

IDPAS # 232

Iron supplementation during pregnancy: is it effective?<sup>1,2</sup>

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During pregnancy, the requirement for absorbed iron is increased to > 4 mg/d, nearly three times what it is in the nonpregnant state (1, 2). This high iron requirement is almost impossible for pregnant women in most developing countries to meet, especially those who already have difficulty meeting their nonpregnant requirement of 1.5 mg absorbed iron/d (3). Routine iron supplementation during pregnancy is a common practice because it is difficult for most women to meet the increased iron requirements of pregnancy from dietary sources alone even when consuming a diet with relatively high iron bioavailability (1).

A comprehensive review and analysis of the published clinical trials of iron supplementation during pregnancy, conducted by the MotherCare Project in 1993, found a total of 24 well-conducted trials (4). These studies were from all major regions of the world. The majority of studies had a sample size of < 100 women in each arm of the study. Virtually all studies demonstrated a positive effect of iron supplementation on maternal iron status, an effect that was proportional to the dose and the duration for which the iron was given. It is important to point out that these studies had adequate supervision and follow-up throughout the trial, which assured good compliance with supplementation. In most cases, noncompliant subjects were excluded from the study analyses. These trials provided evidence of the efficacy of iron supplementation and certainly have played an important role in the adoption of daily iron supplementation during pregnancy as the primary approach for the global effort in the prevention and control of maternal anemia.

It is encouraging that there is clear evidence that iron supplementation is efficacious under careful clinical trials; however, the review by the MotherCare Project raised the concern that there is no good evidence that iron supplementation is effective when implemented as a large-scale program through the primary health care system (4). Proper evaluation of the effectiveness of iron supplementation on a national basis under program conditions is difficult to conduct, and data are not available. However, epidemiologic evidence from countries where iron supplementation is standard practice raises much concern (5, 6). Using the United States as an example of a developed country where universal iron supplementation is practiced, more than 30% of low-income pregnant women are anemic during the third trimester of pregnancy, which indicates significant iron deficiency (7). This is only slightly lower than an estimated 40% prevalence of iron deficiency based on the current iron status of US women of childbearing age and if we assume that no supplement were given during pregnancy (8). In developing countries, there is also evidence that iron supple-

mentation programs have not been effective in reducing maternal anemia in communities. Despite widespread programs of iron supplementation during pregnancy, high rates of maternal anemia are the rule rather than the exception (5). Surveys conducted in India and Indonesia both before and after the introduction of an iron-supplementation program found that the prevalence of maternal anemia persisted at > 80% in India and > 60% in Indonesia (6, 9, 10).

Why is there a discrepancy between the impact of iron supplementation observed in properly conducted clinical trials and that observed in large-scale public health programs? One likely explanation is that small-scale research trials reflect implementation under conditions with sufficient support to ensure that the iron supplement is distributed and consumed. In essence, these are a measure of efficacy, which is the effect under optimal conditions and reflects the maximum achievable impact. However, the effect of the actual program operation of iron supplementation through the primary health care system is a true measurement of effectiveness, which reflects the impact under real world conditions. For most therapeutic regimens, it is expected that the effect based on routine application (effectiveness) will be lower than the effect initially observed during vigorous clinical trials (efficacy). In the case of iron supplementation during pregnancy, the rather large discrepancy between efficacy and effectiveness is disappointing. What might explain this phenomenon? What can we do to improve the program effectiveness of iron supplementation?

There are several key steps for the proper operation of an iron-supplementation program and any constraints in these steps can affect program effectiveness (6). These steps can be summarized as: 1) the supply of iron tablets, which is affected by cost and logistics (availability); 2) the ability of the primary health care system to provide supplementation through service delivery (access to care); 3) the quality of counseling about the need for iron supplementation and its potential benefits and side-effects (provider's behavior); and 4) the willingness of the pregnant women to consume the iron supplement (compliance). A five-country review of the constraints of iron-supplementation programs, conducted by a United Nations Subcommittee on Nutrition in 1991 (Thailand, India, Indonesia, Burma, and the Caribbean), revealed that the greatest obstacles experienced in these countries were the lack of access to maternal

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care and the inadequate supply of iron tablets (6). It is clear that if iron tablets cannot reach the pregnant women, there is no hope for any biological impact or program effectiveness.

