

Prevalence of IDA in pregnancy

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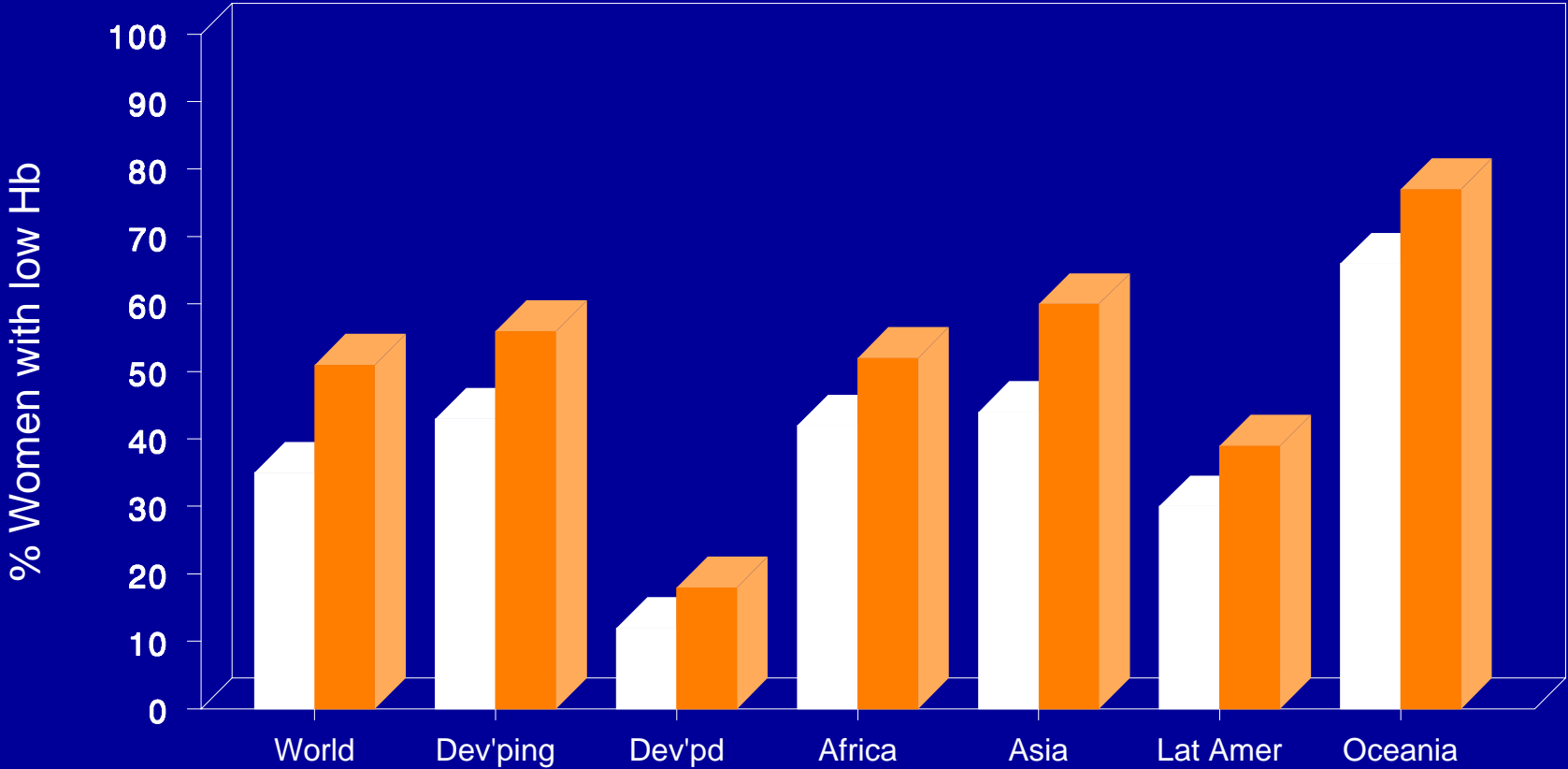
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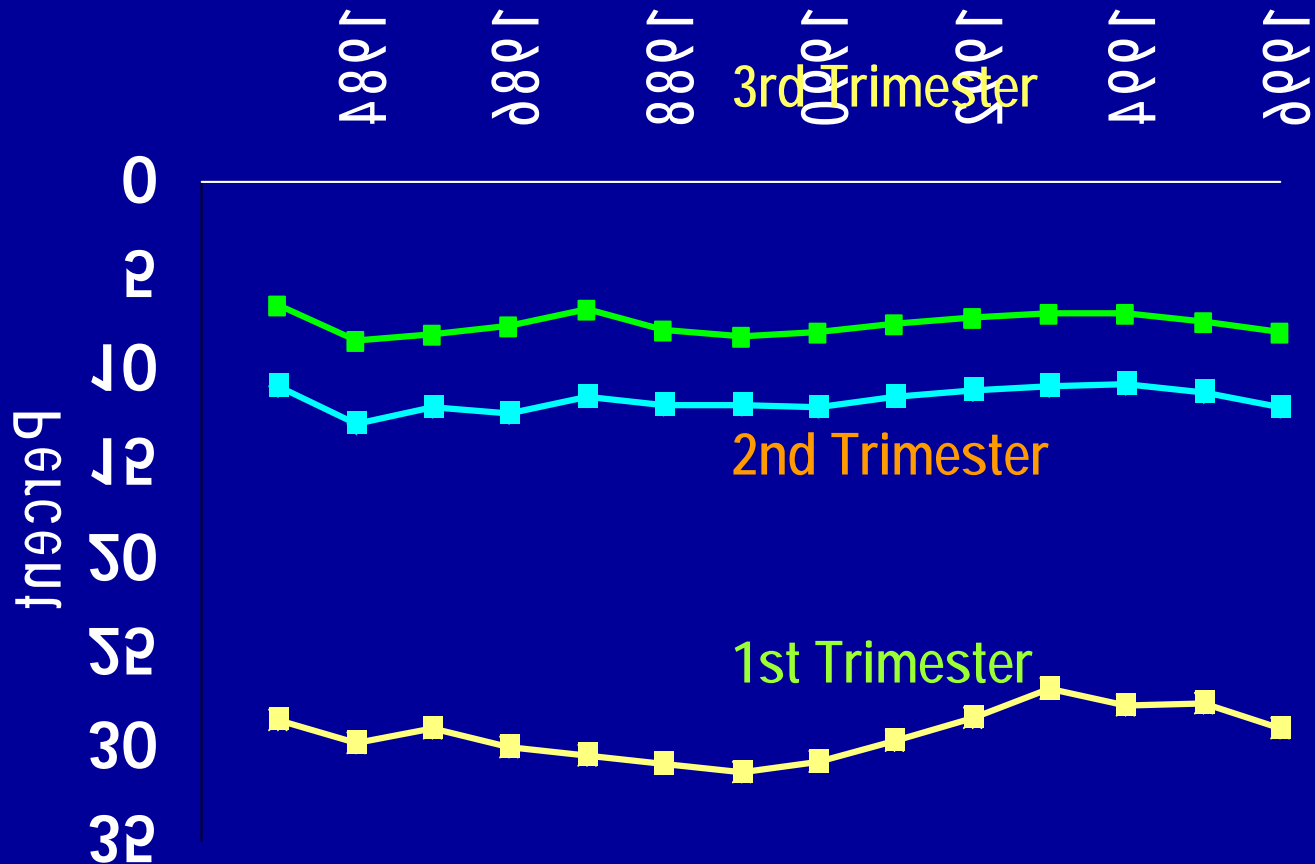
PREVALENCE OF ANEMIA IN WOMEN, 1988

