



### Iron Deficiency of Pregnancy: Time for a New Paradigm

- Michael Auerbach MD, FACP
- Private Practice, Baltimore, Maryland
- Clinical Professor of Medicine
- Georgetown University School of Medicine
- Washington, DC



### Use of Oral Iron

- Sydenham first used iron filings in cold wine to treat “green sickness” (described by Lange) in 1687
- Blaud renamed “chlorosis” in 1832, First to use ferrous sulfate
- By time of American Civil War iron was used to treat war wounds
- Today iron deficiency is the most common micronutrient deficiency on the planet estimated to affect >35% of world’s population, >50% of gravidas
- 100 times more prevalent than cancer
- >300 years later, the often ineffective, usually poorly tolerated oral iron continues to be frontline



## Pretreatment Tongue





## Healed Tongue





# Oral or Intravenous Iron

- Indications for oral iron
  - Mild, uncomplicated iron deficiency without active bleeding
  - First trimester of pregnancy
  - Second trimester of pregnancy if Hb > 10.0 g/dL
- Indications for IV iron
  - Intolerance of, or unresponsiveness to oral iron
  - Second trimester of pregnancy if Hb < 10.0 g/dL
  - Third trimester of pregnancy
  - After bariatric surgery
  - Abnormal uterine bleeding
  - Inflammatory bowel disease
  - Angiodysplasia (HHT)
  - Iron restricted erythropoiesis
  - Co-morbid “inflammatory” condition



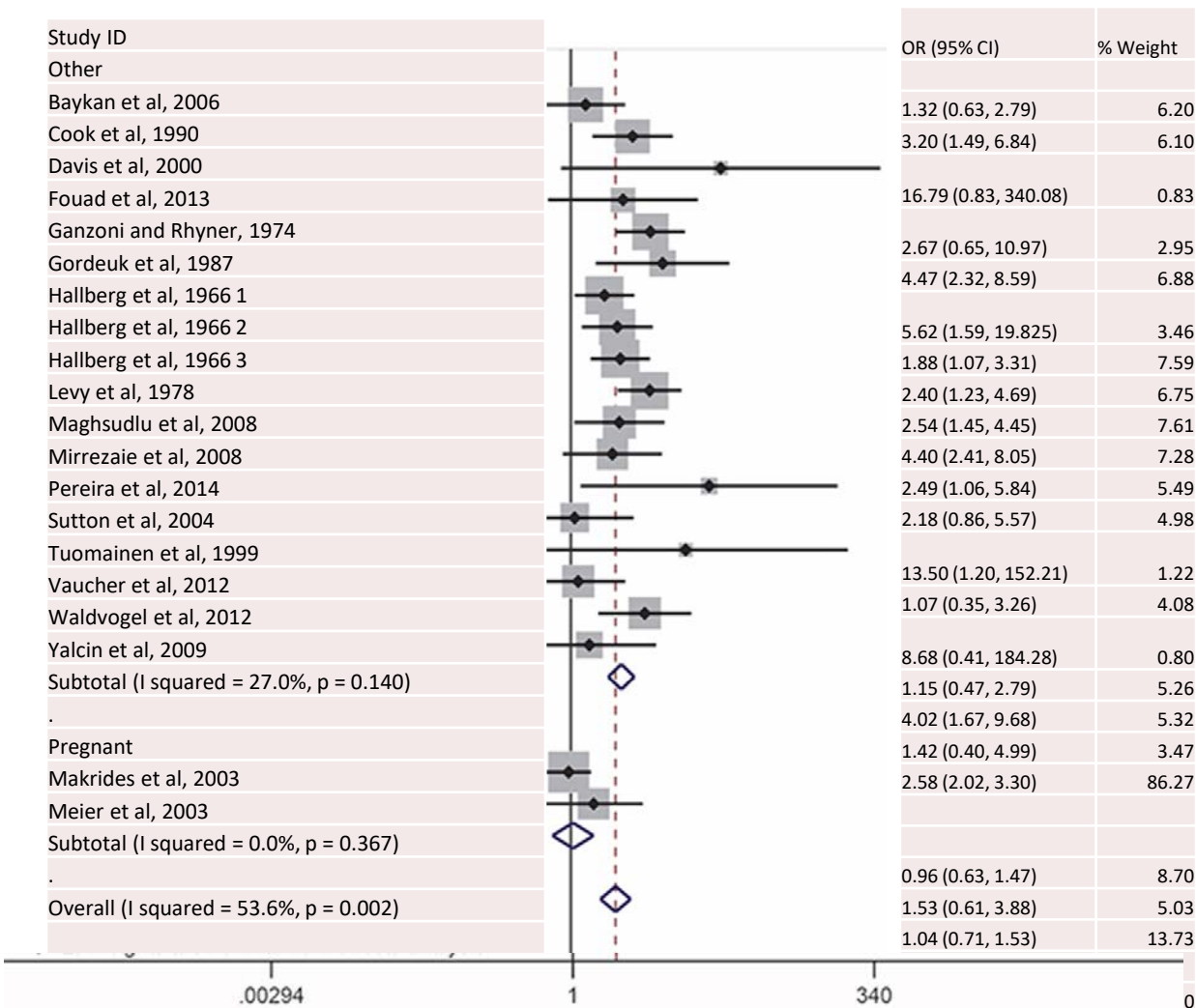
# Adverse Events with Iron Supplementation

