PRETERM BIRTH:

Progesterone

&

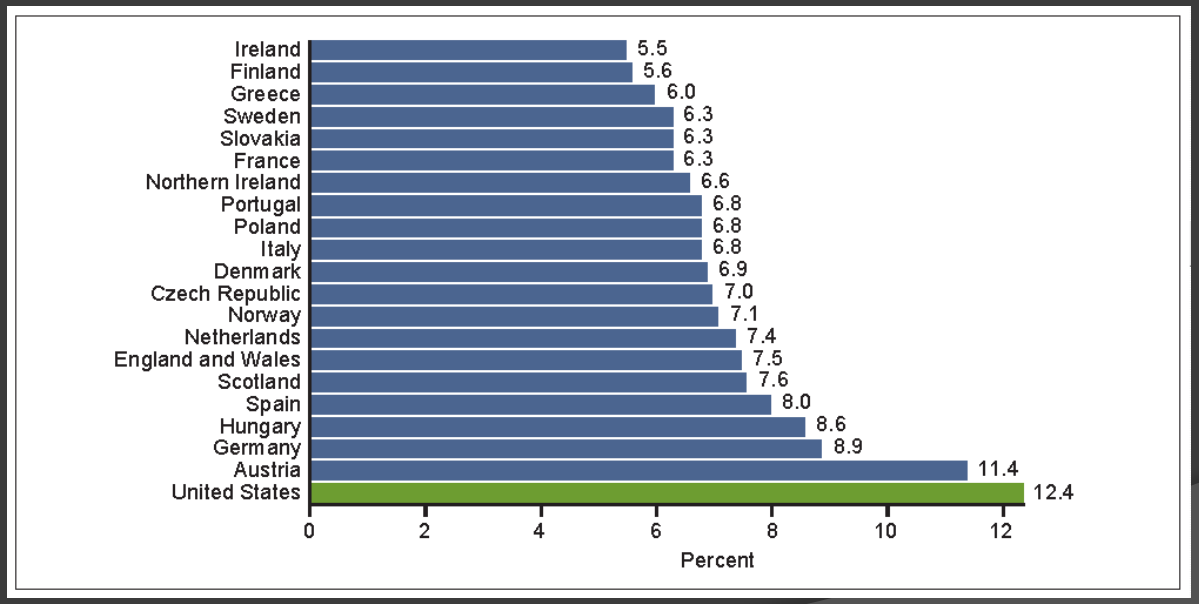
Beyond

Preterm Birth: The BIG Picture

- Recent trends in the PTB rate
  - Where have we seen improvements?
  - What things work and how much to they help?
- Is there anything we can do that does not involve a vaginal probe and some P?
- Where are the next opportunities?

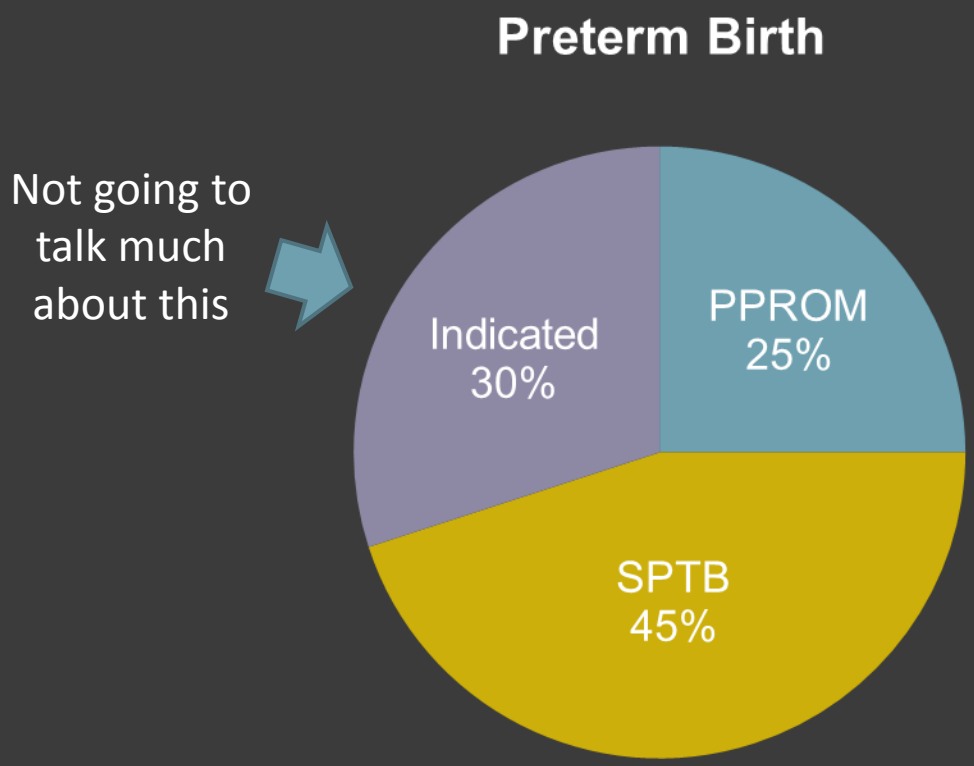
Preterm Birth: Epidemiology

- 4M births in US annually
- Around +/- 500,000 PTBs in US each year
- 35% of deaths in first year of life
- Direct costs = $26B



