Adherence to iron supplementation during pregnancy in Tanzania: determinants and hematologic consequences

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ABSTRACT Limited adherence to iron supplementation is thought to be a major reason for the low effectiveness of anemia-prevention programs. In rural Tanzania, women at 21–26 wk of gestation were randomly given either 120 mg of a conventional (Con) iron supplement or 50 mg of a gastric-delivery-system (GDS) iron supplement for 12 wk. Adherence was assessed by using a pill bottle equipped with an electronic counting device. Adherence in the GDS group was 61% compared with 42% for the Con group. In both groups, women experiencing side effects had about one-third lower adherence. Fewer side effects were observed in the GDS group. In a subgroup of women with a low initial hemoglobin concentration (≤120 g/L), the response to the iron supplements suggested that both of the applied doses were unnecessarily high for adequate hematologic response in a population with a marginal hemoglobin concentration. The GDS group appeared to require a dose one-fourth as high as that of the Con group for an equal effect on improving hemoglobin to normal concentrations. Am J Clin Nutr 1996;64:368–74.

KEY WORDS Compliance, side effects, iron supplementation, pregnancy, gastric delivery system, Tanzania

INTRODUCTION Worldwide it is estimated that 2150 million people are anemic (1). Pregnant women are most affected by anemia. The prevalence of anemia among pregnant women is high, particularly in developing countries where an occurrence rate of 55–60% is common (2). The consequences of anemia include preterm delivery, low birth weight, and increases in perinatal mortality (3–5) as well as maternal mortality (6, 7). Although there are multiple causes of anemia, it is generally estimated that approximately one-half of the cases result from iron deficiency (2).

Clinical studies have shown, in both economically developed and underdeveloped countries, that it is possible to prevent a fall in hemoglobin during pregnancy by providing iron supplements to pregnant women (8–13). However, iron supplementation as a public health measure (eg, as part of antenatal care programs) has not been successful in reducing the prevalence of anemia among pregnant women in developing countries (6), partly because of logistics, such as difficulties in the distribution of the supplement to the clinics (14). Another important constraint has been low coverage of the target group by the clinics; many women register late in pregnancy or attend the antenatal clinics only infrequently or not at all (15).

However, even when supplements are available at the clinics and women register early enough to benefit from supplementation, many do not take enough of a supplement to normalize their hemoglobin concentrations. Thus, low compliance or adherence is believed to be a major reason for ineffective supplementation programs (16–18). One reason women are thought to be reluctant to take iron supplements is because of the gastrointestinal side effects that the supplement sometimes produces (19, 20).

Even though adherence is a major problem in iron-supplementation programs, limited research has been done on this topic (18, 21, 22). Most previous supplementation trials have focused on the biological efficacy of different types of supplements or on appropriate doses. To avoid confounding the results with an unknown level of adherence, the subjects have commonly been closely supervised to ensure that the supplements were taken as prescribed. Thus, it has not been possible to learn much from these studies about adherence and its effect on hemoglobin response.

Despite the limited information available on the actual role of possible side effects on adherence, much effort has been invested in developing iron preparations that produce fewer side effects. A new iron supplement called the gastric delivery system (GDS) is particularly promising (23). Like conventional (Con) iron tablets, it contains ferrous sulfate. However, in the GDS, ferrous sulfate is combined with a hydrocolloid matrix that dissolves after ingestion, forming a mixture that floats on the stomach contents and delivers the iron to the upper part of the intestine over an extended period. Iron in this form causes fewer side effects and is two to four times more readily absorbed (11, 23). It is thought that, because of the fewer side effects, the GDS capsule should be better accepted and, there-

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2 Supported by grants from the World Health Organization and the Tanzanian government. Hoffmann-La Roche (Basel) donated the gastric-delivery-system iron supplement.

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Received November 29, 1995.
Accepted for publication May 9, 1996.

fore, should produce better adherence. However, this has not yet been investigated.