Assuming that the problems of iron tablet supply and access to maternal health service can be overcome, there is also strong evidence that factors related to the behavior of the care provider and the pregnant woman can affect the outcome (11). In an evaluation conducted by the MotherCare Project in Indonesia to investigate factors affecting the usage of iron tablets by pregnant women, several factors were found to affect compliance (12). These factors included the lack of knowledge and concern about maternal anemia by both pregnant women and health care providers, and resistance to the use of iron tablets because of undesirable characteristics of the tablets and because of the side effects experienced by women. Clinical trials that aimed to overcome these barriers through communication strategies found a significant improvement in compliance with iron supplementation (10, 13). It appears that proper communication on the importance of iron supplementation and on the potential side effects is a necessary component of an effective iron-supplementation program. The real challenge is incorporating this communication component into large-scale national programs.

Perhaps the reason that all the small-scale trials of iron supplementation, regardless of dosage, dosing schedule, or the nature of the iron preparation, were able to document a positive effect on maternal iron status is the fact that, in a study setting, all the necessary conditions for an effective iron-supplementation program are met: availability of iron tablets, full access to service delivery, and adequate communication and attention provided by the research team. However, in the routine practice setting, many of the necessary conditions for program effectiveness are absent.

One approach to increasing compliance, and therefore increasing program effectiveness, is to reduce the side effects of iron supplementation. It is well known that gastrointestinal side effects, including metallic taste, epigastric discomfort, and constipation are dose-dependent phenomena (14). Using a lower dose of iron to enhance longer-term compliance has been proposed (15), and in part, is supported by the finding that a daily dose of 30–60 mg Fe is associated with minimal gastrointestinal side effects, and that the incremental gain in hematologic improvement with increasing iron dose is small at higher doses (16). A lower dose of iron also permits the possibility of a less-frequent dosing schedule—once instead of twice or three times daily. It is well established that lower dosing frequency improves compliance with medication.

Another approach to reducing side effects is the use of special preparations, such as ferrous sulfate combined with a gastric delivery system (GDS) that can prolong the gastric retention time of iron has been shown to achieve greater absorption than a comparable dose without GDS (17). There are also several slow-release iron preparations that may reduce upper-gastrointestinal side effects. However, lack of availability or the relatively high cost of these special preparations makes them less feasible for use as alternative approaches in large-scale supplementation programs.

Recently, there is a flurry of activity supported by the United Nations University to test the option of weekly iron supplementation in place of daily supplementation (18). This concept is supported by the observation from animal studies that daily

iron administration reduces the gastrointestinal iron absorption capacity for several days due to mucosal blockage from the recent dose of iron, and that less frequent administration can result in greater absorption from the dose given (19). Currently there are few published clinical trials comparing the effect on iron status between daily and less frequent supplementation schedules (18–22). In a study of nonpregnant nonanemic women, better gastrointestinal absorption with a dosing schedule of less than once daily was not confirmed (20). The study by Ridwan et al (21) in this issue of the Journal, shows that a weekly dose of 120 mg ferrous sulfate and a daily dose of 60 mg achieved comparable effects on hemoglobin and serum ferritin for pregnant women. This is the first major study on this issue in pregnant women. Given the frustration with the lack of effectiveness of the current daily iron supplementation in reducing maternal anemia during pregnancy, it is very tempting to switch to a weekly approach, as proposed by the authors of this study and others (18, 22).