http://www.cdc.gov/nchs/data/databriefs/db23.htm

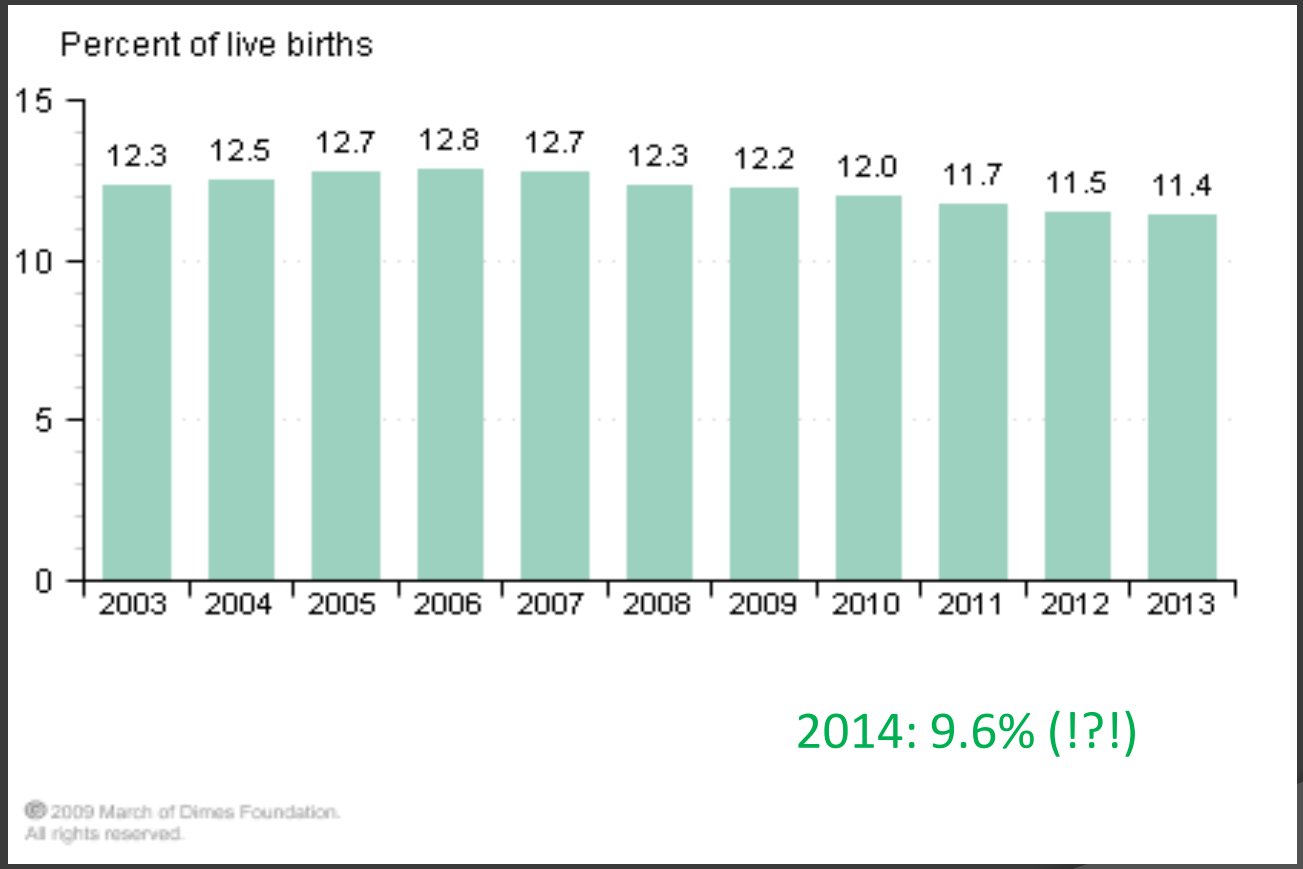
Preterm Birth: Epidemiology



Goldenberg 2008

Preterm birth

United States, 2003-2013



Preterm is less than 37 completed weeks gestation.
Source: National Center for Health Statistics, final natality data. Retrieved November 5, 2015, from www.marchofdimes.org/peristats.

Risk factor	PTB attributable risk (% of PTB due to risk factor)	Approximate impact	Decrease in total PTB rate (% of ALL births)	Comments
Teen births	~ 17% of PTBs occur in teens	28,100 fewer PTB	0.8%	Teen births have declined from 10.1% to 6.9% since 2006
AMA	~ 17% of PTBs occur in women $\geq$ 35	7600 fewer PTB	0.2%	Slight increase in AMA births but PTBs were decreased
Twins	~ 13% of PTBs are due to twins	7500 fewer PTB	0.2%	Twin births were increased but PTBs were reduced
Triplets	< 1% of PTBs are due to triplets	1600 fewer PTB	NS	4400 triplets/yr born in US

Schoen 2015

Progesterone: The current dogma

- ACOG/SMFM recommendations
- Best state-of-the-art consensus
- Works in progress
- Three groups:
  - No prior PTB
  - Prior PTB
  - Twins
- Two subsets
  - Normal (or unknown) CL
  - “Short” CL

		Intervention	
		Vaginal P	17OHP-C
Risk Group	Prior SPTB, normal CL		
	Prior SPTB, short CL		
	No prior SPTB, normal or unknown CL		
	No prior SPTB, short CL		
	Multiple gestation, normal or unknown CL		
	Multiple gestation, short CL		

What works?

