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ABSTRACT
Side-effects of iron supplementation lead to poor compliance. A weekly-dose schedule of iron supplementation rather than a daily-dose regimen has been suggested to produce fewer side-effects, thereby achieving a higher compliance. This study compared side-effects of iron supplementation and their impact on compliance among pregnant women in Bangladesh. These women were assigned to receive either weekly doses of 2x60 mg iron (one tablet each Friday morning and evening) or a daily dose of 1x60 mg iron. Fifty antenatal care centres were randomly assigned to prescribe either a weekly- or a daily-supplementation regimen (86 women in each group). Side-effects were assessed by recall after one month of supplementation and used for predicting compliance in the second and third months of supplementation. Compliance was monitored using a pill bottle equipped with an electronic counting device that recorded date and time whenever the pill bottle was opened. Of five gastrointestinal side-effects (heartburn, nausea, vomiting, diarrhoea, or constipation) assessed, vomiting occurred more frequently in the weekly group (21%) than in the daily group (11%, p<0.05). Compliance (ratio between observed and recommended tablet intake) was significantly higher in the weekly-supplementation regimen (93%) than in the daily-supplementation regimen (61%, p<0.05). Overall, gastrointestinal side-effects were not significantly associated with compliance. However, the presence of nausea and/or vomiting reduced compliance in both the regimens—but only among women from the lower socioeconomic group. In conclusion, weekly supplementation of iron in pregnancy had a higher compliance compared to daily supplementation of iron despite a higher frequency of side-effects. The findings support the view that gastrointestinal side-effects generally have a limited influence on compliance, at least in the dose ranges studied. Efforts to further reduce side-effects of iron supplementation may not be a successful strategy for improving compliance and effectiveness of antenatal iron supplementation.

Key words: Iron supplementation; Pregnancy; Compliance; Bangladesh

INTRODUCTION
Gastrointestinal side-effects of iron supplementation cause poor compliance, resulting in ineffective supplementation programmes. It has been suggested that a weekly-supplementation schedule is likely to produce fewer side-effects and consequently increase compliance (1). Great variation in the occurrence of reported side-
effects in iron-supplementation trials even with similar doses of iron has been observed. Appropriate counselling on what to expect in terms of side-effects may modify the perception of side-effects or counteract their negative effect on compliance (2).

This study was nested into an iron-supplementation trial among pregnant women in Bangladesh, where the response in haemoglobin concentration was compared between daily- and weekly-iron supplementation and in this process differentiating between biologically and behaviourally-induced differences, such as compliance (3). This study aimed at comparing side-effects of iron supplementation, compliance, and impact of side-effects on compliance among pregnant women assigned to either weekly doses of 2x60 mg iron or a daily dose of 1x60 mg iron.

MATERIALS AND METHODS

The study was conducted among pregnant women in rural areas of Mymensingh district of northern Bangladesh. This flat agricultural area has a high population density, low literacy, and high rates of malnutrition. The Bangladesh Rural Advancement Committee (BRAC), a large national private development organization, supports the antenatal care activities of the government, including provision of iron supplementation to pregnant women, through its community-based antenatal care centres (ANCCs). Each ANCC covers a population of about 1,000, is managed by a female voluntary health worker, and operates on a monthly schedule.

Fifty ANCCs were randomly assigned to prescribe either one iron supplement daily or two supplements each Friday (one in the morning and one in the afternoon) to participating women. Each supplement contained the equivalent of 60 mg iron and 250 µg folic acid.

Based on formative research, a uniform message was developed and given to pregnant mothers at the start of the supplementation regarding the rationale for iron supplementation (good for mother’s health), occurrence of gastrointestinal side-effects (black stool, constipation, nausea, and heartburn), and how to manage such side-effects (taking supplement with meals). In the catchment area of these ANCCs, 611 pregnant women with fundal height of <22 cm were identified through house-to-house visits and invited to enroll in the antenatal care programme. The first 4-5 women, who were enrolled in the programme and fulfilled the inclusion criteria for the supplementation trial (i.e. fundal height between 14 and 22 cm and no previous iron supplementation during the current pregnancy), were invited to participate in the next scheduled ANCC meeting. The fieldwork was performed during May 1997-January 1998.