## ORAL (70%)

- Constipation (less often diarrhea)
- Metallic taste
- Nausea
- Gastric Cramping
- Thick, green, tenacious stool

## INTRAVENOUS

- Infusion Reactions (1-3%)
  - Pressure in chest
  - Arthralgia or myalgia
  - Headache
  - Flushing
- Severe Hypersensitivity (<1:250,000)
  - Hives or urticaria
  - Hypotension
  - Wheezing
  - Stridor
  - Periorbital edema



Forest plot for the effect of daily ferrous sulfate supplementation on the incidence of gastrointestinal side-effects in placebo-controlled RCTs.

With Permission: Tolkien Z, Stecher L, Mander AP, Pereira DI, Powell JJ. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. PLoS One. 2015 Feb 20;10(2):e0117383

# IV Iron Safety

- A total of 103 trials performed between 1965 and 2013 were included.
- Pooled together, 10,391 patients were treated with IV iron and were compared to:
  - 4,044 patients treated with oral iron
  - 1,329 with no iron
  - 3,335 with placebo
  - 155 with IM iron



## IV Iron Safety

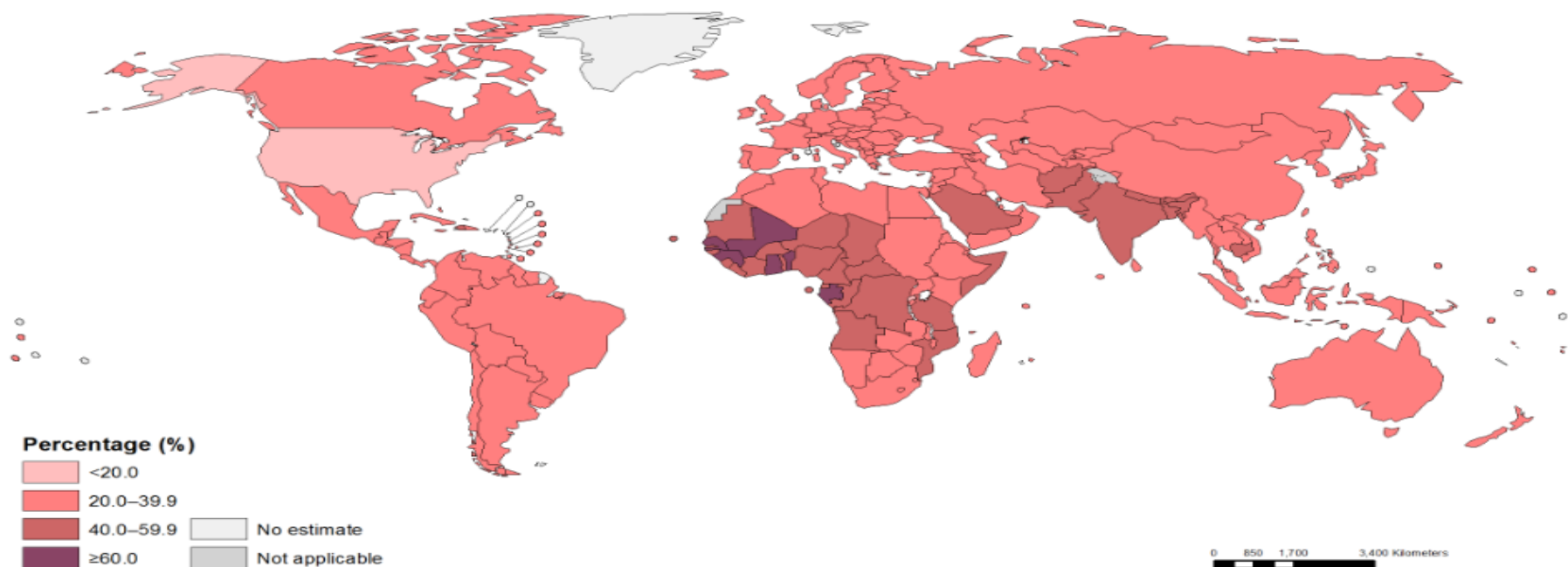
- Overall, there was no increase in the risk of severe adverse events (SAEs) with IV iron compared to control, RR 1.04 (95% CI 0.93-1.17, 97 trials,  $I^2=9\%$ )
- No difference in either efficacy or toxicity among the formulations was observed



### Effects of Intrapartum Anemia

- Children of Iron Deficient Mothers have increased risk of being born iron deficient
- We do not screen our newborns
- Non-anemic Iron deficient in mothers is less severe but associated with increased morbidity in newborns
- Iron deficiency in Mothers is associated with increased risk of preterm labor, low birth weight and child and maternal mortality
- Current ACOG and USPSTF Guidelines ignore these data