- 17OHP-C
  - Meis trial demonstrated 34% reduction of PTB < 37 weeks and 42% reduction of PTB < 32 weeks
  - Should be offered to all women with singleton pregnancies and h/o SPTB 20-36^{6} starting at 16-20 wks
  - Can start as late as 27 wks
  - Remains cost-effective even at current price
    - Meis 2013

17OHP-C

Table 2. Outcomes of Pregnancy According to Treatment Assignment.*

Outcome	Progesterone Group (N=306)	Placebo Group (N=153)	Relative Risk (95% CI)
	no. (%)		
Delivery before 37 wk of gestation	111 (36.3)	84 (54.9)	0.66 (0.54–0.81)
Spontaneous	90 (29.4)	69 (45.1)	0.65 (0.51–0.83)
Indicated because of complications	21 (6.9)	15 (9.8)	0.70 (0.37–1.32)
Black women	64 (35.4)	47 (52.2)	0.68 (0.51–0.90)
Nonblack women	47 (37.6)	37 (58.7)	0.64 (0.47–0.87)
Delivery before 35 wk of gestation	63 (20.6)	47 (30.7)	0.67 (0.48–0.93)
Delivery before 32 wk of gestation	35 (11.4)	30 (19.6)	0.58 (0.37–0.91)

Is vaginal or oral P as good as 17OHP-C for women with previous SPTB?

Trial	Population	Intervention	Outcome	Comment
da Fonseca 2003	142 women, 90% prior SPTB	100 mg vaginal P	RR 0.48 (0.25–0.96)	
O'Brien 2007	659 women with prior SPTB	90 mg vaginal P gel	NS	Patients with short CL excluded
Rai 2009	148 women with prior SPTB	100 mg po BID	39% vs 60% p = 0.002	
Glover 2011	33 women with prior SPTB	400 mg po qday	NS	

I recommend vaginal P per da Fonseca for women that decline 17OHP-C

Previous SPTB

- Okay, so you have your patient with prior SPTB on 17OHP-C
- Do you need to monitor her cervix?
- What if the cervix gets short?
  - Cerclage?
  - Vaginal P?
  - Pessary?

Cerclage

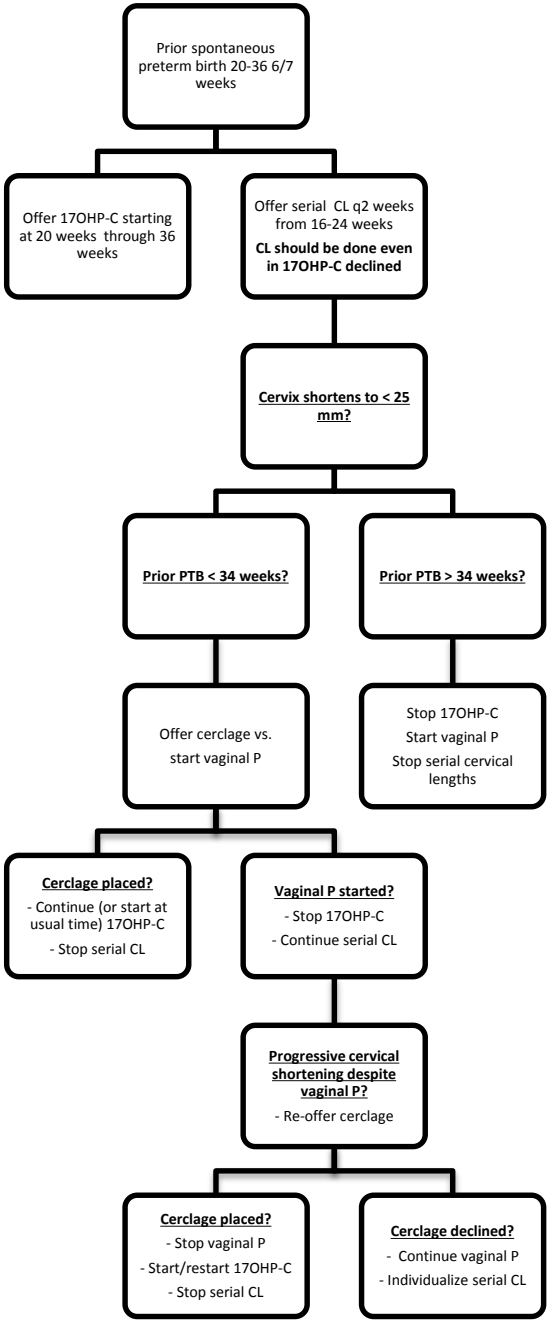
- Owen 2009
  - 302 women with previous SPTB < 34 weeks (some getting 17OHP-C), cervix < 25 mm randomized to cerclage vs. routine care
  - PTB reduced 32% vs. 42%
  - Birth < 24 weeks, PNM also reduced
  - Birth < 35 weeks reduced in group with cervix **< 15 mm**
- Berghella 2011, meta-analysis, 5 trials
  - Confirms above conclusions

Vaginal P

- 1 RCT (Cetingoz 2011), one secondary analysis (DeFranco 2007) and individual patient-level data meta-analysis (IPD-MA) (Romero 2012) all indicate benefit of vaginal P with prior SPTB and short cervix
- IPD-MA (Conde-Agudelo 2013) indicates equal efficacy of vaginal P vs. cerclage in this scenario

What does work?

