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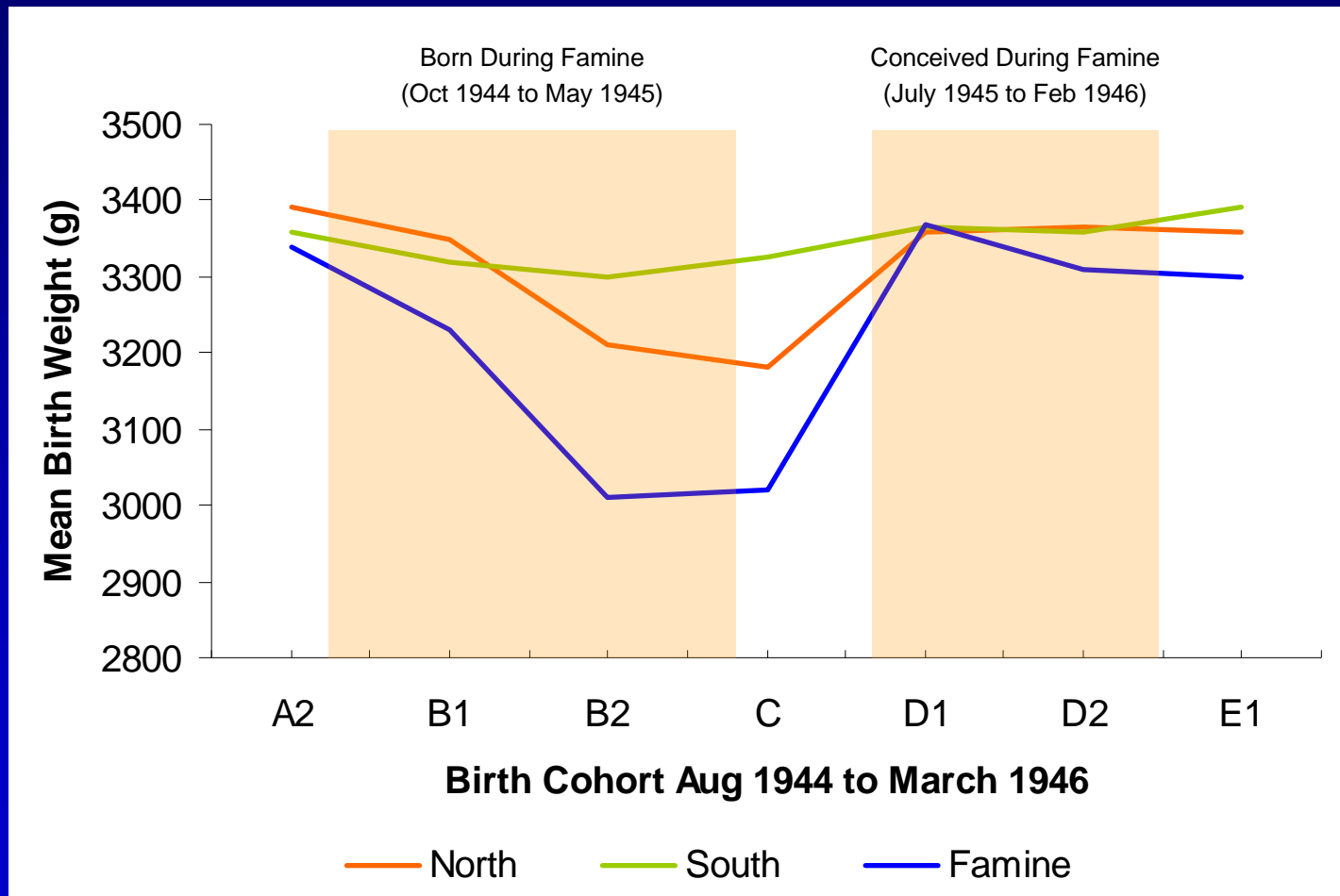


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Lecture 11

Epidemiology of Low Birth Weight, Preterm Delivery, and Intrauterine Growth Retardation II