# Global estimates of the prevalence of anaemia in pregnant women aged 15–49 years, 2011



Source: WHO. The global anaemia prevalence in 2011. Geneva: World Health Organization; 2015.



## Guidelines Differ

- USPSTF: “There is insufficient evidence that routine screening and supplementation for iron deficiency anemia improves maternal or infant clinical health outcomes”
- 2008 ACOG Practice Bulletin: “Intravenous iron is recommended in the “rare patient” who cannot tolerate or will not take modest doses of oral iron” with the caveat that patients with severe malabsorption may benefit from parenteral iron
- 2019 UK guidelines: “Parenteral iron should be considered from the 2<sup>nd</sup> trimester onwards and during the postpartum period for women with confirmed ID who fail to respond to, or are intolerant of, oral iron”.
- Blood 2017 Achebe and Gaftor-Gvili: IV iron for any oral intolerant 2<sup>nd</sup> or 3<sup>rd</sup> trimester patient, for 2<sup>nd</sup> trimester gravidas with [Hb]<10.5 g/dl and all in the 3<sup>rd</sup> with ID
- No guidelines for non-anemic ID pregnant women

# Pregnancy

- Maternal iron deficiency potentially affects fetal, neonatal, and childhood brain growth and development with adverse effects on myelination, neurotransmitters, and brain programming<sup>1</sup>
  - Children born to iron-deficient mothers demonstrate lower cognitive function, memory, and motor development recognizable up to 19 years after iron repletion<sup>2-4</sup>
- Iron deficiency anemia (IDA) in pregnancy has been associated with increased risk of adverse perinatal outcomes, including preterm birth, low birth weight, and small-for-gestational age infants<sup>5-7</sup>

