[15] A possible inflammatory state was considered if CRP was ≥ 5 mg/L, in which case ID was established if ferritin was < 30 ng/mL.[16]

At study initiation, the infant's and their family's sociodemographic data were collected. Weight and height were measured on a monthly basis. Z-scores for weight-for-age (W-A), height-for-age (H-A), and weight-for-height (W-H) were developed according to the tables proposed by the World Health Organization.[17]

In each health checkup, adverse events (refusal to take it, constipation, vomiting, diarrhea and/or abdominal pain) and adherence to supplementation were recorded, taking into account the information provided by the adult in charge. Adherence was considered high if the infant complied with more than 80% of the prescription, moderate if it was between 50% and 80%, and low if it was less than 50%.[18]

The sample size was estimated according to the data from the ENNyS, considering a prevalence of anemia of 50.8% in infants aged 6 to 9 months.[5] The expectation for the intervention was a reduction to 30%, with a 0.95 confidence level and a 0.80 power. We estimated a sample size of 174 children (87 for each form of iron administration), which was adjusted to 204, considering a potential 15% dropout rate.

*Statistical analysis*

The R software, version 4.0.3, was used. Qualitative variables were reported as frequency and percentage. Variables with a normal distribution were reported as mean ± deviation, whereas non-parametric data were reported as median (P25, P75), except for ferritin (log-normal distribution), which was reported as geometric mean and 95% confidence interval (CI).

To compare the different variables among groups, Student's test or the Mann-Whitney test and the ANOVA or the Kruskal-Wallis test (more than 2 groups) were used. The $\chi^2$ test or Fisher's test were used to analyze the association among qualitative variables. *A posteriori* pairwise comparisons were done using the *p* value correction based on Holm's method. The effect of the intervention over time was assessed using the two-way mixed-design ANOVA, taking time as the intra-group factor and the intervention, as the inter-group factor. The linear trend estimation was used to analyze protocol adherence. The analysis was performed by intention to treat. In all cases, a value of $p < 0.05$ was considered significant.

## Ethical aspects

The protocol was approved by the hospital's Ethics Committee. The children's parents or legal guardians signed an informed consent. The study is registered in ClinicalTrials.gov. ID: NVT03359447.

## RESULTS

A total of 299 parents or legal guardians agreed to have their children participate in the study; however, 13 missed the lab tests for the initial sample collection. Out of 287 infants who started the study, 11 were excluded because they had anemia at 3 months old (3.9%). The study was completed by 227 infants (90 in the daily supplementation group, 91 in the weekly supplementation group, and 46 in the control group). The dropout rate was 17.7% (49/276) (*Figure 1*).

The characteristics, nutritional and hematological parameters at birth and at 3 months of age are presented in *Table 1*. No significant differences were observed when comparing the groups (*Table 2*).

At 6 months of age, no significant differences were observed in the nutritional status as assessed by anthropometry among the three groups (*Supplementary material*). However, hematological parameters and ferritin levels were significantly higher in the intervention groups compared to the control group (*Table 2*). Changes in hematological variables after 3 months of intervention are described in *Figure 2*.

The infants who received supplementation had a significantly lower prevalence of ID and IDA compared to those in the control group. In relation to anemia, significant differences were only observed between the daily supplementation group and the control group (*Table 3*).

Regarding adherence to supplementation, 50.6% of the infants with the daily intervention and 57.1% with the weekly intervention had a high level of adherence, with no significant differences between them.

*Table 4* shows a comparison of the prevalence of anemia, ID, and IDA according to the level of adherence to supplementation. In the case of daily supplementation, as the level of adherence increases, all 3 prevalence values decrease. In the case of weekly supplementation, this effect was observed for the prevalence of ID and IDA.