Mean Birth Weights in Maternity Hospitals in the Area Affected by the Dutch Famine, 1944-45, and in two “control” areas



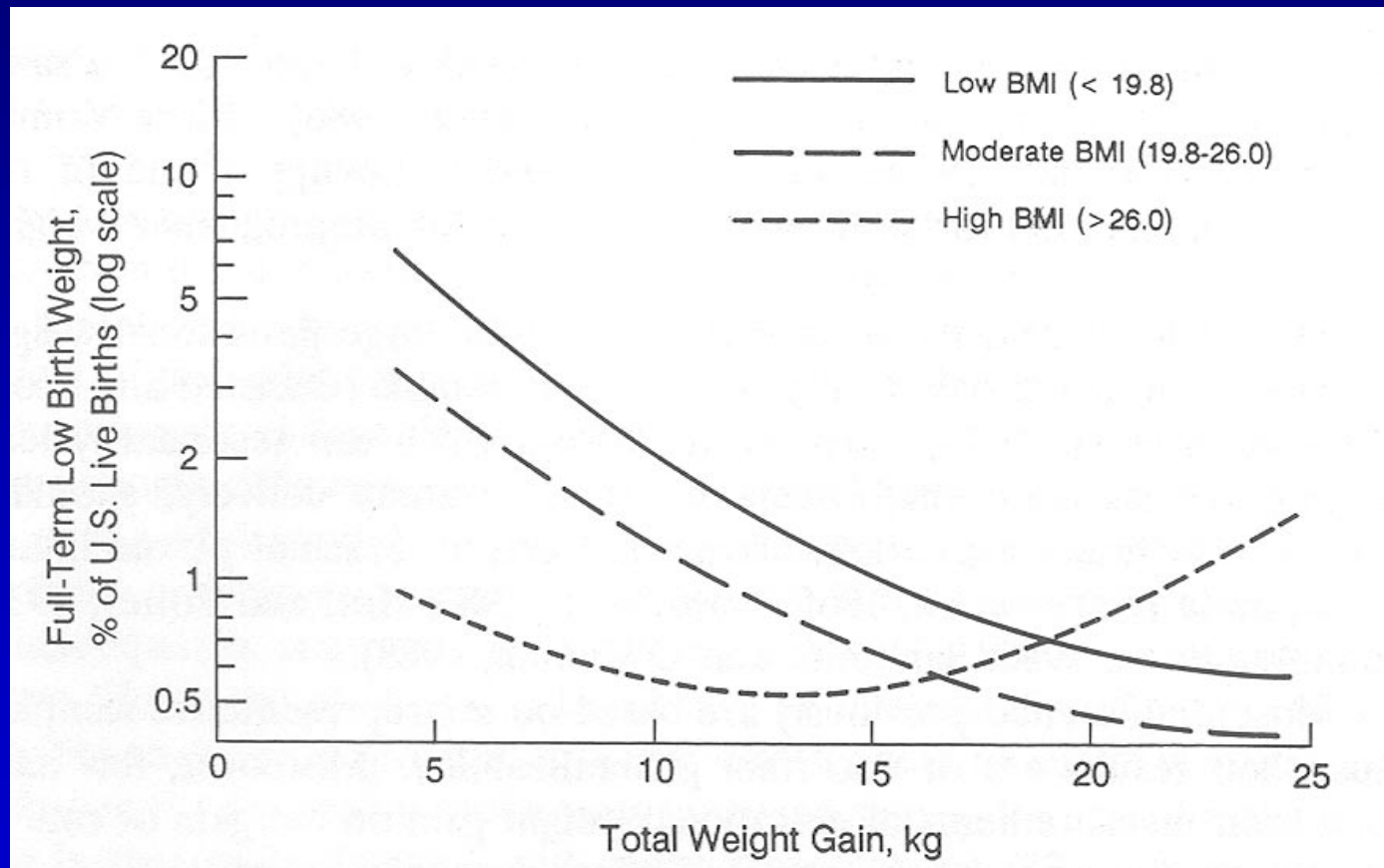
Maternal Nutrition and Poor Pregnancy Outcomes