WHO, 1992

Non-Pregnant Pregnant



Trends in the Prevalence of Anemia During Pregnancy



Uncertainties about iron deficiency assessment in pregnancy

Anemia and Indicators of Iron Status during Pregnancy

- Hb concentration is U-shaped, and cut-off not well established.

Hb concentration at 28 wk associated with best outcome in large surveys

Study		Hb level for best outcome		
	N	LBW	Preterm	Mortality
NCPP-USA	60,000	102-125	112-125	95-105
Cardiff	55,000	104-132	-	104-132
NW Thames	>150,000	96-105 (86-95 BW)	96-105	

Anemia and Indicators of Iron Status during Pregnancy

- Hemodilution alters iron status indicators (Hb, ferritin, transferrin saturation).
- Better to use TfR, RBC protoporphyrin or RBC ferritin?

Serum TfRs in pregnant Swedish women....

Akesson et al., Am. J. Clin. Nutr. 1998

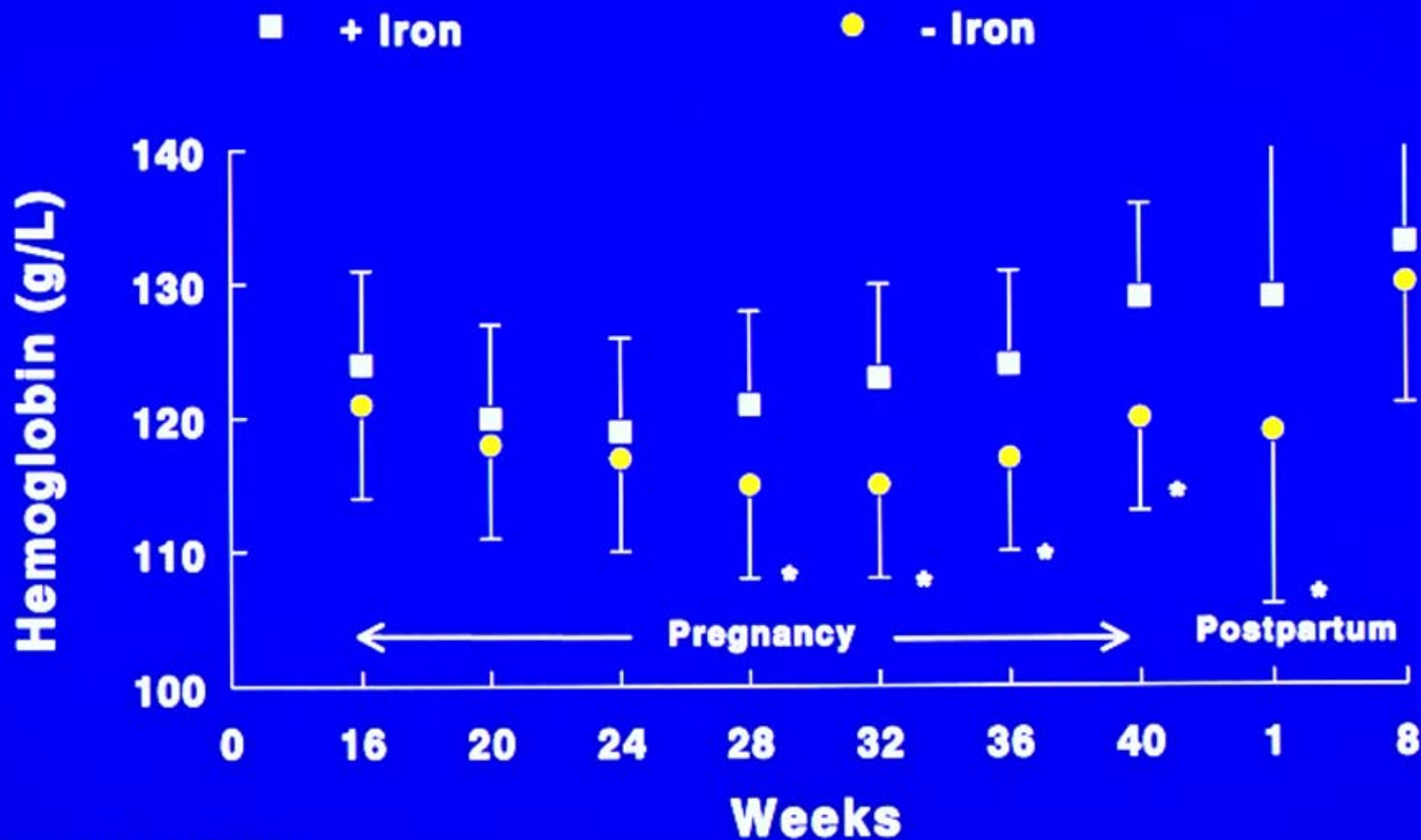
	<u>Trimester 1</u>	<u>Trimester 3</u>
Low Hb	1	7
Low ferritin	10	58
↑ TfR	0	14
All 3 abnormal	0	5

Transferrin receptors in pregnancy

- In US, 63/81 women with low ferritin in trimester 3 had normal TfR values.
- But all with low ferritin had elevated TfR.
- Many more women have depleted stores than depleted tissue iron.
- In Jamaica, TfR best differentiated Fe-supplemented from placebo group in late pregnancy. Iron prevented increase in TfR.