1. Roncagliolo M, Walter T, Peirano P, et al. Am J Clin Nutr 1998;68:683–690
2. Congdon E, Westerlund B, Algarin C, et al. J Pediatr 2012;160:1227–1233
3. Chang S, Zeng L, Brouwer I, et al. Pediatrics 2013; 131:e755–e763
4. Tran T, Tran T, Simpson J, et al. BMC Pregnancy Childbirth 2014;14:8–18
5. Scholl T, Hediger M, Fischer R, et al. Am J Clin Nutr 1992;55:985–988
6. Ren A, Wang J, Ye R, et al. Int J Gynecol Obstet 2007;98:124–128.
7. Radlowski E, Johnson R. Front Human Neurosci 2013;7:585–592
8. Scholl T. Iron status during pregnancy: Am J Clin Nutr 2005;81:1218S–1222S. [PMID:15883455]

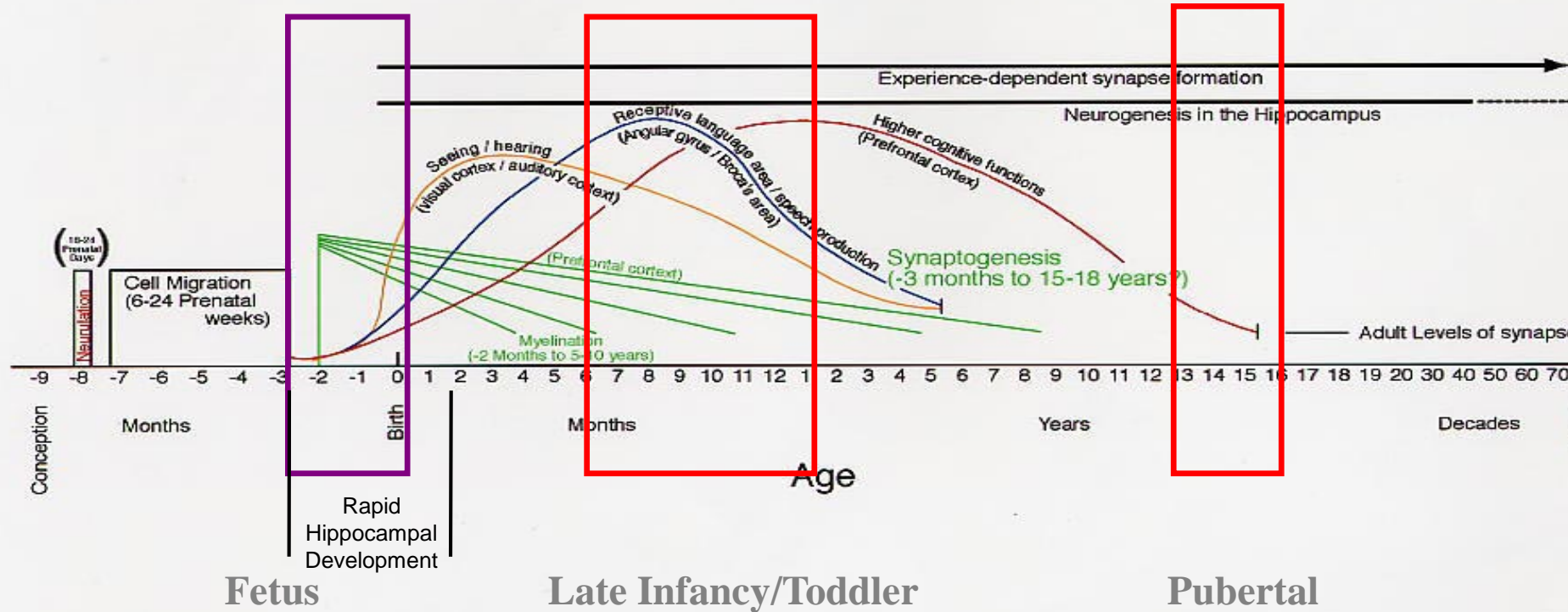


## Fetal Iron Status with Maternal Iron Deficiency

- Reduction in fetal iron status when maternal ferritin is  $<15$  (Shao et al, J Nutrition 2012)
- Prenatal iron supplementation reduces maternal anemia, iron deficiency, iron deficiency anemia but iron deficiency is common in neonates even with iron supplementation (Zhou et al, J Nutrition 2015)