- Short stature: ↑IUGR, no effect on PTD
- Maternal weight
 - Low prepregnancy weight or attained weight during pregnancy leads to ↑ LBW and IUGR; no consistent association with PTD
- Pregnancy weight gain
 - Pregnancy weight loss or low weight gain leads to ↑LBW, IUGR, and PTD

Weight Gain and Poor Pregnancy Outcomes: Trimester & BMI

- Associations with LBW, IUGR, and PTD strongest for weight loss/low weight gain in the 3rd trimester
- Effect of low pregnancy weight gain on LBW and PTD modified by prepregnancy BMI
 - Low weight gain leads to greater increased risk of LBW/PTD among underweight women
 - High weight gain leads to increased risk among obese women

Prepregnancy Weight, Weight Gain and Low Birth Weight



Kleinman, J. Maternal weight gain during pregnancy: Determinants and consequences. Working Paper No. 33. Hyattsville, MD: National Center for Health Statistics, 1990.

Diet/Energy Intake and Poor Pregnancy Outcomes Trials

- **Dietary intake**

- Pune Nutrition Study (India): cohort study
- Higher intake of milk, green vegetables and fruits associated with increased BW
- Green vegetable intake (\geq alternate days): +171 g BW and LBW OR=0.43 (0.12-0.99)

- **Protein/energy supplementation**

- Meta-analysis (Kramer, Cochrane, 2000):
 - maternal weight gain/wk=17 g (5-29)
 - \downarrow SGA risk, OR=0.64 (0.53, 0.78)
 - No effects on PTD

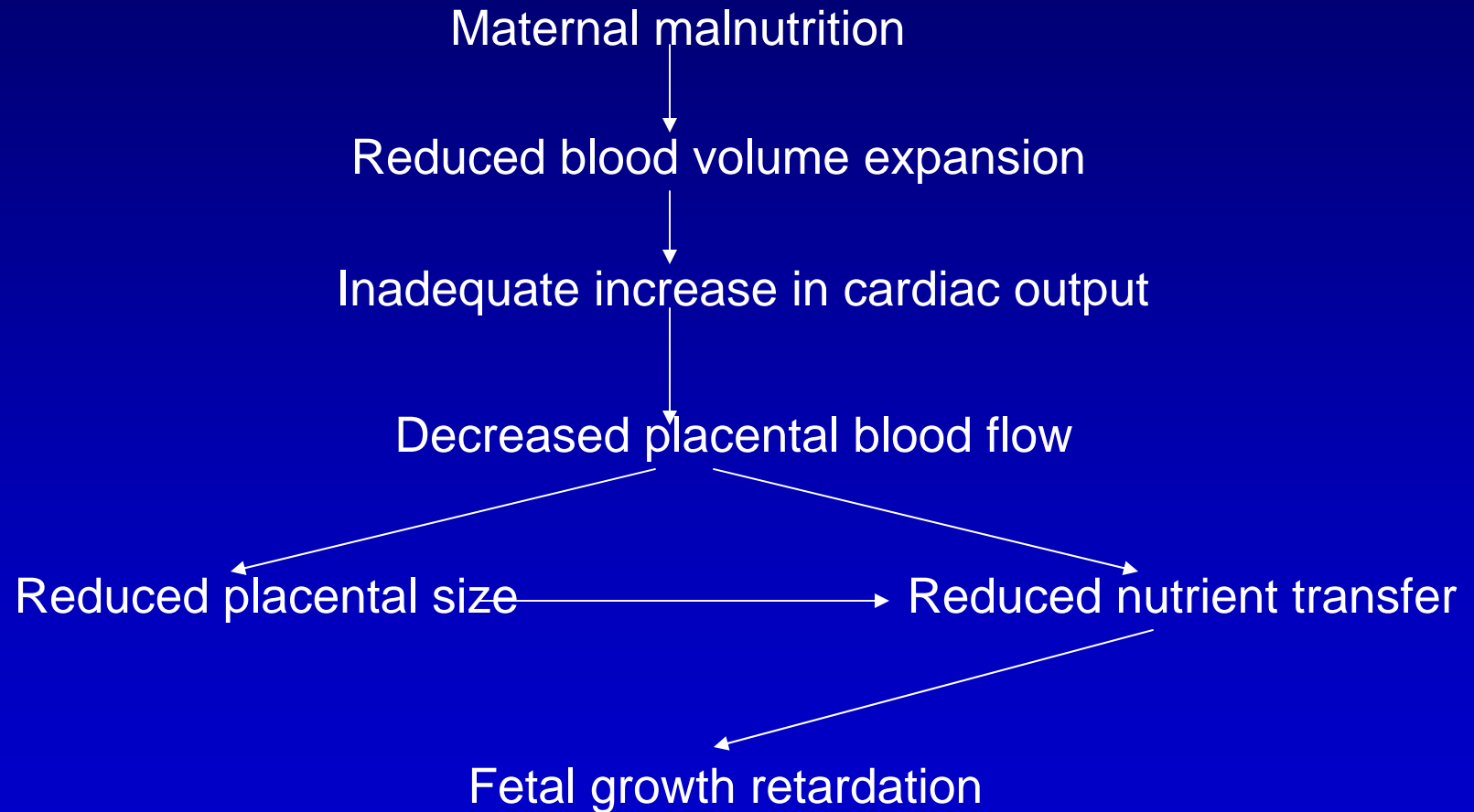
Effect of increased dietary intakes on pregnancy outcomes, The Gambia