- Serial TVUS for 17OHP-C patients
  - q 2 weeks 16-24 weeks (q week if < 30 mm)
  - If cervix < 25 mm offer cerclage (if qualifying PTB < 34 weeks) or switch to vaginal P – equally efficacious
    - I favor cerclage for cervix < 15 mm and vag P if cervix 15-25 mm
  - Don’t use vag P and 17OHP-C together
  - Continue/start/restart 17OHP-C if cerclage placed
    - Stetson Obstet Gynecol 2016 128:983


Prior spontaneous preterm birth 20-36 6/7 weeks
Offer 17OHP-C starting at 20 weeks through 36 weeks
Offer serial CL q2 weeks from 16-24 weeks
CL should be done even in 17OHP-C declined
Cervix shortens to < 25 mm?
Prior PTB < 34 weeks?
Prior PTB > 34 weeks?
Offer cerclage vs. start vaginal P
Stop 17OHP-C
Start vaginal P
Stop serial cervical lengths
Cerclage placed?
- Continue (or start at usual time) 17OHP-C
- Stop serial CL
Vaginal P started?
- Stop 17OHP-C
- Continue serial CL
Progressive cervical shortening despite vaginal P?
- Re-offer cerclage
Cerclage placed?
- Stop vaginal P
- Start/restart 17OHP-C
- Stop serial CL
Cerclage declined?
- Continue vaginal P
- Individualize serial CL

		Intervention	
		Vaginal P	17OHP-C
Risk Group	Prior SPTB, normal CL	Mixed	Yes
	Prior SPTB, short CL	Yes	Add cerclage or switch to vaginal P
	No prior SPTB, normal or unknown CL		
	No prior SPTB, short CL		
	Multiple gestation, normal or unknown CL		
	Multiple gestation, short CL		

How about women with no prior PTB and a short cervix?

Trial	Population	CL cutoff	Incidence	NNS NNT	Intervention	Outcome
Fonseca 2007	250	15 mm	1.7%	604 14	100 mg vaginal P	RR 0.58 (0.25-0.96)
Hassan 2011	458	10-20 mm	2.3%	387 7	90 mg P gel	RR 0.55 (0.33-0.92)
Grobman 2012	657 para 0	< 30 mm			17OHP-C	NS

Universal TVUS CL screening is a tough sell

- Sonographer revolt
- What if you live in a place with no vaginal probe?
- QC (CLEAR, etc.)
- Many institutions use a TA approach with 35 mm cutoff to reflex to TVUS
  - Lower sensitivity (80-90%)
  - > 50% of women still get a TVUS
- Many report lower incidence of short cervix than advertised
- HOWEVER – several published trials showing improved PTB rates in practice!!
- NOT an “official” ACOG recommendation currently

		Intervention	
		Vaginal P	17OHP-C
Risk Group	Prior SPTB, normal CL	Mixed	Yes
	Prior SPTB, short CL	Yes	Add cerclage or switch to vaginal P
	No prior SPTB, normal or unknown CL	No studies	No
	No prior SPTB, short CL	Yes	No
	Multiple gestation, normal or unknown CL		
	Multiple gestation, short CL		

What to do with multiples??

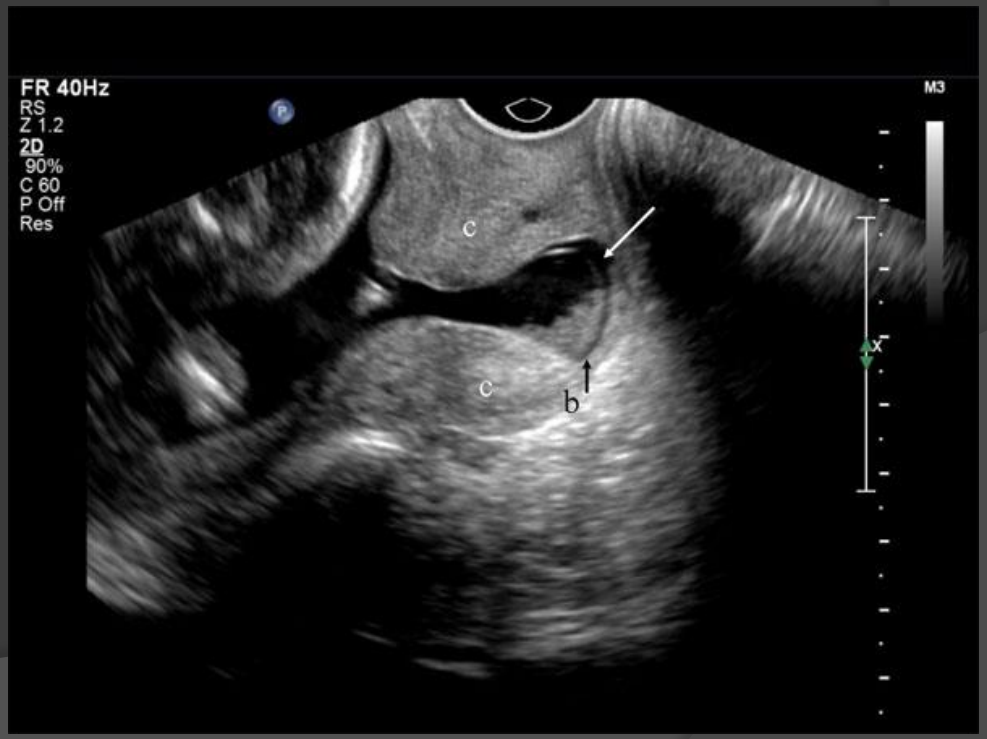
- 17OHP-C does not work! (Combs 2011, Rouse 2007)
- Vaginal P: studies using vaginal P (both for all twins and for twins with a short cervix) are mixed
  - Brubaker 2015 – Worse outcomes
  - Romero 2012 – Less PTB, reduction in NN morbidity
  - Jardes SR/MA 2017 RR 0.82 (NS), less VLBW and vent
- How about cerclage? How about pessary?