Of 209 participating women, 172 (82%) had complete information on side-effects and compliance and were included in this analysis. There was neither a significant difference in background data (socioeconomic status, parity) nor in allocation to randomization groups or occurrence of side-effects between those with and without complete side-effects and compliance information (data not shown).

After one month of supplementation, interviews were conducted at home, including open-ended questions on any morbidity and gastrointestinal symptoms during the past month. Probing regarding heartburn, nausea, vomiting, diarrhoea, and constipation followed this.

The Medication Event Monitor System, MEMS® (Aardex, Switzerland), was used for assessing compliance (or adherence) to the recommended supplementation frequency. It consists of a pill bottle equipped with a cap, which has a counting device and a small microprocessor embedded. Time and date were recorded each time the bottle was opened. A special reader was used for downloading the information from the caps to a computer. Bottle-opening events that occurred on the first and last days of recording were disregarded, as they did not provide information of a full day and included openings at the antenatal centre. Information retrieved from week 5 to week 11 of the supplementation was used in this analysis. Compliance was defined as the ratio between the number of iron tablets taken from week 5 to week 11 and the number of tablets prescribed for that time period.

The following three indicators of socioeconomic status were registered based on interviews at home: formal schooling of woman (never enrolled at school=0, some schooling=1), household landholding (landholding <0.5 acre=0, >=0.5 acre=1), and perceived household economic status (deficit household economy some period last year=0, not deficit=1). A socioeconomic score was constructed using the accumulation of these three indicators, ranging from 0 to 3. The score 0-1 was labelled as ‘lower’ socioeconomic group, and the score 2-3 was labelled as ‘higher’ socioeconomic group. Reproductive history, age, other demographic data, and anthropometry were collected at the beginning of the study. Concentration of haemoglobin (values not
Do side-effects reduce compliance to iron supplementation?

reported here) was measured by HemoCue® at baseline and monthly over the course of the trial. Women with haemoglobin <80 g/L at baseline and with single measurement <75 g/L or two measurements 75-79 g/L during the trial were excluded from the study and provided appropriate additional investigation and treatment.

Informed consents were obtained from the participating women. The study was approved by the Ethical Committee of the Bangladesh Medical Research Council and by the Research Ethics Committee of the Medical Faculty, Umeå University, Sweden.

RESULTS

In the daily- and the weekly-supplementation regimens, 62% of the women reported the occurrence of gastrointestinal side-effects (heartburn, nausea, vomiting, diarrhoea, or constipation) during the first month of supplementation (Table 1). Vomiting was reported more frequently in the weekly-supplementation group, while the occurrence of other suspected side-effects did not differ between the supplementation regimens.

Compliance during week 5 to week 11 of the supplementation was higher in the weekly regimen (mean 93%) than in the daily regimen (mean 61%, p<0.001, Fig.). In fact, the intake of tablets in the weekly regimen ranged beyond 150% of the recommended dose due to the intake of iron supplementation by some women more than once per week. Measured from week 1 to week 11 of the supplementation, the median intake at start of the study, age, or parity did not influence compliance during week 5 to 11 (data not shown).

DISCUSSION

We have shown that compliance to supplementation of iron in pregnancy was higher in a weekly-supplementation regimen than in a daily-supplementation regimen, even though women in the weekly regimen did not have

<table>
<thead>
<tr>
<th>Table 1. Frequency of reported symptoms (possible side-effects) after one month of antenatal iron supplementation in daily (n=86) and weekly (n=86) supplementation groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom</td>
</tr>
<tr>
<td>Heartburn</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Any of the five</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Table 2. Mean compliance (ratio between observed and recommended tablet intake during week 5 to 11 of supplementation, %) to antenatal iron supplementation in daily- and weekly-supplementation groups with and without reported side-effects during week 1 to 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Daily supplements (n=86)</td>
</tr>
<tr>
<td>Weekly supplements (n=86)</td>
</tr>
</tbody>
</table>