Supplements can improve
maternal and infant iron status

IRON SUPPLEMENTATION AND HEMOGLOBIN



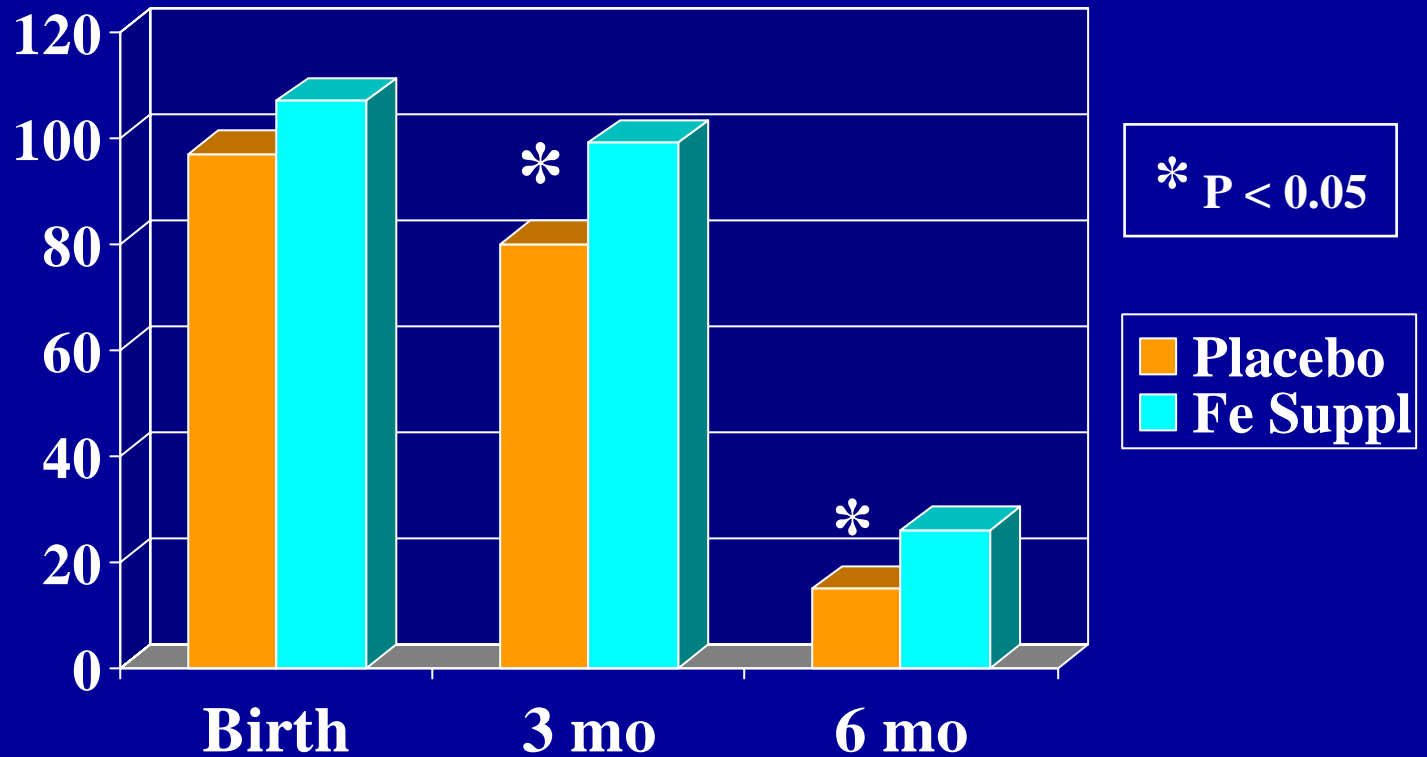
Milman et al., 1992

SERUM FERRITIN AFTER IRON SUPPLEMENTATION IN PREGNANCY

○ Not Suppl ● Suppl



100 mg/d Fe Improved Infant Serum Ferritin



Studies in Which Maternal Iron Status Was Related to Mother's Status

		<u>Obs or Suppl</u>	<u>Hb</u>	<u>Ferritin</u>	<u>Comment</u>
Agrawal	India	O	No	Yes	
Ajayi	Nigeria	O	(Yes)	Yes	
Lao	China	O	(No)	(No)	
Gaspar	Spain	O	Yes	Yes	
Kaneshige	Japan	O	?	Yes	
Hokoma	Japan	O	No	Yes	
DeBenaze	France	S	No	Yes	& 2 mo
Milman	Denmark	S	No	Yes	
Colomer	Spain	O	Yes		& 12 mo

Iron supplementation in
pregnancy reduces risk of
postpartum IDA

Postpartum Anemia is a Major Problem

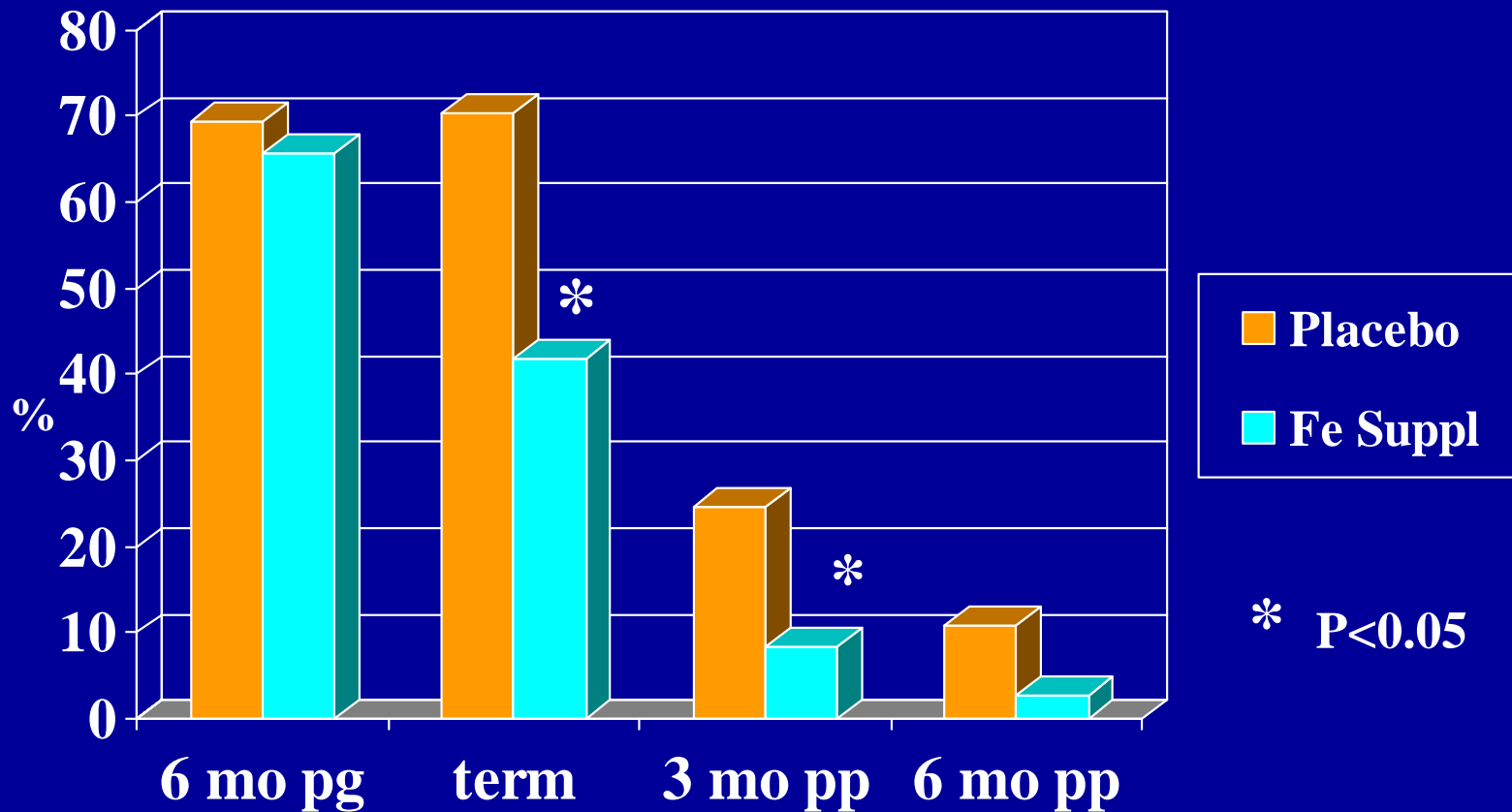
- In the United States, of $\approx 59,000$ women in the Women, Infants and Childrens Program:

Postpartum anemia occurred in

- 27% of all women
- 48% of Black women
- 21% of those non-anemic in Trimester 3
- 49% of those with anemia in Trimester 3

100 mg/d Fe reduced % anemia in Tanzanian women¹

Preziosi et al. 1997.



¹ < 11 g/dL in pregnancy; < 12 g/dL postpartum

Maternal IDA increases risk of
poor pregnancy outcomes

Non-intervention Studies: Anemia and Relative Risk of Poor Outcomes

	<u>Low birthweight</u>	<u>Preterm</u>
Moderate anemia	0.8 – 3.0	0.6 – 3.2
Severe anemia	1.0 – 6.3	0.6 – 4.0
IDA - USA	3.1	2.7
-PNG	6.0 (early only)	-

Conclusions: maternal mortality from anemia

- Relative risk = 1.35 for Hb 40-80 g/L, and 3.51 for Hb <47 g/L.
- Low ↑ risk for mild or moderate anemia.

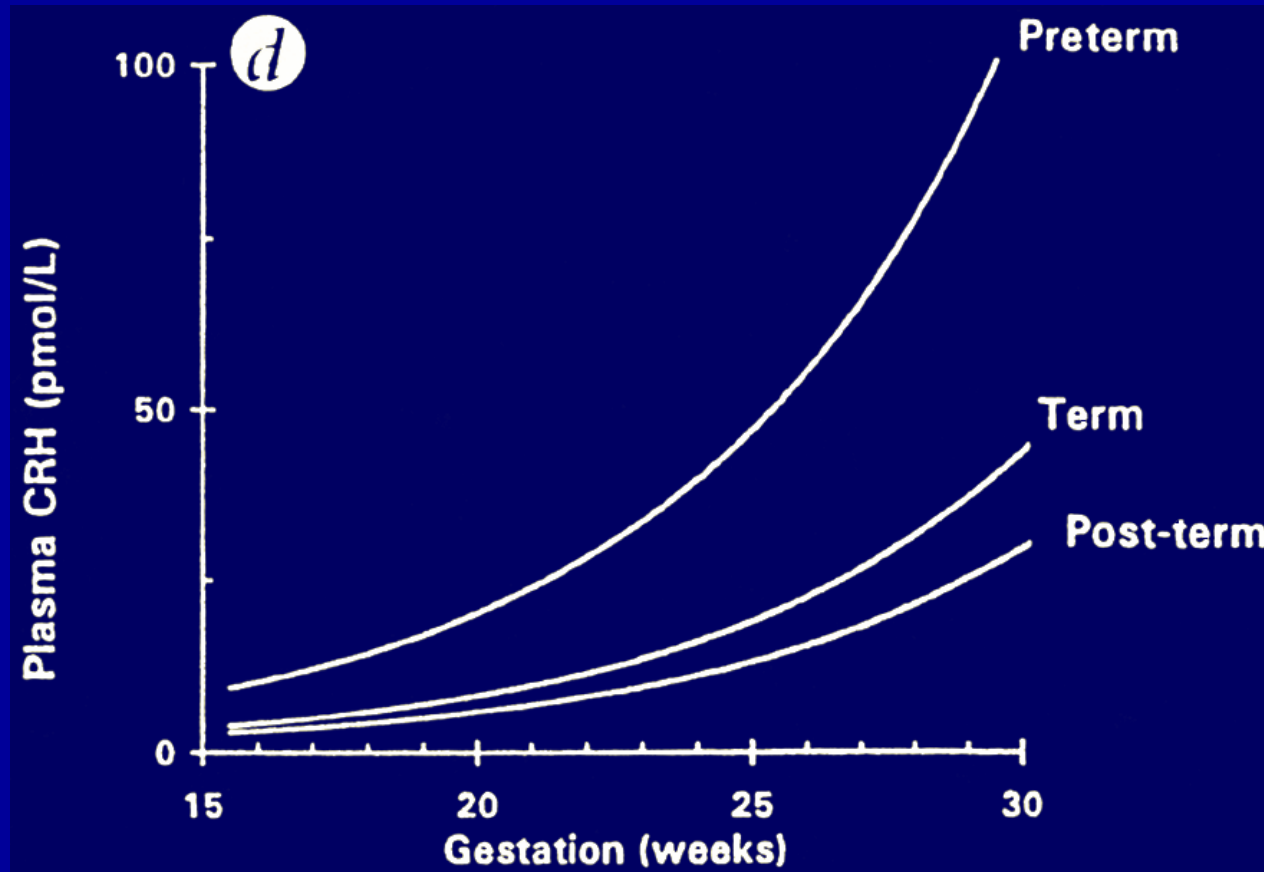
Recent Intervention Trial Shows Effect of Iron Supplements on Birthweight

- Importantly, for ethical reasons there has been lack of RCTs (placebo group).
- But IOM says intervention *may* only be needed if Hb <110 g/L and ferritin <20 ug/L.
- 213 non-anemic (Hb >110 g/L), non-ID (SF >20 ug/L) women in Ohio. (45% of those screened).
- 30 mg Fe/d from wk. 16 – 20 through wk. 28.
- If Hb <110 g/L or SF <12-20 ug/L at 28 wk. or 38 wk., all given 30 mg Fe/d.