The focus of this study was to assess adherence to two different iron-supplementation regimens among pregnant women attending an antenatal clinic. The aim was to test, under conditions similar to what can be expected in an ongoing program, whether the GDS capsule produces fewer side effects than the Con tablet and, further, whether this results in better adherence. To make a fair comparison from a programmatic point of view, dose regimens used were those that in efficacy trials have produced a similar hematologic response. Therefore, the equivalent of 120 mg Fe in Con form was compared with 50 mg Fe in GDS form. Hemoglobin concentrations were also measured to assess the adequacy of the supplement in improving hematologic status.

SUBJECTS AND METHODS

Study population and iron supplements

The study took place in the Ilula village (population of \( \approx 12,000 \) in 1988), Iringa Region, Tanzania (24). The village is \( \approx 500 \) km from Dar es Salaam, along the main road to Zambia. It is a mountainous region on the outskirts of the Rift valley, with an altitude of \( \approx 1300 \) m. The residents are predominantly subsistence farmers. The staple crop is maize, which is commonly eaten with green leaves or beans. The majority of the population belongs to the Wahehe ethnic group. The religious denominations are a mixture of Lutheran, Catholic, and Muslim. From a previous study on maternal mortality in the area (25), anemia was recognized as a problem; 43% of the pregnant women had hemoglobin concentrations < 115 g/L.

Women attending the Ilula Lutheran Health Center’s antenatal service were invited to participate in the study. The women who were eligible to participate were 21–26 wk pregnant as determined by fundus height (25), had a hemoglobin concentration > 80 g/L, and had no apparent illnesses. The women were also examined for parasitic infestations, such as hookworm and malaria, and were treated according to the standard procedure at the clinic if found infected. Oral consent was obtained, and the women were randomly assigned to receive ferrous sulfate, equivalent to 120 mg elemental iron in Con form or 50 mg elemental iron in GDS form. The Con supplement was provided as two white tablets, each with 60 mg elemental iron, and subjects were instructed to take one tablet in the morning and one in the evening. The women who received the GDS supplement were instructed to take one of the red-brown GDS capsules daily together with their evening meal. By dividing the dose of Con into two separate doses, each iron dose was similar to the dose provided by the GDS capsule. Because side effects are dose-dependent, this type of delivery minimized the differences in side effects between the two supplements.

Because of the differences in appearance between the two supplements it was plausible that the women would prefer one of the supplements over the other. To avoid having the women suspect that they purposely had been given a particular supplement type, the women participated in the randomization process by blindly selecting one of two identical white pill bottles presented by the enumerators, who did not know which bottle contained which supplement. One of the pill bottles contained Con and the other GDS. This procedure ensured that the women had not been denied a chance to receive what they might have considered the better choice of supplement. The purpose of the randomization was to be sure that women did not knowingly select themselves into one or the other group.

The research protocol was approved by the Tanzania Food and Nutrition Center’s Research and Ethics Committee and by the University Committee on Human Subjects at Cornell University.

Methods

Adherence was assessed by using a special pill bottle, the medical event monitoring system (MEMS) (APREX Co, Fremont, CA). MEMS consists of an ordinary pill bottle equipped with a cap embedded with a counting device and a small microprocessor. Each time the bottle is opened and closed, the time and date are recorded and this information is stored and later retrieved by a special reader connected to a computer (26). Use of MEMS provided continuous information on adherence over an extended period. Two other methods were used to assess adherence. A count of pills returned at the follow-up visits failed. Even though an excess of pills was distributed, few or no pills were returned by the women. A second method tested for iron in stool samples (27). Because the two regimens contained different amounts of iron, they did not have the same sensitivity to the test, limiting the usefulness of the method in this study.

Because of cost, adherence monitored by MEMS pill bottles was limited to the first part of the supplementation period. The women used the pill bottle from the start of supplementation until the next scheduled visit (=28 d). Bottle-opening events that occurred on the first and last days of use were discarded because they did not provide information on a full day. Furthermore, some of the pill bottles were opened more often on the first day, possibly because the women displayed the supplements to others when reaching home. After the first day, the pill bottles were almost always opened at, or less often than, the prescribed schedule. Adherence reported was for days 2–26 of supplementation.