**Figure 1. Flow chart**

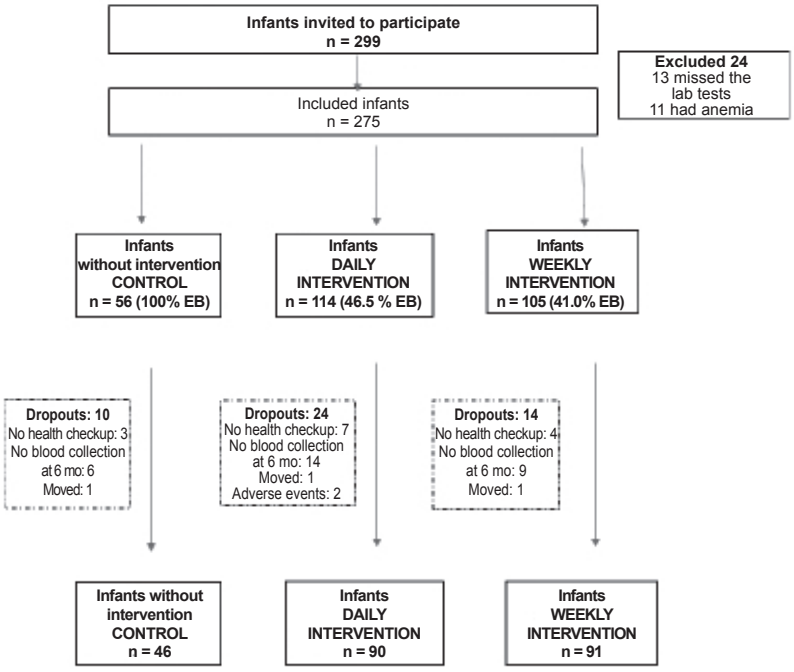


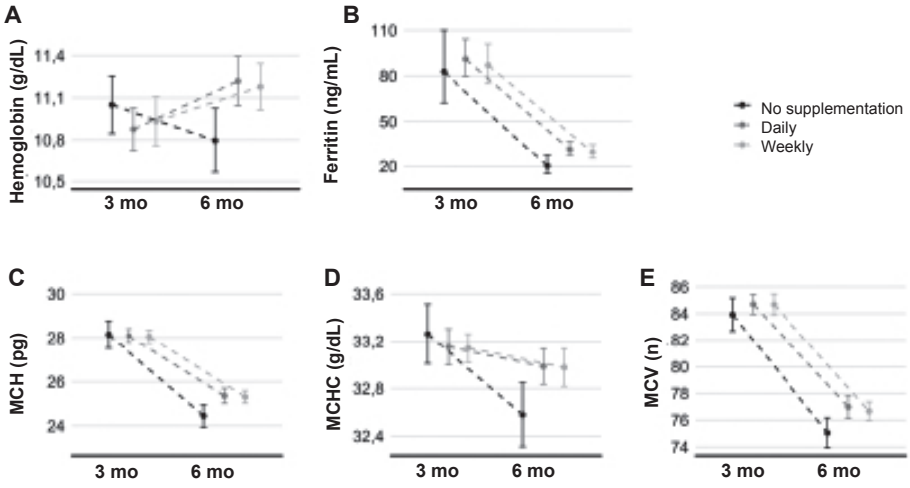

**Table 1. Characteristics and nutritional parameters of study groups at birth and at 3 months old**

| Variables | Control (n = 46) n (%) mean (SD) | Daily intervention (n = 90) n (%), mean (SD) | Weekly intervention (n = 91) n (%) mean (SD) | *p* value |
|---|---|---|---|---|
| | | **Characteristics at birth** | | |
| **Sex (F)** | 22 (47.8%) | 48 (53.3%) | 51 (56.0%) | 0.657 |
| **Gestational age* (weeks)** | 39 (38.3, 40) | 39 (38, 40) | 39 (38, 40) | 0.364 |
| **Birth weight (g)** | 3307.4 (416.4) | 3334.4 (370.9) | 3304.7 (333.5) | 0.845 |
| **Birth length (cm)** | 49.10 (1.92) | 49.67 (2.07) | 49.63 (2.09) | 0.304 |
| | | **Anthropometric variables at 3 months old** | | |
| **Weight (g)** | 6353.5 (623.6) | 6184.9 (828.5) | 6227.6 (850) | 0.506 |
| **Height (cm)** | 60.79 (2.07) | 60.34 (2.45) | 60.27 (2.20) | 0.429 |
| **Z-score for W-A** | 0.06 (0.82) | -0.09 (1.02) | 0.01 (1.00) | 0.668 |
| **Z scores for H-A** | -0.23 (0.94) | -0.32 (1.05) | -0.31 (0.94) | 0.891 |
| **Z-score for W-H** | 0.38 (0.80) | 0.28 (0.96) | 0.38 (1.16) | 0.790 |
| **Z-score for BMI** | 0.27 (0.77) | 0.13 (0.97) | 0.25 (1.13) | 0.645 |
| **Type of feeding (EB)** | 46 (100.0%) | 40 (44.4%) | 36 (39.6%) | 0.548† |
| | | **Sociodemographic characteristics** | | |
| **Maternal age (years)*** | 23 (20, 28) | 24 (20, 28) | 25 (21, 32) | 0.225 |
| **Maternal level of education* (years)** | 11.5 (9, 12) | 12 (8, 12) | 11 (8.5, 12) | 0.722 |
| **UBNs** | 19 (41.3%) | 42 (46.7%) | 42 (46.7%) | 0.816 |