Cerclage for twins

- No great studies!!
- Berghella 2005, IPD-MA – Composite of three studies over several years plus some unpublished patients
  - Significant **increase** in PTB < 35 weeks in twins with short cervix, RR 2.15 (1.15-4.01)
- Three other meta-analyses show worse outcome or no effect on PTB
  - Jorgensen 2007
  - Rafael 2014
  - Saccone 2015
  - Jarde 2017
- Recent reanalysis stratified by cervical length shows **4 week pregnancy prolongation** for twins with CL < 15mm! Roman 2015

Cerclage for twins

- My personal bias: Cerclage has a role in twins, just not sure which twins!
- Need to define appropriate patient selection criteria
- Ripe for an RCT!



		Intervention		
		Vaginal P	17OHP-C	Comment
Risk Group	Prior SPTB, normal CL	Mixed	Yes	Consider vaginal P if decline 17OHP-C
	Prior SPTB, short CL	Yes	Add cerclage or switch to vaginal P	Prefer cerclage if CL < 15 mm
	No prior SPTB, normal or unknown CL	No studies	No	
	No prior SPTB, short CL	Yes*	No	
	Multiple gestation, normal or unknown CL	No	No	Cerclage likely to make it worse
	Multiple gestation, short CL	Mixed	No	NO cerclage for CL < 25 ? Cerclage if CL < 15mm

Pessary

Trial/Year	Entry	Significant findings
Goya	Singleton, short cx	PTB OR 0.18
Nicolaides	Singleton, short cx	RR PTB 1.12
Jarde 2017	SR/MA Twins	NS
Saccone 2017	SR/MA Twins	NS

SMFM: Unapproved device, unapproved indication, don't do outside of clinical trial

So how much does all of this affect the PTB rate??

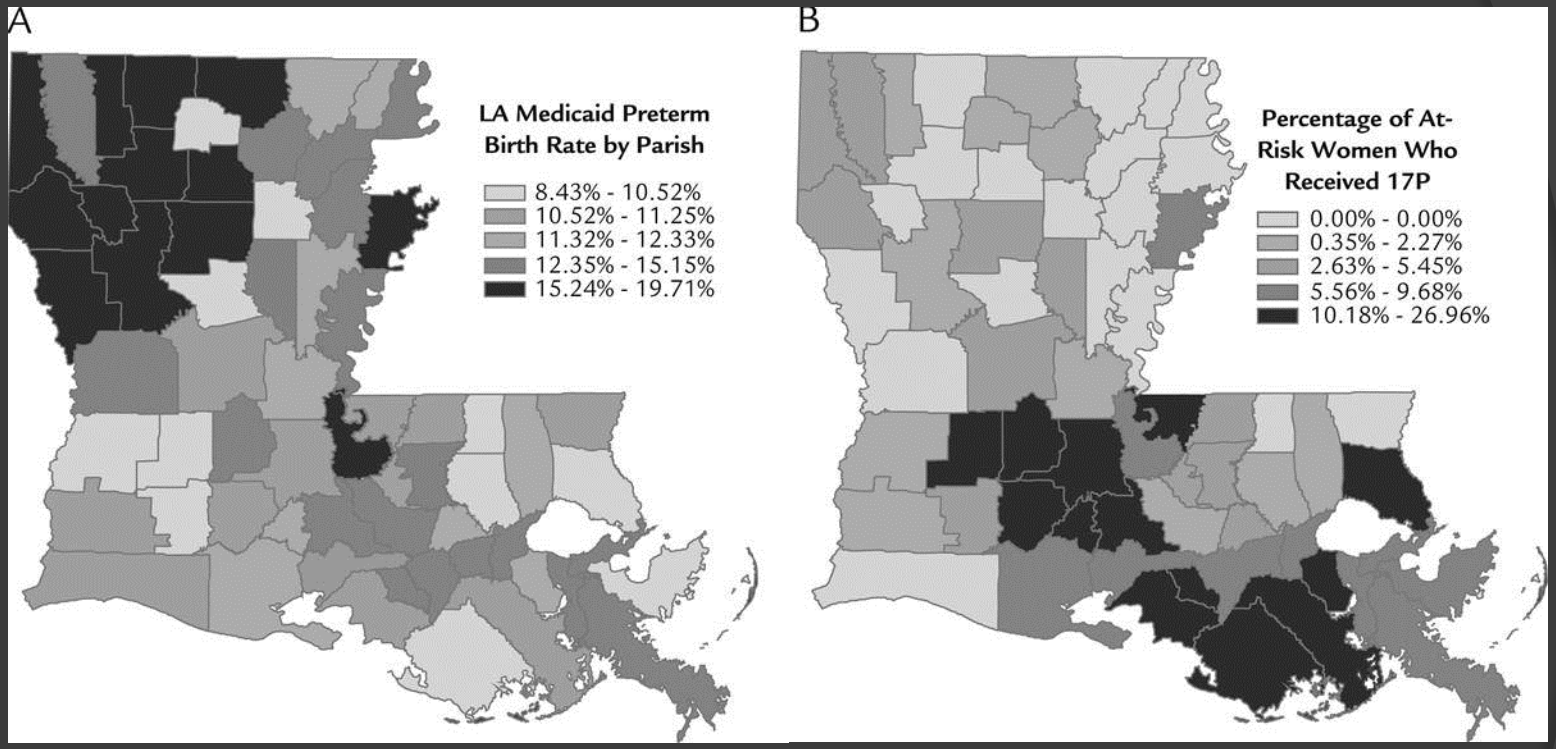
Intervention	Number of PTBs prevented	Reduction in PTB rate	Reference
17OHP-C	10,000	0.3	Petrini 2005
TVUS screening, previous SPTB	23,000	0.7	Berghella 2011
TVUS screening, no previous SPTB	19,000**	0.6	Werner 2011