Adherence was defined as the proportion of supplements prescribed that were taken according to the MEMS. Thus, for full adherence during a 26-d period, 26 opening events for the GDS group and 52 events for the Con group would represent 100% adherence. Adherence for these first 26 d of supplementation was used as an indicator of adherence for the complete supplementation period. To estimate the amount of iron taken during the 12-wk period, adherence was multiplied with the dose of iron that each supplement would provide during this period if the supplement had been taken as directed.

At the 4-wk follow-up visit, the MEMS bottle was replaced with an ordinary pill bottle. Supplements were provided to last to the next scheduled visit at the clinic. Follow-up-visits were made at 4, 8, and 12 wk of supplementation. After 12 wk of follow-up, the women were given enough supplements to last until parturition.

The hemoglobin concentration was assessed at the time of study entry and after 12 wk of supplementation. Blood was drawn by finger prick and the hemoglobin concentration determined by the HemoCue system (HemoCue AB, Helsingborg, Sweden). The HemoCue system uses a disposable microcuvette that contains reagents for hemoglobin assessment.
based on the methemoglobin method, and is comparable with standard methods (28, 29). The hemoglobin concentration was validated with microhematocrit and a good correlation was found ($r = 0.97$).

The prevalence of side effects was assessed by recall at the 12-wk follow-up visit. First, the women were asked whether they had experienced any side effects from the supplement they had been taking. This question was followed by asking all mothers for one symptom at a time, if they had experienced nausea, vomiting, heartburn, diarrhea, or lack of appetite after taking the iron supplement. All 32 possible mutually exclusive combinations of these side effects were examined and a sign test of the difference in prevalence between the Con and GDS groups was performed.

Statistical analysis

The questionnaires were coded and their data entered by using the EPI-INFO statistical package (30). Data were verified by the double-entry procedure. For data analysis, the EPI-INFO, SYSTAT (31), and SPSS-PC (32) statistical packages were used. The statistical methods used included Student’s $t$ tests, analysis of variance (ANOVA), and multivariate-regression analysis with pooled variances. A sign test was used to test the significance of the pattern in prevalence of side effects. Significance was set at $P < 0.05$ for main effects. Interactions were evaluated at $P < 0.20$ unless otherwise specified.

Subsamples

A total of 176 women were initially enrolled in the study; however, MEMS measurements of adherence were obtained for only 121 (69%) subjects (Table 1). About 50% of the loss of information was due to an insufficient number of available MEMS pill bottles and the other 50% included technical problems in retrieving the information stored. The loss of information was similar in the two groups (Table 1).

One hundred thirty-six (77%) of the 176 women completed the 12-wk supplementation period (Table 1). The two major reasons for drop-out were that women delivered their babies before completing the 12 wk of supplementation or that their pregnancies ended with stillbirth or miscarriage. There was a tendency ($P = 0.14$) toward greater loss to follow-up for women receiving the GDS supplement (27%) than for women taking the Con supplement (18%). More women in the GDS category delivered before the end of the trial period, but the difference was not significantly different ($P = 0.18$).

Ninety-seven women completed the 12-wk supplementation period and provided complete measures of adherence. The incremental hemoglobin concentration exceeded $\pm 2$ SD of the mean increment for 10 women. These values occurred in sequential pairs in the laboratory runs and we believe they occurred because identification numbers were mixed. These cases were omitted from the analyses, resulting in complete information for 87 women.

The prevalence of side effects was assessed on the subsample of 136 women who completed the 12 wk of supplementation. Adherence to iron supplementation, the effect of side effects on adherence, as well as hematologic effects were analyzed for the 87 subjects who had completed all measurements.

The prevalence of anemia in the complete study population ($n = 87$) was unexpectedly low, only 8% (hemoglobin concentration $< 110$ g/L). To evaluate women who would be expected to respond to the iron supplement with an increase in hemoglobin concentration, a subsample of subjects with a low initial hemoglobin concentration ($\leq 120$ g/L, $n = 27$) was selected for analysis. The subsample of women with an initial hemoglobin concentration $> 120$ g/L ($n = 60$) was also examined. No hemoglobin response to iron supplementation would be expected in this subsample.