# The Effect of Timing of ID on Brain Development

## Human Brain Development



## Iron Deficiency in Early Life

- Iron deficiency in children is common and limits their developmental, educational and job potential as adults
- ID in children is likely due in part to fetal iron underloading
- Fetal iron underloading occurs in the following contexts
  - Maternal ID (Ferritin <13.4; Hgb <100)
  - Intrauterine growth restriction
  - Premature delivery
  - Maternal diabetes mellitus



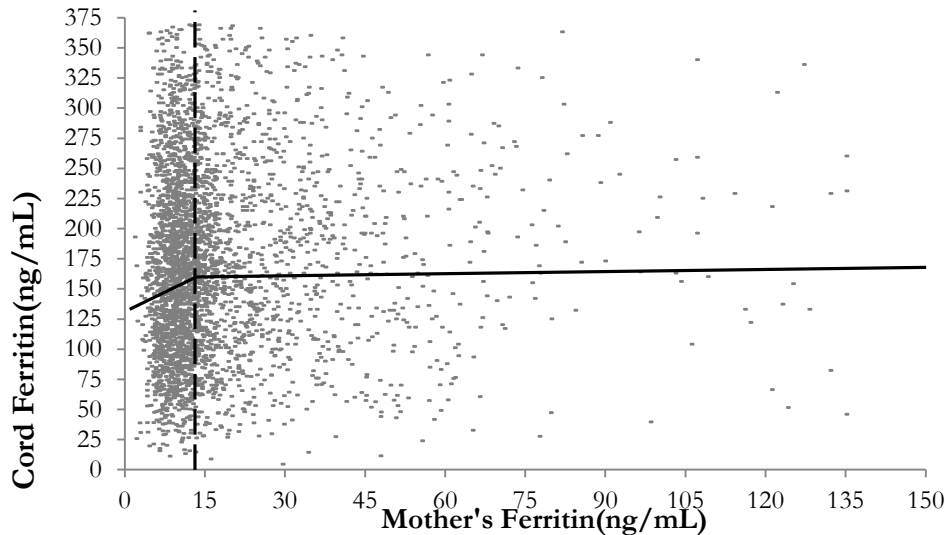


### Infants at risk for neonatal iron deficiency

- From IRON DEFICIENT mothers OR those previously treated with IDA
- From mothers underweight or obese or with diabetes
- From Vegetarian mothers
- From multiparas
- From mothers with inflammatory bowel disease
- From mothers with HIV or smokers
- From mothers with inter-partum period of <6 months
- From mothers with history of abnormal uterine bleeding

# When Is Fetal Iron Status Compromised with Maternal Anemia?

- Maternal Hgb < 85 g/L
- Sliding scale between 85 and 105 g/L
- Maternal Ferritin < 13.4 mcg/L



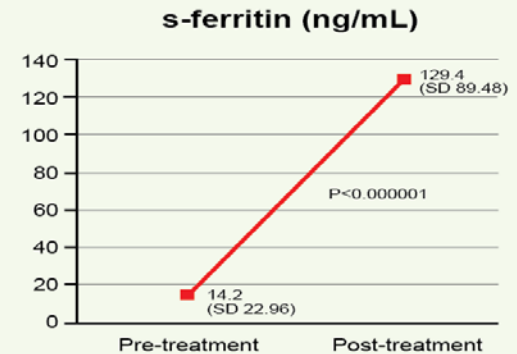
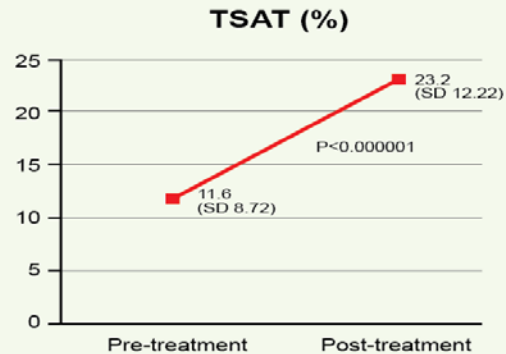
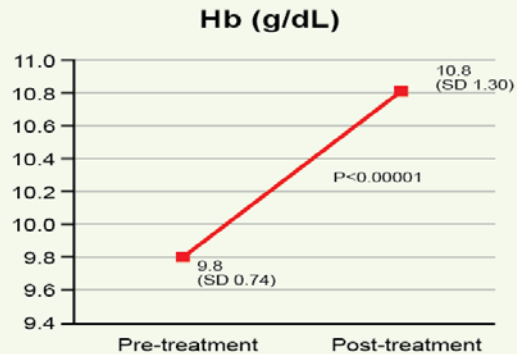
Shao et al,  
J. Nutrition, 2012