Risk of Adverse Birth Outcomes for Non-Anemic,
 Iron-Replete Women is Reduced by Iron
 Supplements for 2-3 Months (Cogswell et al. 2002)

<u>Outcome</u>	<u>+ Iron</u>	<u>Placebo</u>	<u>Difference</u>
Birth wt	3277	3072	206**
% low BW	4.3	16.7	-12.4***
Gest. age (wk)	38.9	38.3	0.6*
% preterm	12.8	12.5	ns
% SGA	6.8	17.7	-10.9*

Maternal CRH in pre-term, term, & post-term deliveries



Iron supplementation in pregnancy – what we have learned

- ↑ Hb and ferritin in late pregnancy in many women - IDA or non-IDA early in gestation.
- ↑ maternal Fe status for up to 6 mo postpartum.
- ↑ birthweight (↓ preterm?).
- ↑ infant Fe stores for many months.
- May improve maternal care-taking postpartum.
- Weekly supplementation works, daily more effective.
- Hb increase is proportional to total amount of Fe consumed.
- Optimal time to start supplements is uncertain but even relatively late can improve maternal and infant Fe status in gestation and postpartum . Earlier to improve BW?



Impact of birth weight on iron status

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How does birthweight affect iron stores at birth?

- Dallman (1974); iron stores at birth are approximately proportional to body weight.
- LBW infants also grow faster.
- So LBW infants deplete stores at 2-4 months (vs. 4-6 months).
- LBW infants need iron supplements or iron-fortified food.

Guidelines for Iron Supplementation (INACG/WHO/UNICEF, 1998)

- Where the prevalence of anemia is 20-40%,
 - For infants age 6-24 mo give 12.5 mg Fe/d + 50 ug folic acid, starting at 6 mo and continuing until 24 mo if possible, if not until 12 mo.
 - For LBW infants, start at 2 mo.
- Where the prevalence of anemia is >40%,
 - Continue supplementation until 24 mo.

Guidelines for Iron Supplementation (INACG/WHO/UNICEF, 1998)

<u>Age</u>	<u>Dose (mg)</u>	<u>Birth Wt</u>	<u>Duration</u>
6-24 mo	12.5 + FA	Normal	6-12 mo
		LBW	2-12 mo
2-5 y	20-30		
6-11	30-60		
Adol/adult	60		
Preg	60 + FA		6 mo
Preg, high prevalence	60 + FA		6 mo + 3 mo lact

Dose is doubled for 3 mo if severe anemia (<70 g/L)

Dewey et al. 1999

- Honduran infants
- 50% of LBW infants had Hb <100 g/L by 2 months of age.

Low birthweight vs. risk of infant anemia at 4.5 mo

de Pee et al. 2002

Maternal Hb and birthweight	% Hb <100 g/L	OR
≥ 120 g/L, > 2500 g	32	1.0
≥ 120 g/L, ≤ 2500 g	37	1.15
< 120 g/L, > 2500 g	45	1.81
> 120 g/L, ≤ 2500 g	64	3.68

How can guidelines be improved?

- Is it reasonable to continue longer in areas where prevalence of anemia is higher?
- When supplements stop, how long does depletion take?
- Is <2500 the right cut-off?
- Start intervention at an earlier age?
- Recommend weekly preventative dosing?

Improving strategies for supplementation of pregnant and lactating women

1. Be more specific about number of tablets women need to take. (Frequency of consumption less important?)

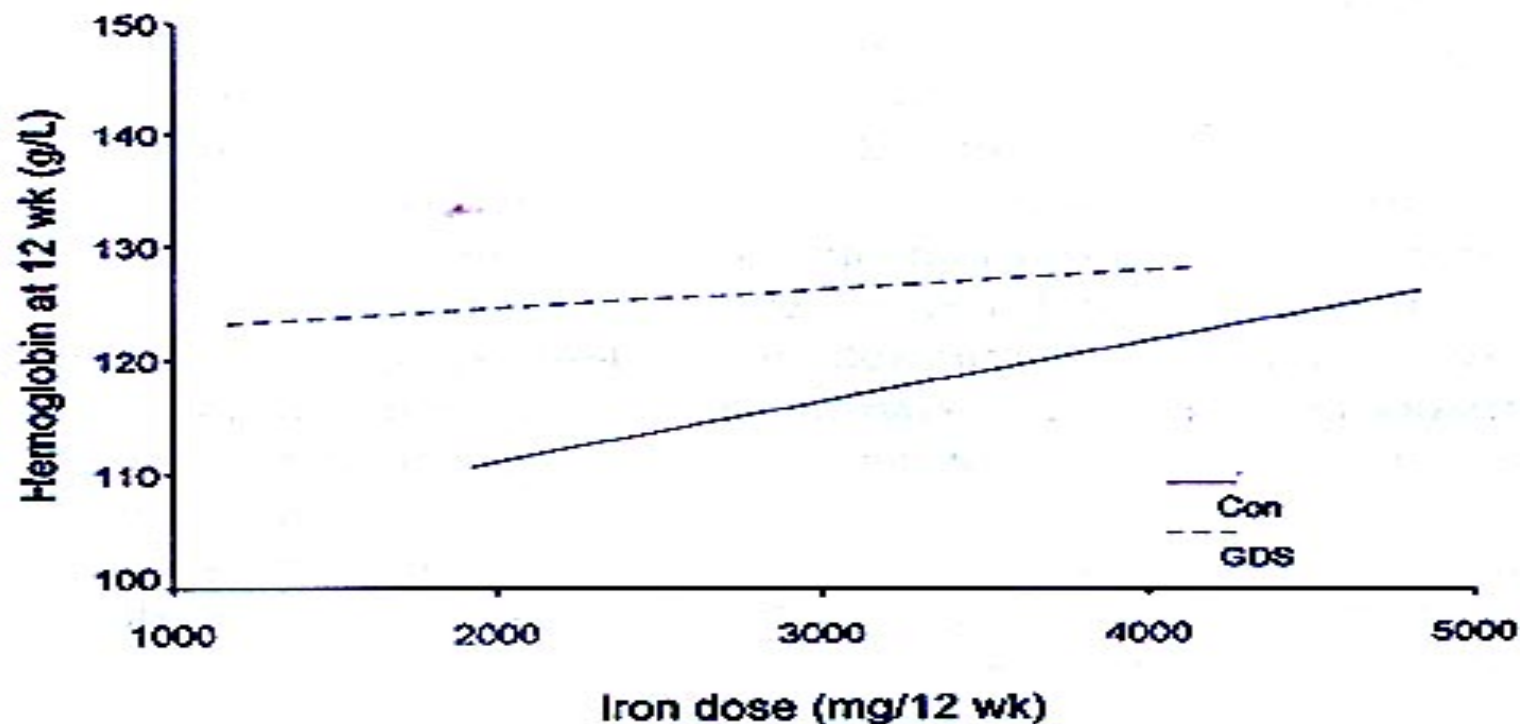


FIGURE 4. Effect of iron dose on hemoglobin concentration at 12 wk: comparison between the gastric-delivery-system (GDS) and conventional (Con) iron supplements in women with an initial hemoglobin concentration ≤ 120 g/L.