RESULTS

Comparability of subsamples

The characteristics of the women with complete measures were compared with the characteristics of women initially enrolled but without complete measures (Table 2). The sample

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Number of women enrolled and reasons for loss to follow-up in the subsamples and supplementation groups</th>
<th></th>
<th>All</th>
<th>GDS</th>
<th>Con</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>176</td>
<td>92</td>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adherence measures for 26 d</td>
<td>121</td>
<td>61</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects lost to follow-up</td>
<td>55</td>
<td>31</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Technical problems</td>
<td>27</td>
<td>15</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No pill bottle</td>
<td>19</td>
<td>9</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lost or returned pill bottle before day 26</td>
<td>9</td>
<td>7</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron supplementation for 12 wk</td>
<td>136</td>
<td>67</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects lost to follow-up</td>
<td>40</td>
<td>25</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delivered</td>
<td>14</td>
<td>10</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscarriage or stillbirth</td>
<td>13</td>
<td>7</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refused</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moved, sick, referred to regional hospital</td>
<td>10</td>
<td>6</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adherence measures for 26 d and iron supplementation for 12 wk

| Errors | 97 | 48 | 49 |
| Errors in laboratory records | 10 | 6 | 4 |

All measures complete

| Initial hemoglobin $\leq 120$ g/L | 87 | 42 | 45 |

Complete measures

| Hemoglobin concentration | Incomplete measures | Complete measures |
|---|---|---|---|
| GDS | All | $> 120$ g/L | $\leq 120$ g/L |
| Characteristics | ($n = 89$) | ($n = 87$) | ($n = 60$) | ($n = 27$) |
| Age (y) | $24.9 \pm 6.0^1$ | $24.9 \pm 6.0$ | $25.0 \pm 6.2$ | $24.6 \pm 5.6$ |
| Parity | $2.2 \pm 2.2$ | $2.2 \pm 2.2$ | $2.2 \pm 2.2$ | $2.2 \pm 2.1$ |
| Fundus height (cm) | $21.4 \pm 1.5^2$ | $21.4 \pm 1.5$ | $21.5 \pm 1.6$ | $21.3 \pm 1.3$ |
| Malaria (%) | 7 | 13 | 10 | 18 |
| Hookworm (%) | 9 | 7 | 15 |
| Hemoglobin (g/L) | $126 \pm 16$ | $127 \pm 14$ | $133 \pm 10$ | $112 \pm 6^3$ |

1 $\bar{x} \pm$ SD.
2 Significantly different from women with incomplete measures, $P < 0.05$.
3 Significantly different from women with a hemoglobin concentration $> 120$ g/L, $P < 0.05$. |
of 87 women with complete measures and the remaining women were comparable in terms of age, parity, hemoglobin concentration, and parasitic infestation. Fundus height was less in the women with incomplete measures because these women tended to give birth before the 12-wk trial had been completed. Within the sample of women with complete measures, the subsample of 27 women with an initial hemoglobin concentration \( \leq 120 \) g/L was comparable with the subsample of 60 women with a hemoglobin concentration > 120 g/L in terms of age, parity, fundus height, malaria, and hookworm infestation (Table 2).

Side effects and adherence

Side effects were less common in the GDS group than in the Con group (12% compared with 22%, \( P = 0.13 \)). This was corroborated by the observation that women taking GDS capsules had fewer complaints of each of the specific side effects (Figure 1). Ten of the 32 possible combinations of side effects occurred in the study population. In these 10 groups, women in the Con group always reported a higher prevalence than the GDS group (sign test, \( P = 0.001 \)). Of the five groups with more than one symptom, all had nausea, three had vomiting, three had lack of appetite, two had diarrhea, and none had heartburn.

Mean adherence was higher in the GDS group (61%) than in the Con group (42%, \( P < 0.01 \)). For both groups, adherence was about one-third lower in women who experienced side effects (\( P < 0.05 \)). In the GDS group, adherence was 64% for women without side effects and 44% for women with side effects (Figure 2). In the Con group, adherence was 44% for women without side effects and 30% for those with side effects. Thus, the proportional effect associated with side effects was similar for both groups (20/64 = 0.31 and 14/44 = 0.32).