Table 1. TSAT and ferritin levels for all patients and for primigravida and multigravida patients.

	<b>All patients</b> N=102	<b>Primigravida</b> n=30	<b>Multigravida</b> n=72	<b>P-value<sup>1</sup></b>
<b>TSAT, mean (SD)</b>	27.2 (14.2)	25.4 (15.6)	28.0 (13.6)	.39
<b>TSAT, median (IQR)</b>	23 (16, 38)	20.5 (15, 33)	24 (17, 39)	.22
<b>Ferritin, mean (SD)</b>	66.1 (43.6)	77.1 (56.1)	61.6 (36.7)	.17
<b>Ferritin, median (IQR)</b>	57.5 (36, 90)	68 (41, 94)	47 (35, 82.5)	.16
<b>TSAT &lt;19, n(%)</b>	38 (37)	13 (43)	25 (35)	.41
<b>Ferritin &lt;20, n(%)</b>	5 (5)	4 (13)	1 (1)	.02
<b>Ferritin &lt;25, n(%)</b>	6 (6)	4 (13)	2 (3)	.06
<b>Ferritin &lt;30, n(%)</b>	14 (14)	6 (20)	8 (11)	.24

# Results

- 73 of 74 enrolled subjects were treated
- Paired follow-up data were available on 60/73 mothers (4 weeks post infusion)



# Anemia in Pregnant Women in India

## (The RAPID Trial)

n=4000 -- the largest randomized clinical trial employing IV iron

- To be conducted at academic centers in 2 States in India (Karnataka, Rajasthan)
- Pregnant women to be randomized to either of 2 approved single infusion IV iron formulations or to oral iron (all receive folic acid) in early second trimester of pregnancy (dating ultrasound). Additionally, a window for study inclusion:
  - Hb 7 - 9.9 gms/L
  - Ferritin < 30 ngm/ml
  - Transferrin saturation (TSAT) < 20%
- 2 primary outcomes:
  - Conversion to a non-anemic state
  - Rate of low birthweight
  - Cord Blood iron parameters

# The RAPID Trial

## Key Secondary Outcome

- Maternal and neonatal mortality
- Rates of preterm birth
- Small for gestational age (SGA)
- Rate of stillbirth
- ICU admissions
- Rates of antepartum and postpartum hemorrhage
- Rate of C/S
- # of women who fall below 7gms/L Hb and require rescue therapy
- Changes in hemoglobin terciles (7-7.9, 8-8.9, 9-9.9)
- Quality of life assessment

A cost effectiveness (economic) analysis built in to address issues of scalability



## Key Points

- Oral iron is frontline therapy for uncomplicated iron deficiency in those who tolerate it
- High quality published evidence suggests alternate day oral iron is preferable
- For heavy uterine bleeding, late pregnancy, IBD, CIA and other comorbid conditions associated with iron lack, GB, OWR and oral iron intolerance the intravenous route is preferred and should be moved to the frontline
- The preponderance of published evidence suggests the USPSTF recommendations for screening for iron deficiency in pregnancy should be revisited
- Four formulations are able to be administered in a single total dose infusion obviating multiple visits and decreasing infusion reactions and increasing adherence: LMWID, FCM, isomaltoside (renamed ferric derisomaltose by WHO and FDA) and ferumoxytol
- Intravenous iron is likely safer than most physicians believe and should be moved forward in the treatment paradigm