(Ceesay et al, 1997)

Outcome	Change
Birth weight, LBW	↑ 136 g, ↓ 39%
Head circumference	↑ 3 mm
Stillbirths	↓55%
Perinatal deaths	↓49%
Neonatal deaths	↓40%
Post-neonatal deaths	--

~1000 additional kcal/d, routine prenatal care, Iron/FA, tetanus toxoid, weekly chloroquine.

Postulated mechanisms of placental and fetal growth retardation caused by maternal malnutrition



Micronutrients and Poor Pregnancy Outcomes

- Micronutrient deficiencies are common in pregnant women
- Numerous observational studies link micronutrient deficiencies to poor pregnancy outcomes (mostly LBW)
- Few supplementation trials have demonstrated a significant impact on LBW; only one on PTD

Micronutrients and Pregnancy Outcomes: Vitamin A & Zinc Trials

- **Vitamin A**

- Nepal: No effects (LBW, PTD, SGA)
- Tanzania (HIV+): No effects (LBW, PTD, SGA)
- Malawi (HIV+): ↓ LBW (14 vs. 21%)

- **Zinc**

- Bangladesh: No effects (LBW, PTD, SGA)
- Peru: No effects (LBW, PTD, SGA)
- U.S. (low-income): ↓ LBW (effect stronger among thinner women)

Iron and Pregnancy Outcome Trials

- Iron

- Nepal: Iron-folate ↓ LBW and SGA (borderline), but not PTD
 - However, increased mortality in highly malarious areas (Zanzibar)
- U.S.: iron-replete, non-anemic women until 28 wks gestation
 - ↓ LBW and PTD-LBW
 - ↓ gestational age, but no effect on PTD

Iron Supplementation and Pregnancy Outcomes

U.S. women until 28 weeks gestation (n=213)

	Iron supplement %	Placebo %	Risk difference
Birth weight (g)	3277	3072	206*
BW<2500 g (%)	4.3	16.7	-12.4*
Preterm (%)	12.8	12.5	0.3
PTD/LBW (%)	2.6	10.4	-7.8*

* p<0.05

Cogswell et al., AJCN 2003;78:773-81.