From a programmatic point of view, if the weekly approach can achieve the same effect as the daily approach, the implication for cost savings on the purchase of iron tablets is great, because the weekly program requires only about one-third as many tablets as the daily program. However, one important issue that needs to be considered before widespread implementation of the weekly approach is the same concern we now face with the daily approach: does the demonstrated efficacy from supplementation trials translate to adequate effectiveness in supplementation programs? The reason for caution is that the weekly supplementation program may very well have the same operational pitfalls in community settings (6, 11). We must consider the risk of substituting one approach with limited effectiveness with a second approach that has no assurance of improved effectiveness.

Can an iron-supplementation program based on weekly supplementation address the major limiting factors that have rendered the daily program ineffective? Let us consider the four necessary conditions required for an effective iron-supplementation program in the context of a weekly approach. In terms of availability, the weekly approach has the clear advantage of lower cost and therefore should be easier to sustain. However, the logistics of a multiple-step distribution system is still at risk for breakdown, which is one of the major limitations of the existing iron-supplementation programs. In terms of access for pregnant women to maternal health services and of adequate attention on the care provider's part in communicating information concerning the need for iron and the potential side effects related to the iron tablets, both the daily and weekly approaches will be subject to the same degree of constraint.

In terms of the fourth necessary condition—compliance—the weekly approach may have the advantage of improved compliance because it has less frequent dosing. Even though it is clear with most medications that a less frequent dosing schedule within the same day results in greater compliance, there is little information to compare the compliance of a daily versus weekly medication schedule. Thus far, limited evidence from the evaluation of a weekly malaria prophylaxis program with chloroquine in Malawi, which found a compliance of 36% during a 4-wk period, is not encouraging (23). There is no assurance that in a nonsupervised setting not under research conditions, the long-term compliance with a weekly regimen will be better than that with a daily regimen. In fact, there

some risk that the larger weekly dose of 120 mg Fe may have greater side effects than the smaller daily dose of 60 mg, as was used in the current study, and that this may adversely affect compliance (14, 24). Overall, based on the limited information available, the weekly approach may potentially improve some of the necessary conditions for an effective supplementation program, but some of the major limitations of the current daily approach are still not addressed: a functional iron-supplementation program also needs the assurance of adequate access to maternal health care, and proper communication and education about the iron supplementation regardless of whether it is based on a daily or a weekly dosing schedule.

The evidence of efficacy based on smaller scale studies on weekly iron supplementation does suggest one potential programmatic format: the administration of a weekly iron dose under supervision. For example, administration in schools by teachers or at work sites by nurses. It is also possible that in some settings, where there is good coverage by community health workers or birth attendants, weekly iron doses can be administered to pregnant women by such health workers. Weekly supplementation may very well make supervised administration feasible in some settings.

Given the evidence thus far for iron self-administered on a weekly basis, it would be prudent to wait for the evaluation of large-scale demonstration projects or operational research that can define the true effectiveness under program conditions before it is widely implemented. The issue at hand is not whether a weekly iron dose is beneficial or not, but whether pregnant women are able to receive and take the iron tablets as prescribed. Perhaps the frustration related to the ineffectiveness of the current daily iron-supplementation programs that led to the development of the weekly approach can also be directed toward the development of other alternative approaches beyond supplementation during pregnancy. It is likely that any and all strategies to improve iron nutrition are needed to achieve meaningful effects (3). It is not a matter of selecting one strategy over another. The experience of sugar fortification with iron-EDTA in Guatemala reported by Viteri et al (25) is encouraging evidence to consider for large-scale implementation in suitable developing countries.

In the case of iron supplementation, it appears that the challenge in achieving program effectiveness requires the improvement of all the key components of the program operation, ranging from iron tablet supply and distribution to the knowledge and behavior of care providers and pregnant women. The adjustment of one component without addressing the limitation of other components may not be sufficient to obtain adequate program effectiveness. ■

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*See pages 884-90 for the corresponding article.*

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