Compliance during week 5 to 11 of the supplementation was higher in the weekly regimen (mean 93%) than in the daily regimen (mean 61%, p<0.001, Fig.). In fact, the intake of tablets in the weekly regimen ranged beyond 150% of the recommended dose due to the intake of iron supplementation by some women more than once per week. Measured from week 1 to week 11 of the supplementation, the median intake at start of the study, age, or parity did not influence compliance during week 5 to 11 (data not shown).
less but slightly more gastrointestinal side-effects. Side-effects during the first month of supplementation did not have any major effect on compliance, although nausea and/or vomiting were followed by reduced compliance in the women of a lower socioeconomic stratum.

The design of the study included careful recall of side-effects during the first month of supplementation, followed by as valid measurements of compliance as possible during the subsequent two months of supplementation by an electronic counting device in the pill-bottle cap (4). The women were unaware of the microprocessor in the cap, which had an appearance of an ordinary pill-bottle cap.

The prospectively-collected data make causal interpretation of side-effects and subsequent compliance plausible. The perceptions of side-effects and the level of compliance to a certain supplementation regimen may vary between geographical settings, culture, and socioeconomic group. Some gastrointestinal symptoms associated with the use of iron supplementation are also frequently caused by pregnancy itself, e.g. nausea, vomiting and, especially later in pregnancy, heartburn, and constipation. Despite probing of symptoms due to use of supplements, the total frequency of reported gastrointestinal symptoms may be a mix of pregnancy-induced and iron supplement-induced symptoms. However, this did not confound the analysis, because the focus was on the comparison between supplementation regimens, and not on the assessment of the absolute level of side-effects.

<table>
<thead>
<tr>
<th>Socioeconomic group</th>
<th>Vomiting and/or nausea</th>
<th>Estimated mean (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>No</td>
<td>81.9</td>
<td>73.0-90.9</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>47.9</td>
<td>30.5-65.3</td>
</tr>
<tr>
<td>High</td>
<td>No</td>
<td>80.5</td>
<td>68.3-92.7</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>82.5</td>
<td>55.6-109.3</td>
</tr>
</tbody>
</table>

CI=Confidence interval

Side-effects are dose-dependent (5), and current data suggest that a dose of 30-60 mg per day may have a low or acceptable level of gastrointestinal side-effects (6). The weekly dose of 60 mg iron in Friday morning and evening, used in this study, resulted in a slightly-elevated frequency of reported side-effects compared to a daily dose of 60 mg. This may be due to a larger daily amount of iron ingested. The occurrence of side-effects has not been reported to vary with type of iron compound used (7), but with type of iron preparation. The so-called sustained-release preparations produce fewer side-effects but carry a higher cost (8).

Gastrointestinal side-effects are considered to be the main reason for limited compliance (9,10), but others do not share this view (11). Our findings support the view that gastrointestinal side-effects have a limited influence on compliance, at least in the dose ranges studied.
We did not find any variation in the frequency of side-effects between the socioeconomic groups, but we found a differential influence of side-effects on compliance in the groups. The ability to understand and interpret side-effects may counteract any negative effects on compliance (2). This may hypothetically vary with socioeconomic group and explain our finding.

Actual information on the occurrence of side-effects in iron-supplementation programmes and their impact on compliance is limited. Results of a study in Tanzania showed that women experiencing side-effects reduced the intake of iron supplementation by one-third, but a large part of non-compliance remained unexplained when the impact of side-effects had been taken into account (12).

Emphasis has been given to the reduction of side-effects, for example by alternative iron preparations (12,13) or by intermittent dose regimens, e.g. weekly-dose schedules (1). The seemingly rational thought to reduce side-effects, thereby increasing compliance and effectiveness of supplementation, may not be so rewarding. Efforts to improve compliance should rather be focused on appropriate and acceptable supplementation regimens and motivation of recipients of supplements.

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REFERENCES