EDITORIAL

# Anemic Data for Preventive Screening and Supplementation to Address Iron Deficiency Anemia in Pregnancy

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**The US Preventive Services Task Force** (USPSTF) recently released a Recommendation Statement examining the data to support screening for iron deficiency anemia in pregnancy and finding them lacking.[1] It also found insufficient evidence to make a clear recommendation for or against preventive iron supplementation in pregnancy,[2,3] which has been a routine practice for decades, with up to 77% to 89% of patients reporting supplement use.[4] As highlighted previously by the USPSTF and others, there is an urgent need for studies and clinical trials to support evidence-based medicine in the obstetric population, and this can only be accomplished by ceasing paternalistic approaches that have led to the exclusion of pregnant patients in research.[5-11] All of this remains true, and there is still so very far to go.

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In the updated USPSTF review, an additional 5 randomized clinical trials (RCTs) were included with the 12 RCTs carried forward from the 2015 review. The USPSTF determined that the availability of good- and fair-quality RCTs was sufficient; observational studies were included only for the association questions. However, it is important to acknowledge that while RCTs provide rigor and purity for evaluating medical interventions, they may not always be the best study design for all clinical questions. Indeed, the many traditional RCT designs and implementation approaches limit real-world applicability, discourage involvement and thus applicability to marginalized and underserved populations, and decrease the likelihood that the effect on rare outcomes such as severe maternal morbidity will be detected. Large, population-based studies provide additional useful evidence when examining uncommon outcomes with a high impact such as severe maternal morbidity and mortality, transfusion, and death. An RCT examining such rare outcomes may be cost-prohibitive and thus an ineffective method to approach several aspects of the question at hand.

Importantly, it is vital to ensure that the outcomes assessed in studies are physiologically plausible. Some of the outcomes reviewed by the USPSTF, such as gestational diabetes, hypertensive disorders, and cesarean delivery, have been associated with iron deficiency anemia in observational studies but not in RCTs. It is more likely that the association in observational studies was due to confounders such as nutritional status, body mass index, healthy lifestyle choices, socioeconomic status, and systemic racism rather than iron deficiency anemia. Future research must look at outcomes that are both biologically plausible and important to patients. While there is no readily apparent physiologic reason that iron deficiency anemia would cause postpartum hemorrhage, antepartum iron deficiency anemia is associated with increased risk of transfusion at or after delivery, which is often guided by symptoms and hematologic indices.[12-16] Decreasing the risk of postpartum transfusion via routine iron supplementation is an outcome of interest for future studies, because routine use of iron supplements in the pregnant population has been associated with decreased need for nonemergent transfusion in observational studies.[17]

The USPSTF acknowledges that routine supplementation with iron in pregnancy carries minimal risk of harm and improves hematologic indices. However, no definitive evidence of the benefit of improved hematologic indices at delivery exists in the form of RCTs and likely never will. While recovery of red blood cell volume in the postpartum period is usually swift, in a small number of cases transfusion and/or intravenous administration of iron are required, and these interventions are not without cost and risks.[18-22] In assessing the role of prevention through routine iron supplementation, there is a role for comparisons, including cost analyses and evaluations of patient experience, assessing whether the improved hematologic indices associated with routine iron supplementation prevents more costly interventions such as intravenous iron therapy and transfusion at delivery.

No definitive benefit to routine screening for iron deficiency anemia in pregnancy was noted by the USPSTF, although the evaluation of hemoglobin and/or hematocrit at the start of pregnancy, in the third trimester, and at delivery are widespread practice, supported by the American College of Obstetricians and Gynecologists.[23] Unfortunately, the best definition of anemia in pregnancy is difficult to discern. Thresholds are defined by population percentiles, rather than risk of adverse outcomes, and median maternal hemoglobin levels vary between trimesters as blood volume expands, with plasma volume outpacing red blood cell production by the third trimester.[24,25] This is reflected in the wide variation in rate of iron deficiency anemia found by the USPSTF across gestation for different populations, ranging from 1.8% to 30%. The field of obstetrics requires an evidence-based definition of iron deficiency anemia in pregnancy that is based on outcomes, rather than defining a disease based on population nomograms.

The USPSTF attempted to examine the benefits associated with screening for iron deficiency without associated anemia in pregnancy, which is thought to be a precursor to iron deficiency anemia, but evidence was insufficient to recommend for or against the practice. There is limited evidence of the benefit of identifying and treating iron deficiency ane-

mia, so it is not surprising that the same holds true for iron deficiency alone. Establishing the benefit of screening for iron deficiency without anemia in pregnancy would prove exceptionally difficult to investigate via RCT, given the large sample size required to identify pregnant patients who could potentially receive benefit from this early intervention.

Regardless of the definition selected, the incidence of iron deficiency anemia is much more common in pregnancy when compared with nonpregnant populations. It has been established that treatment of iron deficiency anemia outside of pregnancy benefits the treated patient, which provides evidence of value in screening and treating generally, without regard to the specifics of the obstetric outcomes in pregnancy. The lack of data in pregnant populations should not lead clinicians to withhold this practice that is routine in all populations, as this would be yet another form of exclusion for this population. Perhaps now more than ever, it is important to remember that benefit to the pregnant patient is reason enough for an intervention; benefit to the fetus or neonate is not required to make an intervention worthwhile.

There remain significant knowledge gaps in the understanding of the utility of screening for iron deficiency anemia and routine supplementation with iron in pregnancy, especially in the form of rigorous RCTs. However, there are even larger, and perhaps more important, knowledge gaps in relation to health-related social needs which may influence the development of iron deficiency anemia. The need for rigorous RCTs that are resource-intensive to conduct to answer basic questions about the benign clinical practices of screening and supplementation must be balanced with the need to better understand what factors place patients at risk for iron deficiency anemia in pregnancy. If the lens to consider the patient and their environment in entirety is widened, the greatest rewards may be found.

## ARTICLE INFORMATION

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