Hematologic response

In women with an initial hemoglobin concentration > 120 g/L there was neither a significant change in hemoglobin concentration during the 12-wk supplementation period nor a difference between the GDS and the Con groups at 12 wk (Table 3). In the subsample of women with an initial hemoglobin concentration \( \leq 120 \) g/L, in both groups combined, there was a significant increase in hemoglobin concentration (from 112 to 123 g/L, \( P < 0.01 \)) as well as a difference in hemoglobin concentration between the two regimens at 12 wk. At 12 wk the GDS group had a significantly higher hemoglobin concentration than the Con group (Table 3). Adherence was also significantly different between groups.

Multivariate-regression analysis modeling final hemoglobin concentration as a function of initial hemoglobin, adherence, supplement type, and the interaction of adherence and supplement type was applied to evaluate the dose-response effect of adherence. In the subsample of women with an initial hemoglobin concentration > 120 g/L there was no significant effect of adherence (Table 4). The significant effect of initial hemoglobin concentration was most likely due to the physiologic effects related to the reversal of hemolysis, which occurred during this period of pregnancy, and to the effect of regression to the mean. The same multivariate-regression model was also used to evaluate the effect of adherence in women with an initial hemoglobin concentration \( \leq 120 \) g/L. In this subsample,

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Effect of supplement type on prevalence of specific side effects: comparisons between the gastric-delivery-system (GDS) and conventional (Con) iron supplements in women who completed 12 wk of iron supplementation.

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Effect of supplement type and side effects on adherence: comparisons between the gastric-delivery-system (GDS) and conventional (Con) iron supplements in women with complete measures.

### Table 3

<table>
<thead>
<tr>
<th>Hemoglobin</th>
<th>GDS</th>
<th>Con</th>
<th>GDS</th>
<th>Con</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 120 g/L</td>
<td>134 ± 9</td>
<td>133 ± 11</td>
<td>111 ± 6</td>
<td>112 ± 7</td>
</tr>
<tr>
<td>( \leq 120 ) g/L</td>
<td>136 ± 10</td>
<td>134 ± 10</td>
<td>125 ± 8</td>
<td>118 ± 8^2</td>
</tr>
<tr>
<td>Change</td>
<td>2 ± 10</td>
<td>1 ± 13</td>
<td>14 ± 10</td>
<td>6 ± 10</td>
</tr>
<tr>
<td>Adherence</td>
<td>58 ± 27</td>
<td>45 ± 33</td>
<td>66 ± 23</td>
<td>34 ± 9^2</td>
</tr>
</tbody>
</table>

^1 \( \pm \) SD. GDS, gastric-delivery-system iron supplement; Con, conventional iron supplement.

^2 Significantly different from GDS: \( ^1 P = 0.03, ^2 P < 0.01 \).
adherence in the GDS group ranged from 27% to 100% adherence with an overall mean hemoglobin concentration of 125 g/L at 12 wk. Over this range the multivariate analysis indicated no significant dose-response effect of adherence (0.05 g hemoglobin/L, \( P = 0.56 \); Table 5). Among women in the Con group, adherence varied between 19% and 48%. In this interval, there was a positive effect of adherence (0.58 g hemoglobin/L, \( P = 0.05 \); Table 5) that was different (\( P = 0.10 \), Table 5) from the effect of adherence in the GDS group. These differential effects of adherence in the GDS and Con groups are illustrated in Figure 3. At all levels of adherence in the GDS group, a mean hemoglobin concentration of 125 g/L was attained, whereas in the Con group a similar hemoglobin concentration was only obtained at the top of this group’s adherence range.

**DISCUSSION**

The aim of this study was to test whether the effectiveness of iron-supplementation programs could be increased by using the GDS supplement instead of the Con supplement. An increased effectiveness was proposed to be produced by a reduction in side effects, which would lead to better adherence. Because of the higher efficacy reported for the GDS supplement, this test involved a comparison of supplementation regimens rather than a test of two types of iron supplements with comparable doses of iron.