Multivitamins and Pregnancy Outcome Trials

- **Multivitamins**

- Nepal (2 studies): ↓ LBW, but no effect on PTD or SGA
- Tanzania (HIV+): ↓ LBW, severe PTD, and SGA
- Mexico: MV vs. placebo (60 mg iron)
No effects on LBW, SGA or PTD

Multivitamin Supplementation and Pregnancy Outcomes in HIV+ women

MV vs. placebo, HIV+ women in Tanzania (n=941)

	Multivitamins %	No multi- vitamins, %	Relative risk (95% CI)
BW<2500 g	8.8	15.8	0.56 (0.38, 0.82)
Preterm (<37 wks)	21.1	24.5	0.86 (0.68, 1.10)
Severe preterm (<34 wks)	6.2	10.2	0.61 (0.38, 0.96)
Small-for- gestational age	10.0	17.6	0.57 (0.39, 0.82)

Malaria in Pregnancy

- Malaria is more prevalent in pregnant than in non-pregnant women, especially HIV+
- Malaria prevalence and parasitemia are higher in first pregnancies (nulligravida) than in later pregnancies (multiparous)
- Maternal cellular immune response is suppressed in pregnancy (prevents rejection of foreign fetal antigens)
- Immune suppression may explain why malaria is more frequent and severe in pregnancy

Malaria and Poor Pregnancy Outcomes

- Malaria during pregnancy increases the risks of low birthweight, preterm birth, stillbirths and perinatal death
- Effects are more severe in first pregnancy and decrease with subsequent pregnancies
- Mechanisms:
 - Fetal/congenital malaria (parasites in cord blood)
 - Placental malaria (impaired placental function and inflammation)
 - Maternal malaria (anemia, fever)
- HIV+ women, adverse effects seen in all pregnancies

Malaria and PTD/IUGR

(versus normal weight-for-age infants)

	OR (95% CI)	Adjusted OR (95% CI)	OR (95% CI)	Adjusted OR (95% CI)
Cord blood parasitemia present	3.33 (1.36-8.18)	3.34 (1.26-8.82)	2.78 (0.98-7.89)	
Placental parasitemia present	2.40 (1.17-4.94)		1.99 (0.85-4.63)	
Maternal peripheral parasitemia, delivery	2.91 (1.36-6.26)		1.92 (0.76-4.81)	
Parasitemia &/or clinical malaria, antenatal	0.78 (0.39-1.56)		3.72 (1.21-11.43)	5.46 (1.55-19.29)

A.Sullivan, et al. *J.Inf.Dis.* 1999; 179:1580-3.

Smoking and Pregnancy Outcomes

- Smokers have smaller babies with higher infant mortality risk (across the BW distribution)
- LBW incidence in U.S. population (2002):
 - 12.2% among smokers, 7.5% among non-smokers
- Smoking associated with decreased BW and IUGR in cohort studies
- Randomized trials of smoking cessation: BW increases of 100-200 g
- Smoking associated with PTD (meta-analysis of 20 studies: RR ~ 1.27, CI 1.21-1.33)
- Smoking cessation offsets adverse effects

Smoking and Poor Pregnancy Outcomes: Possible Mechanisms

- Premature placental senescence – impairs placental function
- Carbon monoxide (CO) binds to hemoglobin, causing fetal hypoxia
- Nicotine and CO → vasoconstriction → ↓ blood flow
- Nicotine → increased BP & heart rate → ↓ uterine blood flow

Infant birth outcomes by maternal smoking during pregnancy

Smoking variable	Birth weight reduction (g)	Ponderal Index reduction (cm)
Light smoking continued	-135.57 ^a (13.49)	0.029 ^a (0.006)
Heavy smoking continued	-174.78 ^a (14.43)	0.040 ^a (0.007)
Stopping smoking by week 32 of pregnancy	-26.46 (17.86)	0.027 ^b (0.009)

a: p<0.001; b: p<0.01

Ponderal Index = birth wt/length³ x 100

Lindley A. Am J Epidemiol 2000; 152:219-25.