** Optimistic, implementation issues, etc.

Reducing PTB: Why this is so hard!

- Example:
  - 17OHP-C reduces the recurrent SPTB rate by 34% - **a pretty huge effect!**
  - How much will this reduce PTB?
  - 4M births per year in US
    - 58% occur in parous women
    - 8% of parous women have a h/o SPTB 20-36[6]
    - 88% get care in time
  - **If all get 17OHP-C**, the PTB rate is reduced by 0.3% (i.e., from 12% to 11.7%)

Reducing PTB: Why this is so hard!



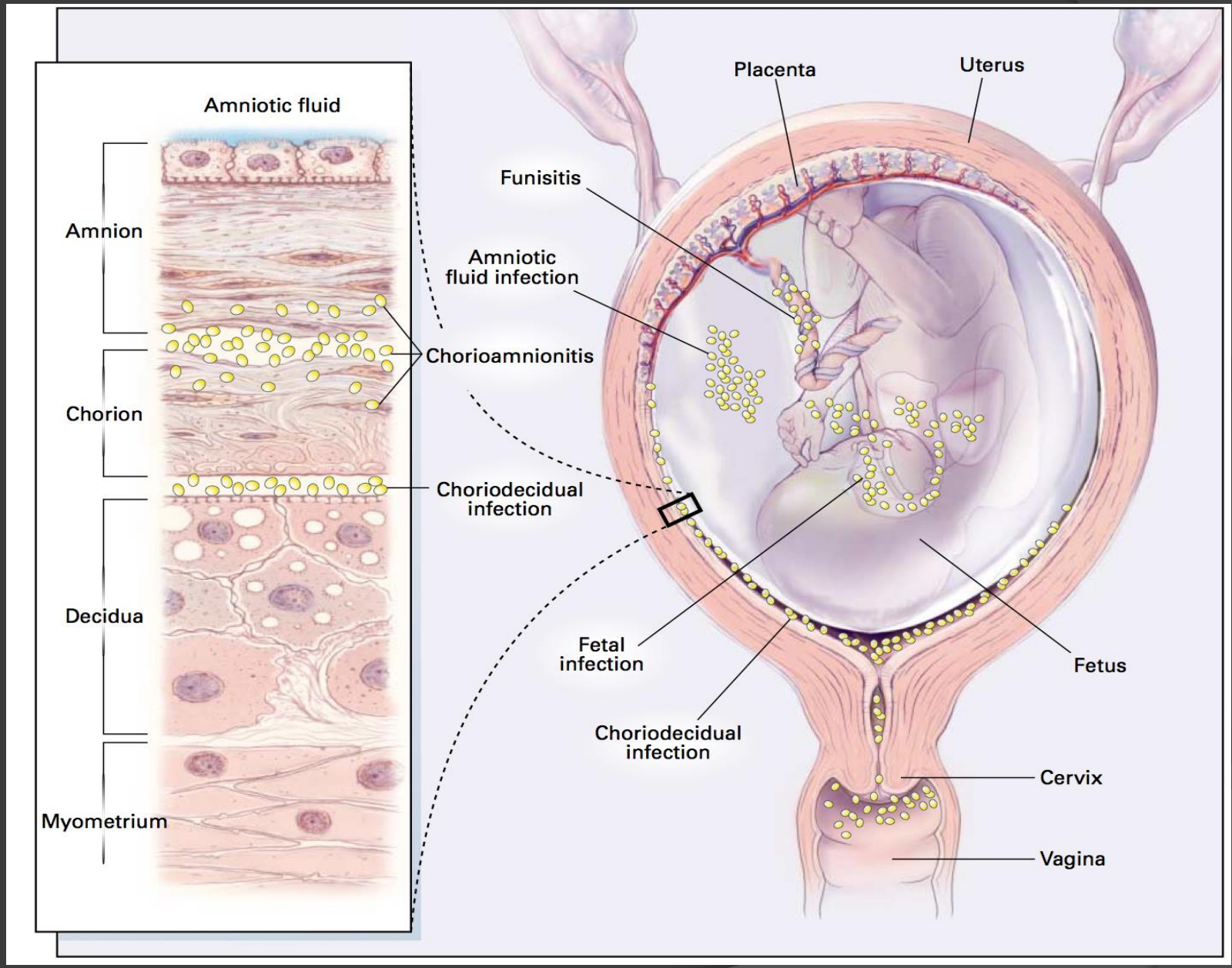
Overall 17% of eligible patients received 17OHP-C…