Weekly dosing in at least some
situations?

2. Minimize Side Effects

- “There is little evidence that side effects are the major cause of non-compliance” (Galloway, 1994).
- Blot, Simmons, IOM 2000
- with 65 mg x 3, 25% symptoms vs 13% placebo
- with 130 x 3 40% symptoms
- “unlikely that 60 mg x 2 would affect compliance”
IOM 1993

Side Effects: IOM Report, 2001

- High dose supplements associated with constipation, nausea, vomiting, diarrhea
- Less effect at lower dose, with food, slow release
- “Lower Observed Adverse Effect Level” = 60 mg/d suppl + 11 mg diet = 71 mg/d, and
- “No Observed Adverse Effect Level” = “Upper Limit” = 45 mg/d

“Critical Study”

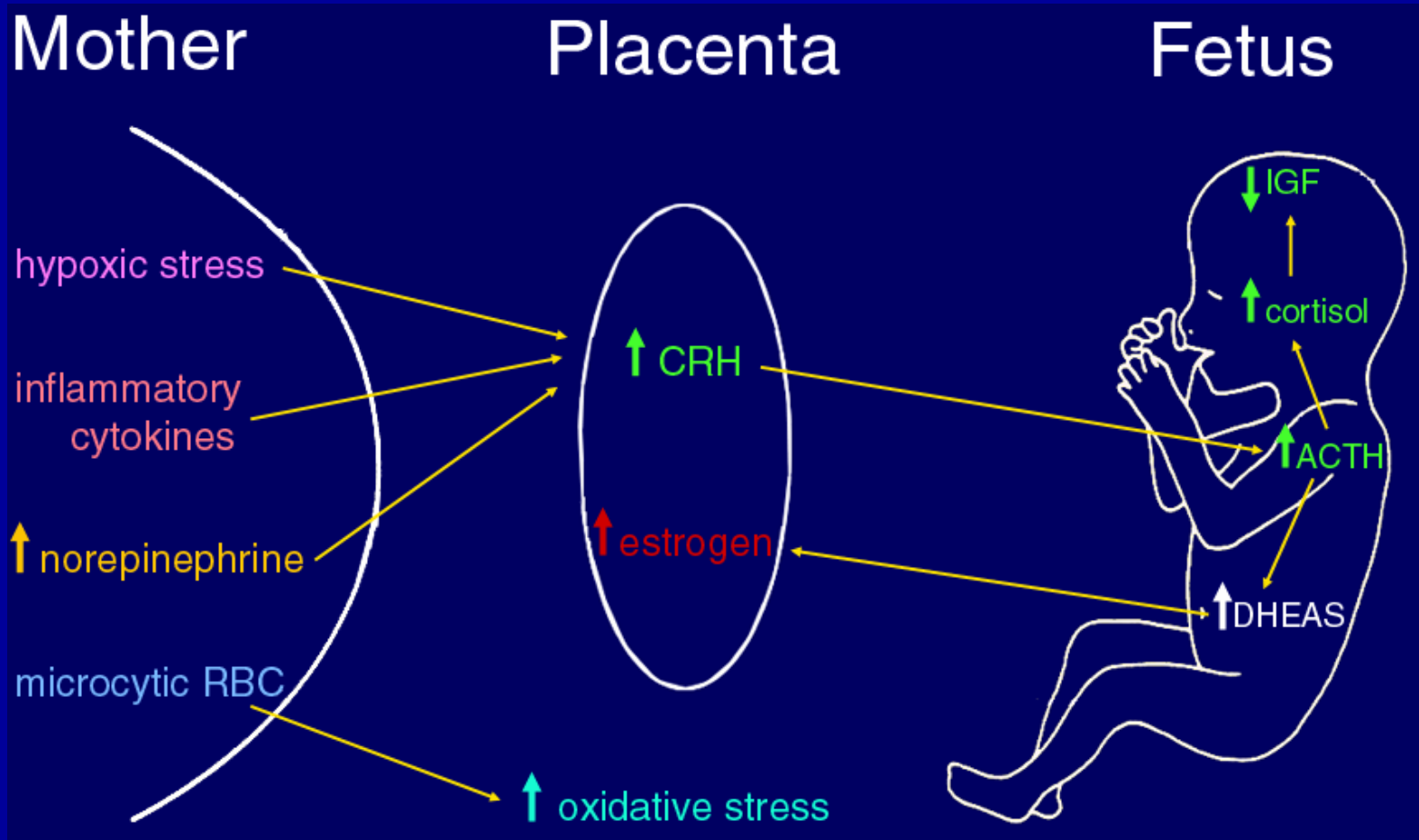
<u>Effect</u>	<u>Placebo</u>	<u>60 mg Fe</u>
Nausea	4	6
Gastric pain	10	19
Constipation	20	35*
Diarrhea	19	37
All effects	14	25*



Unanswered Questions

- How much supplemental iron is needed to improved pregnancy outcomes in IDA women?
- What are the norms for iron status indicators in pregnancy?
- Is there a risk of excessive iron intake? What are the risks?
- When is the best time to begin iron supplementation for improving outcomes in anemic women?
- What is the expected impact on maternal and infant iron status when supplements are given to anemic women prior to and/or during pregnancy?