**Median (IQR), † p value corresponding to daily versus weekly intervention.*
*SD: standard deviation; W-A: weight-for-age; H-A: height-for-age; W-H: weight-for-height; BMI: body mass index; EB: exclusive breastfeeding; UBNs: unmet basic needs.*

The frequency of adverse events was low (less than 13%), with no significant differences as to whether supplementation was daily or weekly. Only 2 infants in the daily intervention group had to be discontinued from the study for this reason (*Flow chart*). Vomiting was the most frequent adverse event (12.2% in the daily supplementation group and 11.9% in the weekly supplementation group), followed by diarrhea (2.2% and 3.3% in the daily and weekly supplementation groups, respectively),

**Figure 2. Changes in hematological variables from 3 to 6 months old**




**Ferritin reported as geometric mean (95% CI); the rest of the values are reported as median (95% CI). The analysis was performed using a two-way mixed-design ANOVA: time and intervention group, with interaction.*
*(A) Hemoglobin at 3 and 6 months old for each group, with significant interaction ($p < 0.001$).*
*(B) Ferritin at 3 and 6 months old for each group, with significant interaction ($p = 0.006$); the analysis was performed using log-transformed values.*
*(C) Mean corpuscular hemoglobin at 3 and 6 months old for each group, with significant interaction ($p < 0.001$).*
*(D) Mean corpuscular hemoglobin concentration at 3 and 6 months old for each group, with significant interaction ($p < 0.001$).*
*(E) Mean corpuscular volume at 3 and 6 months old for each group, with significant interaction ($p = 0.133$).*