**TABLE 4**

<table>
<thead>
<tr>
<th>Covariate</th>
<th>( \beta ) estimate</th>
<th>SEE</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence (%)</td>
<td>-0.04</td>
<td>0.05</td>
<td>0.44</td>
</tr>
<tr>
<td>GDS</td>
<td>-0.02</td>
<td>0.08</td>
<td>0.79</td>
</tr>
<tr>
<td>Supplement type</td>
<td>0.86</td>
<td>5.65</td>
<td>0.88</td>
</tr>
<tr>
<td>Adherence ( \times ) supplement type</td>
<td>0.02</td>
<td>0.09</td>
<td>0.82</td>
</tr>
<tr>
<td>Initial hemoglobin</td>
<td>0.31</td>
<td>0.13</td>
<td>0.02</td>
</tr>
<tr>
<td>Constant</td>
<td>94.63</td>
<td>17.61</td>
<td>0.00</td>
</tr>
</tbody>
</table>

\(^7\) Con, conventional iron supplement (coded 0); GDS, gastric delivery system (coded 1). \( R^2 = 0.11, F = 1.65, P \) value for regression model = 0.17 \((n = 60)\).

**TABLE 5**

<table>
<thead>
<tr>
<th>Covariate</th>
<th>( \beta ) estimate</th>
<th>SEE</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence (%)</td>
<td>0.58</td>
<td>0.28</td>
<td>0.05</td>
</tr>
<tr>
<td>GDS</td>
<td>0.05</td>
<td>0.09</td>
<td>0.56</td>
</tr>
<tr>
<td>Supplement type</td>
<td>23.40</td>
<td>12.10</td>
<td>0.07</td>
</tr>
<tr>
<td>Adherence ( \times ) supplement type</td>
<td>-0.53</td>
<td>0.30</td>
<td>0.10</td>
</tr>
<tr>
<td>Initial hemoglobin</td>
<td>-0.14</td>
<td>0.27</td>
<td>0.61</td>
</tr>
<tr>
<td>Constant</td>
<td>114.31</td>
<td>27.71</td>
<td>0.00</td>
</tr>
</tbody>
</table>

\(^7\) Con, conventional iron supplement (coded 0); GDS, gastric delivery system (coded 1). \( R^2 = 0.33, F = 2.7, P \) value for regression model = 0.06 \((n = 27)\).

**FIGURE 3**. Effect of adherence on hemoglobin concentration at 12 wk: comparisons between the gastric-delivery-system (GDS) and conventional (Con) iron supplements in women with an initial hemoglobin concentration \( \leq 120 \) g/L.

The results show that it is possible to improve adherence by using the GDS iron supplement instead of the Con supplement. Despite efforts that had been made to reduce the side effects in the Con group, the prevalence of side effects was lower in the GDS group. This difference in side effects could in part explain the improved adherence among women in the GDS group. Nevertheless, even in women without important side effects, users of the Con supplement still only reached an adherence level 69% of that of the GDS group’s adherence. Thus, part of the difference between the two supplements does not result from reported side effects.

One reason that adherence was higher in the GDS group than in the Con group may be that the GDS capsule was taken once per day and the Con tablet twice per day. Adherence has been reported to decrease when the dose frequency of iron supplements increases (22). Similar findings were reported from other long-term treatments (33). The higher level of adherence for women using the GDS capsule, regardless of side effects, may also have been due to its appearance. The GDS capsule is red and brown and may be more appealing than the plain white Con tablet. It may also be that some women have had positive experiences with antibiotic treatment in capsule form, and thus think that the iron supplement in capsules is more effective than ordinary tablets. However, appearance could also have the opposite effect. Anecdotal stories from Dar es Salaam indicate that some women believe that antibiotic capsules are dangerous to take during pregnancy. Thus, if they had been offered the GDS capsule, they may not have felt comfortable taking it.

Whatever the relative contribution of side effects, the role of dose frequency and appearance of the supplements on the greater adherence to the GDS supplement, even under the best conditions (ie, no side effects from the GDS capsule) \( \approx 40\% \) of the prescribed dose still was not taken, indicating that important determinants of adherence were unexplained. Therefore, apart from continuing the efforts to reduce side effects, it is important also to consider other possible determinants of adherence and, once these are identified, to conduct cost-effectiveness analysis of the effect of different types of interventions.