Illicit Drug Use and Poor Pregnancy Outcomes

- **Cocaine** use leads to ↑ LBW and heavier use has a greater effect (meta-analysis: Hulse, Addiction, 1997)
 - LBW RR for any exposure = 1.77 (1.15, 2.71)
 - BW reduction of 112 g (62, 161)
 - More frequent exposure → ↑ LBW risk
- Cocaine can cause premature labor, PROM and PTD
- **Marijuana and heroin** use: inconsistent findings of LBW and PTD effects

Illicit Drug Use and Poor Pregnancy Outcomes: Measurement Issues

- Need to control for other lifestyle factors such as smoking, alcohol use, low SES, etc.
- Studies based on maternal history of illicit drug use problematic (respondent recall)
- Biological measures of drug use more definitive, e.g. measurement of cocaine in blood or urine (acute use) or hair (chronic use)

Cocaine Use During Pregnancy and Intrauterine Growth Retardation

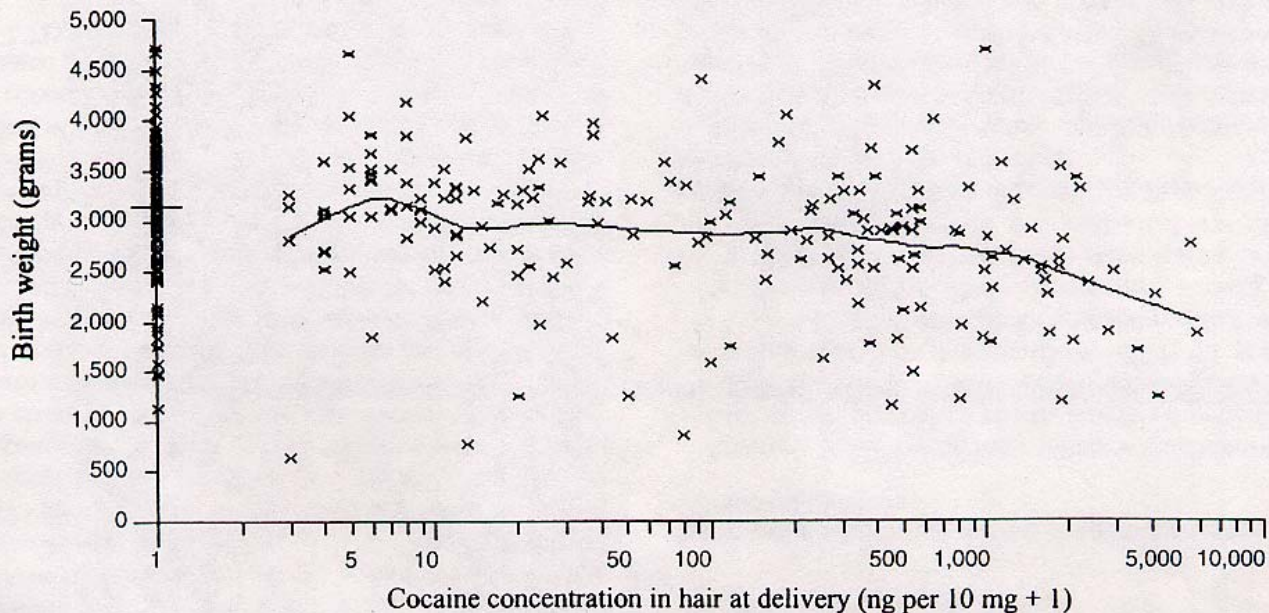


FIGURE 2. Smoothed scatterplot of birth weights (g) by cocaine concentration (ng per 10 mg) in the mother's hair at delivery among 339 women, New York City, 1990–1992. The plot was generated using locally weighted regression (LOWESS).

Source: Kuhn L, Kline J, Levin B, Susser M. Cocaine use During Pregnancy and Intrauterine Growth Retardation: New insights based on maternal hair tests. *Am J Epidemiol* 2000; 152:112-9. Copyright © 2000 Oxford University Press. All Rights Reserved

Antenatal Care (ANC)

- No ANC, fewer visits or delayed ANC associated with \uparrow LBW/PTD
- Is this because ANC reduces risk?
- Is this self-selection of higher risk women with poorer ANC attendance?
- What is the optimal ANC?