Possible Biological Mechanisms



Similarities and Differences Between Risk Factors for IUGR and Preterm Delivery

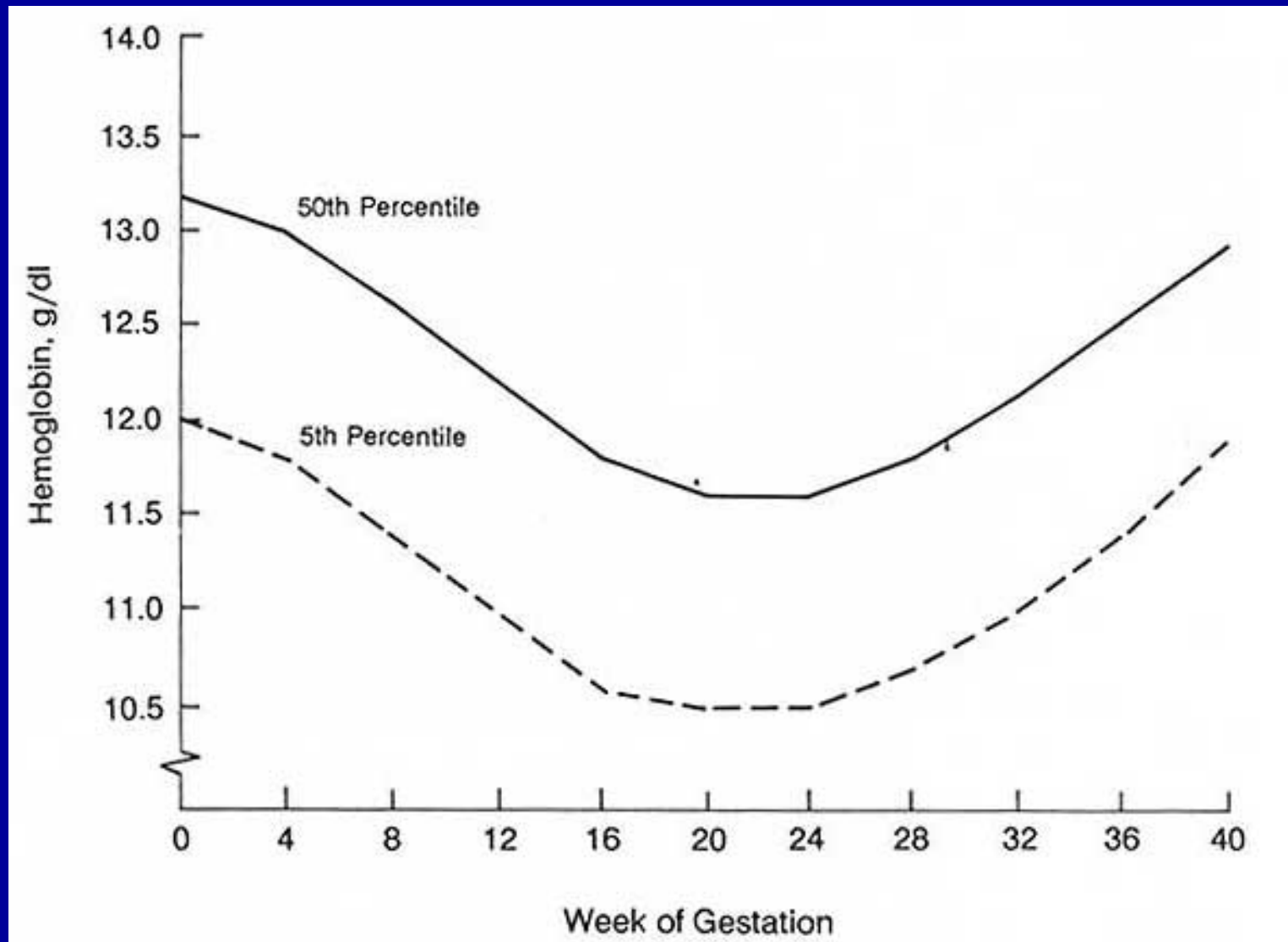
- **“The degree of overlap between the sets of risk factors for preterm delivery and IUGR is so great that it is easiest to list the discrepancies”**

(Yu and Wood, 1987)

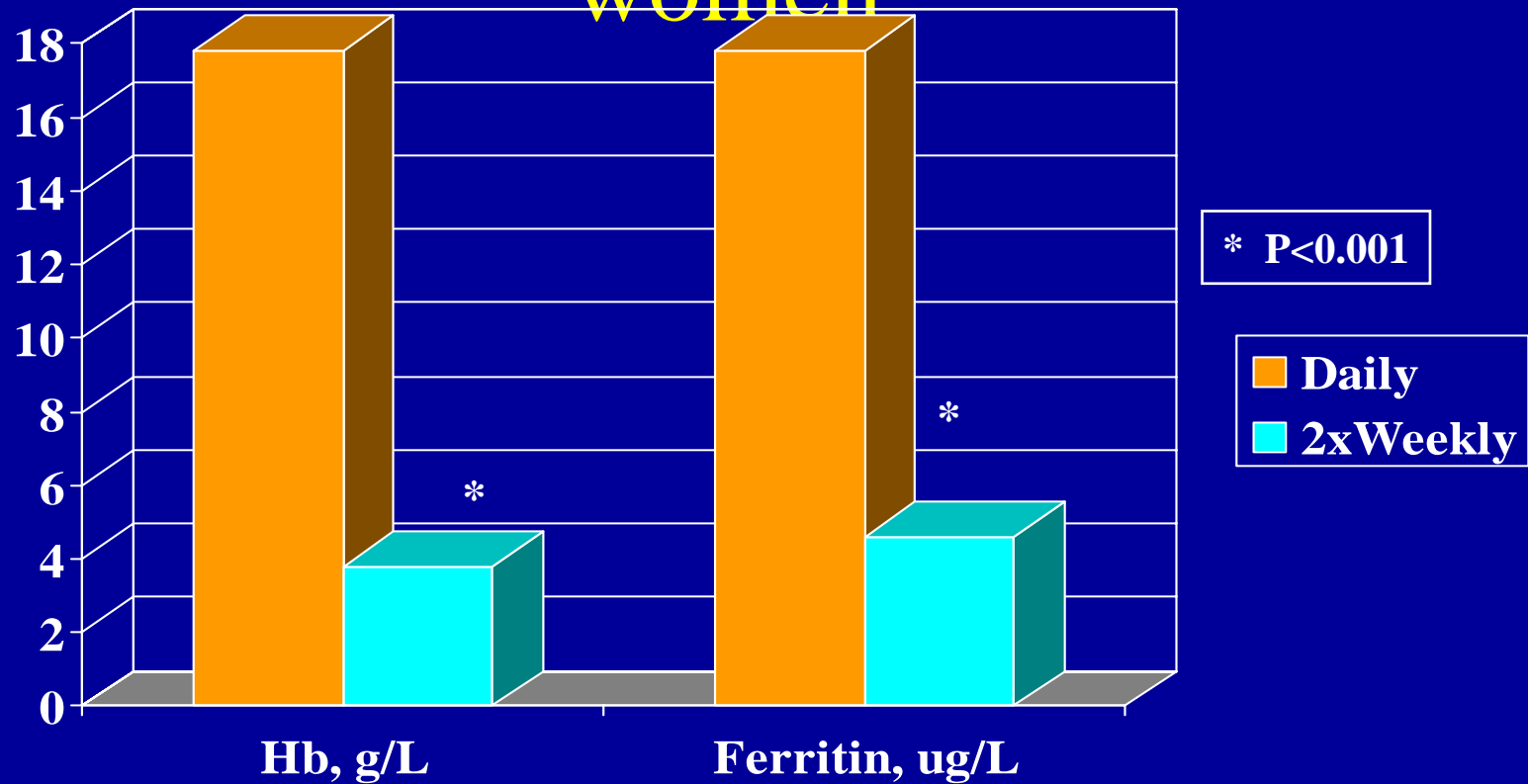
Placental Iron Transfer

- Fe transport via transferrin receptors and ferritin receptors on placental trophoblasts.
- Liao et al. 2001, placental Fe transfer:
 - If Fe adequate, placental Fe transport via TfR and FnR
 - In mild ID/A, \uparrow #TfR and #FnR, but \downarrow TS
 - In severe ID/A, no further \uparrow receptor #s and also low TS and low ferritin.