**Table 2. Anthropometric variables at 3 and 6 months old**

| | | Control mean (SD) | Daily mean (SD) | Weekly mean (SD) | *p* value |
|---|---|---|---|---|---|
| **Hb (g/dL)** | 3 mo | 11.05 (0.71) | 10.88 (0.73) | 10.93 (0.84) | 0.467 |
| | 6 mo | 10.80 (0.79)[a] | 11.22 (0.84)[b] | 11.18 (0.80)[b] | 0.012 |
| **MCH (pg)** | 3 mo | 27.92 (1.71) | 28.10 (1.47) | 28.05 (1.42) | 0.806 |
| | 6 mo | 24.45 (1.78)[a] | 25.36 (1.66)[b] | 25.30 (1.40)[b] | 0.004 |
| **MCHC (g/dL)** | 3 mo | 33.26 (0.87) | 33.15 (0.73) | 33.14 (0.59) | 0.616 |
| | 6 mo | 32.58 (0.93)[a] | 32.99 (0.73)[b] | 32.98 (0.78)[b] | 0.010 |
| **MCV (fl)** | 3 mo | 83.91 (4.32) | 84.69 (3.66) | 84.67 (3.90) | 0.493 |
| | 6 mo | 75.04 (3.89)[a] | 76.98 (4.13)[b] | 76.66 (3.41)[a,b] | 0.017 |
| **Ferritin (ng/mL)*** | 3 mo | 79.89 (61.20, 104.29) | 91.76 (80.16, 105.03) | 87.86 (75.57, 102.13) | 0.585 |
| | 6 mo | 20.24 (15.04, 27.23)[a] | 31.95 (27.47, 37.17)[b] | 29.52 (25.25, 34.51)[b] | 0.007 |

** For the analysis of ferritin, a natural log-transformation was used. Anti-transformed data are reported as geometric mean (95% CI).*
*[a,b] Pairwise comparisons with p value adjusted by Holm's method, different letters indicate $p < 0.05$.*
*Hb: hemoglobin; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume.*

**Table 3. Prevalence of anemia, iron deficiency, and iron-deficiency anemia at 6 months old by type of intervention**

| | Control | Daily intervention | Weekly intervention | *p* value |
|---|---|---|---|---|
| **Anemia** | 28 (60.9%)[a] | 32 (35.6%)[b] | 39 (42.9%)[a,b] | 0.019 |
| **ID*** | 17 (40.5%)[a] | 12 (13.5%)[b] | 15 (16.7%)[b] | 0.002 |
| **IDA**** | 15 (33.3%)[a] | 7 (7.8%)[b] | 9 (10.0%)[b] | < 0.001 |

[a,b] A posteriori *comparisons with p value correction by Holm's method. Different letters indicate a statistically significant difference among groups.*

**For ID, there are 4 missing data for the control group, 5 in the daily intervention group, and 3 in the weekly intervention group.*

***For IDA, there are 2 missing data: 1 for the control group and 1 for the weekly intervention group.*

*ID: iron deficiency; IDA: iron-deficiency anemia.*

**Table 4. Prevalence of anemia, iron deficiency, and iron deficiency anemia according to the level of adherence to supplementation between daily or weekly supplementation compared to controls**

| | Anemia | | ID | | IDA | |
|---|---|---|---|---|---|---|
| **Group** | **n/N (%)** | ***p* value†** | **n/N (%)** | ***p* value†** | **n/N (%)** | ***p* value†** |
| Daily control | 28/46 (60.8%) | < 0.001 | 17/42 (40.5%) | < 0.001 | 15/45 (33.3%) | < 0.001 |
| Moderate/low level of adherence | 19/42 (45.2%) | | 7/41 (17.1%) | | 4/42 (9.5%) | |
| High level of adherence | 10/41 (24.4%) | | 3/41 (7.3%) | | 1/41 (2.4%) | |
| Weekly control | 28/46 (60.8%) | 0.063 | 17/42 (40.5%) | 0.010 | 15/45 (33.3%) | 0.005 |
| Moderate/low level of adherence | 18/37 (48.6%) | | 6/36 (16.7%) | | 4/36 (11.1%) | |
| High level of adherence | 20/48 (41.7%) | | 8/48 (16.7%) | | 5/48 (10.4%) | |

*† Linear trend estimation.*

*ID: iron deficiency; IDA: iron-deficiency anemia.*

abdominal pain (3.3% and 1.1% in the daily and weekly supplementation groups, respectively), and constipation (1.1% in the daily supplementation group).

## DISCUSSION

This is the first study in our region to compare the effectiveness of daily versus weekly preventive iron supplementation in healthy, 3-month-old infants. Our results show that both forms of iron administration were effective in decreasing the prevalence of ID and IDA at 6 months of age.