The prevalence of anemia was low in the study population, which reduced the number of potential responders for the
sample as a whole. Thus, only a subsample of the women who could respond to the iron supplementation with an increase in hemoglobin concentration was available for assessing the hematologic effect, limiting the statistical power of these analyses. Despite these constraints, there were significant differences in hemoglobin concentrations at 12 wk due to both the GDS and Con supplements. Although a dose-response effect was shown in the Con group at an adherence interval of \( \approx 20-50\% \), it seems that the GDS group had already reached a maximum hemoglobin response at an adherence level of \( \approx 30\% \).

Although no women in the Con group had an adherence level > 50\%, which is comparable with the upper part of the adherence range of 30–100% obtained in the GDS group, the statistical analysis suggests that if adherence was \( \approx 50\% \) for the Con group, it would lead to a hemoglobin response as good as that associated with the GDS capsule. Thus, with these particular dose schedules it seems that the efficacy of the GDS and Con supplements was comparable when adherence to the Con tablet of \( \approx 50\% \) was reached. This may explain why it was not possible to show a difference in hemoglobin response in a previous study in Jamaica in which the hematologic response of daily doses of Con and GDS supplements were compared (11). In that study, the reported adherence was > 90\% and, although both the GDS and Con groups showed a higher hemoglobin concentration than the placebo group after 12 wk of supplementation, there was not a significant difference between them.

To more clearly illustrate the difference in efficacy between ferrous sulfate in the form of the GDS capsule and Con tablet, adherence was converted to the amount of iron ingested during the 12 wk of supplementation and the same multivariate analyses were performed as in Table 5. The results show a dose-response curve for the Con supplement, which provided \( \approx 2000-5000 \text{ mg Fe (0.58 g hemoglobin/L per 100 mg Fe, SEE 0.28, } P = 0.05; \text{ Figure 4). There was no significant dose-response function after the GDS supplement (0.07 g hemoglobin/L per 100 mg Fe, SEE 0.13, } P = 0.56; \text{ Figure 4), indicating that at a dose of } \approx 1200 \text{ mg Fe, the hemoglobin response had already reached a plateau. This lack of response from the GDS supplement was significantly different from the dose response to the Con supplement (} P = 0.13). \text{ Thus, it appears that in this Tanzanian population, a lower rate of adherence was required in the GDS group than in the Con group to achieve a similar or better hemoglobin concentration.}

The implication from a programmatic point of view is that the GDS supplement, at the dose schedule used, is less sensitive to limited adherence than is the Con supplement at a standard dose. If, for example, a cutoff for a maximum hemoglobin response of 30\% of adherence is applied for the GDS supplement, then 90\% of the women in this population had attained an adequate adherence level. A similar calculation at an adherence level of 50\% as a cutoff for the Con supplement would indicate that 60\% of the women using the Con supplement took a sufficient number of tablets.

However, it needs to be stressed that the amount of iron and the level of adherence that are necessary to produce maximum benefits depend on the iron and hematologic status of the target population for iron-supplementation programs. In a population with a higher prevalence of anemia than in our study population, a larger amount of iron and thus better adherence may be required for a hematologic response similar to that in our study population. If further research validates our findings, incomplete adherence to presently used doses is a less serious concern for the GDS than for the Con supplement. Furthermore, the high efficacy of the GDS supplement suggests that it is as effective on a much less frequent dose schedule than is the Con supplement, despite the lower dose of iron in each GDS capsule.

In practical terms, our study shows a much better adherence to commonly used doses of the GDS supplement than to the Con supplement. This better adherence is associated, in part, with fewer side effects from the GDS supplement than from the Con supplement as well as an improved hematologic response. Furthermore, the dosing schedules used were higher than necessary for both the Con and GDS supplements. For the women with a marginal hemoglobin concentration, the dose schedules used were twice as high as necessary for the Con group and three times as high as necessary for the GDS group to obtain the maximum hemoglobin response.

We thank the Ilula Lutheran Health Center for hosting the study.

REFERENCES

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FIGURE 4. Effect of iron dose on hemoglobin concentration at 12 wk: comparison between the gastric-delivery-system (GDS) and conventional (Con) iron supplements in women with an initial hemoglobin concentration ≤ 120 g/L.