Reducing PTB: Why this is so hard!

- It doesn't do any good to discover a great new prevention strategy if it isn't implemented!!
- Barriers
  - Provider education
  - Payers
  - Access
  - Logistics
  - Etc.

Is there anything we can do that does not involve a vaginal probe and some P?

- Urogenital infection
- Teen pregnancy
- Cigarettes



Goldenberg 2000

Infection and PTB

- The data linking genital tract microbiome, infection/inflammation and PTB are incredibly robust and compelling
- The intervention trials have been disappointing
- The causal pathways remain incompletely understood
- We need more studies!!

Teen Pregnancy: What to do?

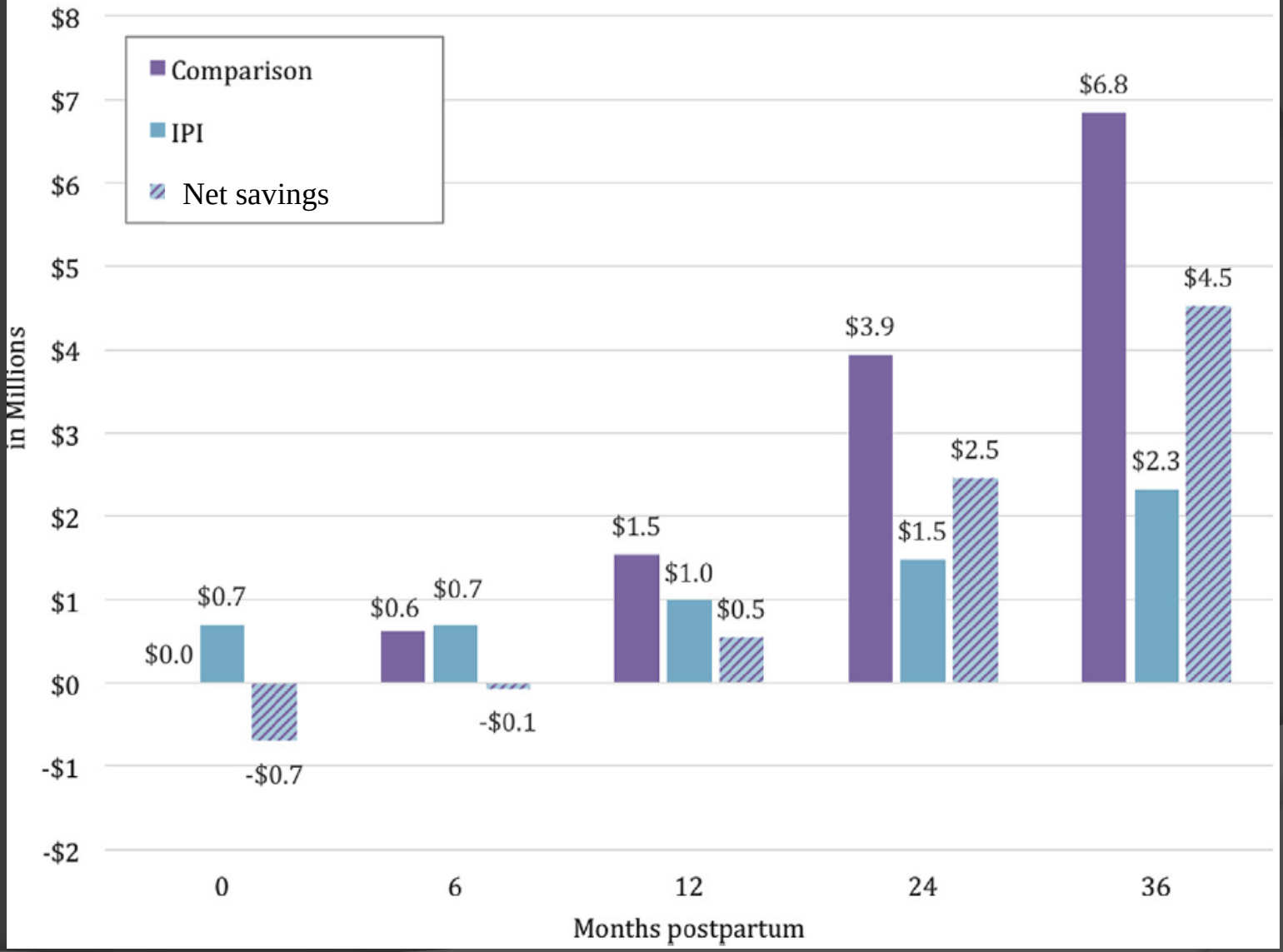
- 17% of PTBs
- Teen pregnancy rate has fallen 10.1% -> 6.9% over last decade – still higher than rest of developed world!
- Major contribution to fall in total PTB rate
- Teen pregnancy prevention mired in social politics
- How about if we give all teens FREE immediate postpartum contraception??