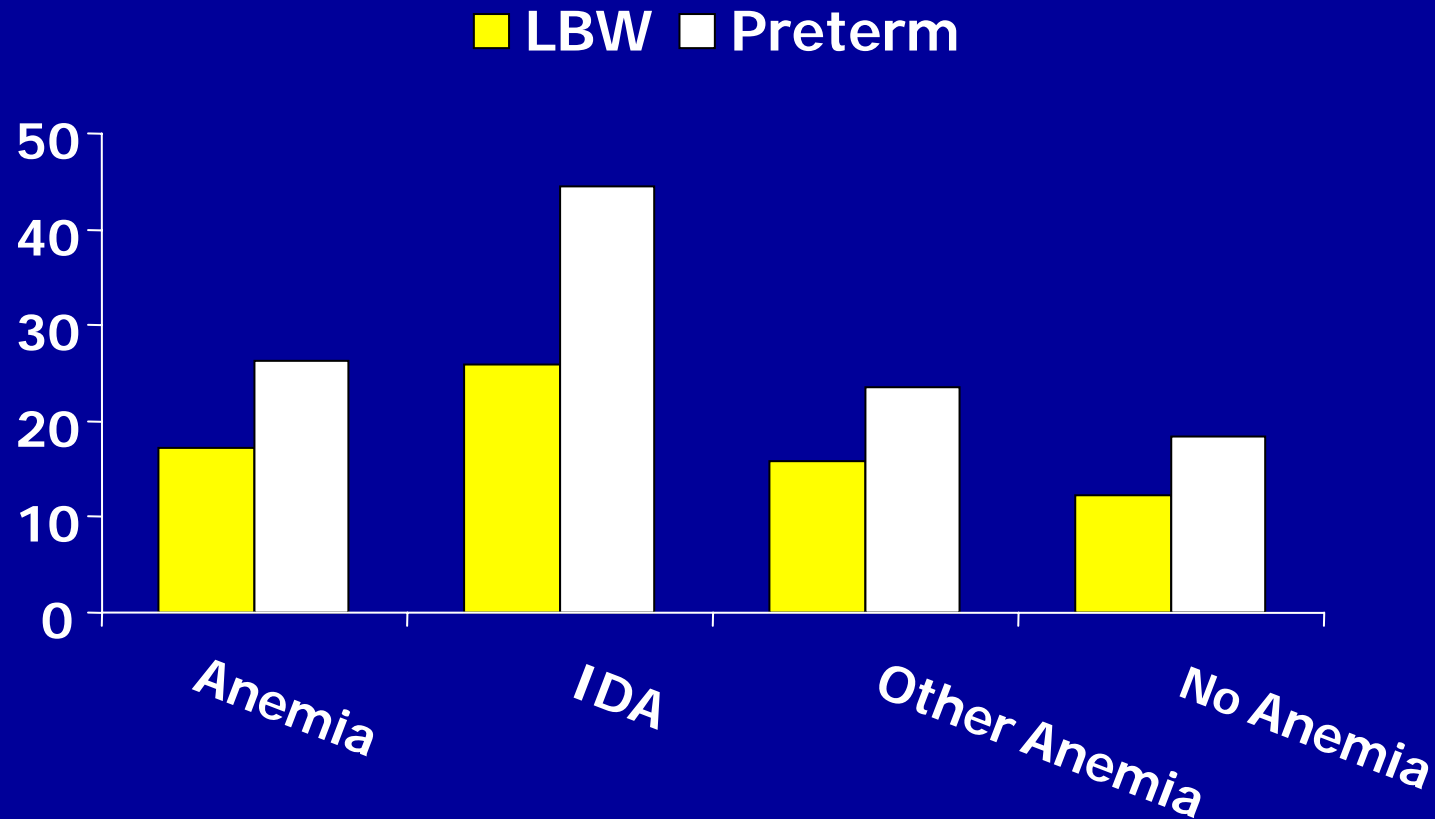
Normal hemoglobin values during pregnancy



Change in hemoglobin and serum ferritin after 10 weeks of supplementation in anemic pregnant women



Iron Status in Trimester I Predicts Low Birth Weight and Prematurity (New Jersey USA)



Scholl, Am. J. Clin. Nutr. 1992

Anemia and Indicators of Iron Status during Pregnancy

- Hb concentration is U-shaped, and cut-off not well established.
- Hemodilution alters iron status indicators (Hb, ferritin, transferrin saturation; better to use TfR, RBC protoporphyrin or RBC ferritin?).
- Maternal iron status does not alter the pattern of changes, but it directly influences absolute values
- Hb concentrations in third trimester
 - unsupplemented women: 10.5-11.0 g/dL
 - supplemented women: ~ 1 g/dL greater

Attributing Mortality to Anemia is Difficult

- **Usually hospital data, from moribund women.**
- **Anemia often not reported, or is 1 cause of death.**
- **Confounders (infection, hemorrhage, malaria).**
- **No RCT with Fe because ethically difficult, and transfusion used if anemic near term.**

Maternal Mortality Due to Anemia (WHO)

<u>Region</u>	<u>All cause deaths /100,000</u>	<u>% attributed to anemia</u>
Africa	640	6.4
Asia	420	7.3
Latin America	270	3.0

Conclusions from Meta-Analysis of Daily or Weekly Supplementation

Beaton & McCabe, 1999

- *BOTH daily and weekly reduced IDA*
- Daily more efficacious to ↑ Hb and ferritin; *daily caused 2 g/L higher Hb and 34% lower risk anemia.* Relative efficacy did not vary by group.
- Weekly may be more effective when supervision feasible with weekly but not with daily.
- Many studies had high prevalence of anemia AFTER intervention, even with daily - compliance a likely explanation.