WHO Trial of ANC

(Villar *Lancet* 2001;357:1551)

- Clinic randomized trial
- Intervention: New reduced model ANC package (27 clinics)
 - Risk assessment screening at 1st visit then if at low risk, women receive 3 subsequent visits with screening for anemia, wt, BP, urine, syphilis, plus obstetric evaluation at 4th visit for detection of breech presentation
- Control: standard of care (26 clinics), i.e. more visits and intensive repeat assessments

WHO Antenatal Care Randomized Trial for the Evaluation of a New Model of Routine Antenatal Care

Outcome	New model	Standard model	Adjusted OR (95% CI)
Low birthweight (<2,500 g)	7.68%	7.14%	1.05 (0.97-1.15)
Preeclampsia/eclampsia	1.69%	1.38%	1.26 (1.02-1.56)
Postpartum anemia	7.59%	8.67%	1.01*
Treated urinary tract infection	5.95%	7.41%	0.93 (0.79-1.10)

* Effect was heterogeneous across sites and strata, therefore pooled estimates may hide site-specific effect. CI not shown because computational methods assume homogeneity.

Source: Villar J. Lancet 2001; 357:1551-64.

WHO Antenatal Care Randomized Trial

Pregnancy outcomes

Outcome	New model (11,672) %	Standard model (n=11,121) %
Small for dates	15.2	15.1
Preterm delivery (< 37 wks)	7.9	7.7
Very low birthweight (<1,500 g)	1.1	1.0
PROM (< 35 wks)	0.7	0.6
Apgar score 1 min. <7	3.5	3.2
Admission to neonatal intensive care >2 days	5.4	6.4
Fetal death	1.4	1.1
Perinatal mortality	2.0	1.7

Source: Villar J. Lancet 2001; 357:1551-64.

WHO Antenatal Care Randomized Trial Referral and Hospitalization

	New model (11,672)	Standard model (n=11,121)
Any referral to higher level of antenatal care	1583 (13.4%)	811 (7.3%)
Hospital admissions for women referred	524/1563 (33.5%)	420/811 (51.8%)

Source: Villar J. The Lancet 2001; 357:1551-64.

WHO Trial Conclusions

- In women with no current or prior pregnancy complications, reduced number of ANC visits and goal-oriented activities does not increase the risks of adverse outcomes
- Simplification of ANC could reduce costs, increase attendance and is acceptable to staff and patients

Fetal Fibronectin Measurement and PTD

- Fibronectin is a basement membrane protein produced by the fetus and placenta and probably promotes adherence of the chorioamniotic membranes to the endometrium
- Elevated fetal fibronectin is thought to indicate disruption of chorion-decidual interface
- Fetal fibronectin detected in the vagina during 2nd trimester is predictive of PTD (RR ~ 60)
- 3-4% of women have positive fibronectin

Fetal Fibronectin and PTD

Fetal Fibronectin (ng/mL)	n	% births <28 wks GA	% births <37 wks GA
0	2253	1.2	8.9
1-24	3341	2.3	12.4
25-49	378	4.8	15.9
≥50	536	7.8	22.0

Tocolytics to delay labor

- Drugs
 - Oxytocin receptor antagonists (Atosiban)
 - Calcium channel blockers (nifedipine)
 - Beta mimetics
 - MgSO₄
- Trial outcomes
 - Delayed onset of labor
 - Infant outcomes
 - Maternal complications

Randomized trials Cochran reviews

- Cytevai Obstet Gynecol 1999;94:869
 - Delayed labor 7 days, OR = 0.6 (.4-0.95) for:
 - Betamimetics, atosiban, indomethacin
 - No improvement in neonatal outcomes
 - CVD and respiratory maternal complications

Cochran Review of Oxytocin antagonists (Atosiban) vs placebo.

(Cochran Data Base Review 2005:20:CD004452)

- Prevention of labor 20-36 weeks
- 6 RCTs
 - No reduction of PTD
 - No improvement in neonatal outcomes
 - One trial IMR RR 6.2 (1.4-27.2)
 - Births <1500 gm RR 1.96 (1.2-3.4)

Meta-analysis

(Tan Singapore Med J, 2006;47:361)

- Delayed delivery 24 hours
 - OR = 0.54 (0.3-0.9)
- Delayed delivery 48 hours
 - OR = 0.47 (0.3-0.8)
- Immediate outcomes, not PTD or neonatal health