Teen Pregnancy

- Colorado Adolescent Maternity Program (CAMP) Study
- Immediate Postpartum Implant (IPI) vs standard
- IPI (Nexplanon) paid by grant as not generally covered
- Tracked both groups for 36 months
- Repeat pregnancy rate at 36 months in IPI group was 18%
- Rate in control group was 84%
  - Han 2014

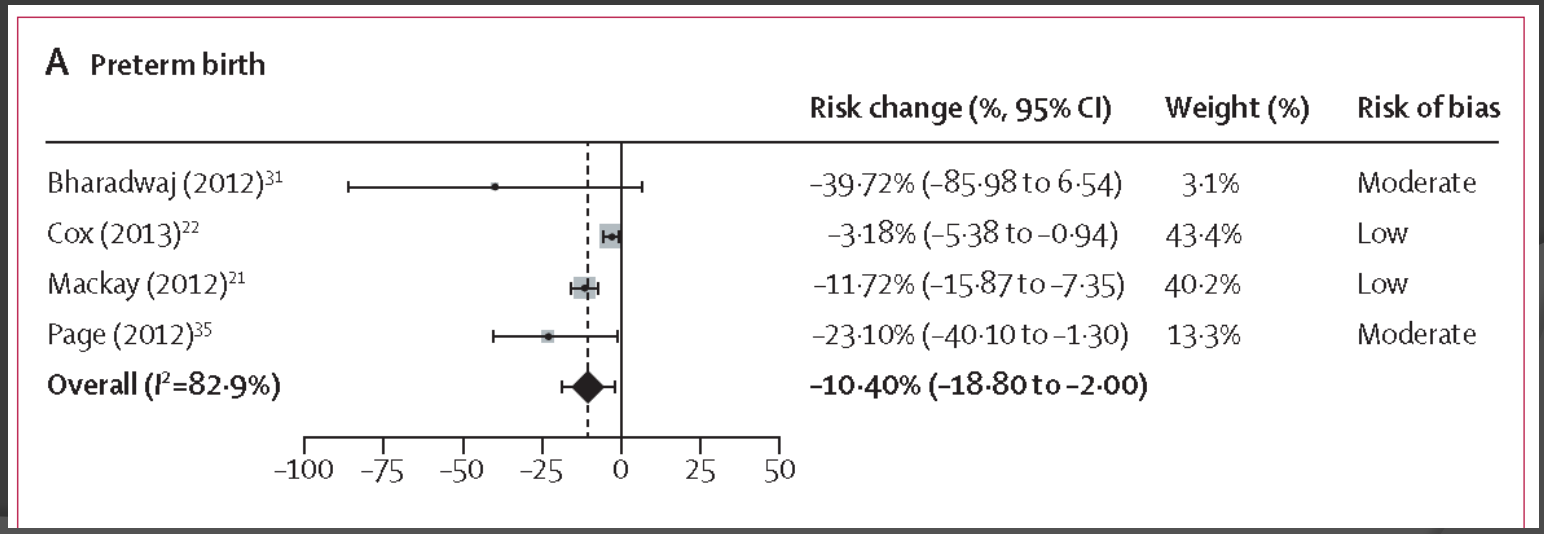
FIGURE 2

Total and net costs per 1000 women



Smoking

- PTB PAR due to smoking 4-13% (as many as 60,000 PTBs annually)
- Effect of smoke-free legislation on perinatal and child health: a systematic review and meta-analysis (Been 2014)
- 11 studies (6 Europe – national bans; 5 US – local bans)



Second hand smoke

- 691 non-smoking AA women reporting SHS randomized to behavioral intervention
- PTB < 34 weeks reduced in intervention group (OR 0.22, 0.07-0.68)
- In group with serum cotinine < 20 ng/mL (true non smokers), PTB < 34 weeks also reduced (0.5 vs 5.5%, p=0.01)
  - El-Mohandes 2010

Summary

- We have a long way to go!!
- We have some things that work – USE THEM!!
  - 17OHP-C
  - Vaginal P
  - Cerclage

Summary

- Don’t forget Public Health
  - Teens
  - Smoking
- Things I skipped entirely
  - Aspirin
  - Mental health

Summary

- Areas in desperate need of research
  - Twins – we need an evidenced-based intervention
  - Infection – we need intervention trials
  - LDA – beyond pre-e prevention
- We will be more successful with incremental changes in large populations than with big changes in small populations