It is difficult to compare this study to other studies reported in the bibliography because those comparing the effectiveness of both forms of iron supplementation in young infants are scarce and differ in terms of age range, dose, and form of administration. We found only 1 study that started a preventive intervention before 6 months of age in term infants. That study compared daily (1 mg/kg/day) versus weekly (7 mg/kg/week) administration in 4-month-old infants, but who were exclusively breastfed and received the intervention for 3 months and, unlike our results, the authors found that neither intervention was effective in preventing ID and IDA. The authors mentioned the small number of subjects was a limitation.[19]

The other studies reported in the bibliography that used preventive doses of iron were conducted in infants who were 6 months of age or older. This hinders interpretation, since from that age onwards, supplementary feeding is started, which adds a confounding variable that was not taken into account by the authors. In Khademloo's study, infants aged 6 to 24 months received supplementation for 3 months, and it was found that both daily and weekly supplementation increased Hb levels, but only daily supplementation increased ferritin levels.[20] In Engstrom's study, 6-month-old infants were divided into 3 groups –daily supplementation (12 mg/day), weekly supplementation (25 mg/week), and a control group (no supplementation)– and received the intervention for 6 months. Azeredo's study included 103 non-anemic infants aged 6 to 18 months who received the intervention for 6 months: daily supplementation (1 mg/kg/day) and weekly supplementation (25 mg/week). Both studies reported that only daily supplementation

was effective in reducing anemia. In these studies, ferritin was not measured to estimate IDA.[21,22]

In relation to adherence, no statistically significant differences were observed between daily and weekly administration. The same was reported in Regil's meta-analysis, which included 5 studies with 1130 participants and reported that, although there were no statistically significant differences, a greater level of adherence was observed in children who received intermittent iron supplementation.[12]

The presence of adverse events was similar in both interventions, which is consistent with other studies that point out the absence of benefits of one scheme over the other.[19,23]

In this study, the prevalence of ID and IDA at 6 months old in the control group was more than double that in the intervention groups. The prevalence values found exceed those reported by other authors from different regions.[24,26] Supplementation in infants with EB before 6 months of age is controversial. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition does not recommend iron supplementation for breastfed infants in countries where the prevalence of ID is low,[27] whereas the American Academy of Pediatrics recommends supplementation with 1 mg/kg/day as of the fourth month of age until weaning with iron-rich foods.[28] In Argentina, the SAP recommends supplementation for *infants in "risk groups,"* but does not make an explicit reference for those who are exclusively breastfed until 6 months of life.[8] Our findings evidence the clear need for preventive iron supplementation in exclusively breastfed infants in populations with vulnerable socioeconomic conditions.

This randomized clinical trial demonstrated that weekly or daily iron administration starting at 3 months of age improves iron status and decreases the prevalence of ID and IDA in healthy infants at 6 months old. The data suggest that weekly supplementation is an alternative to daily supplementation. However, this study has limitations. Our data are only representative of infants seen at a public health care facility and cannot be extrapolated to the general population; in addition, the assessment of adherence via the information provided by the adult in charge of the infant is an indirect method and may imply an over- or underestimation of adherence. Lastly, although the indicators used to define ID are the most accessible ones, they may not be sufficient.

In view of these findings, and considering the consequences that ID has in infants, we believe it is necessary to strengthen health actions that allow the systematization of preventive measures. In this regard, weekly supplementation may be a viable public health intervention in settings where daily supplementation has failed or has not been implemented.

## CONCLUSIONS

No significant differences in effectiveness were observed between daily and weekly iron administration for the prevention of infant IDA. Infants who received supplementation as of 3 months old had a significantly lower prevalence of ID and IDA than infants who were exclusively breastfed and did not receive the intervention. ■

Supplementary material available at: https://www.sap.org.ar/docs/publicaciones/archivosarg/2023/2815_AO_Varea_Anexo.pdf

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