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Prevention of preterm birth in twins

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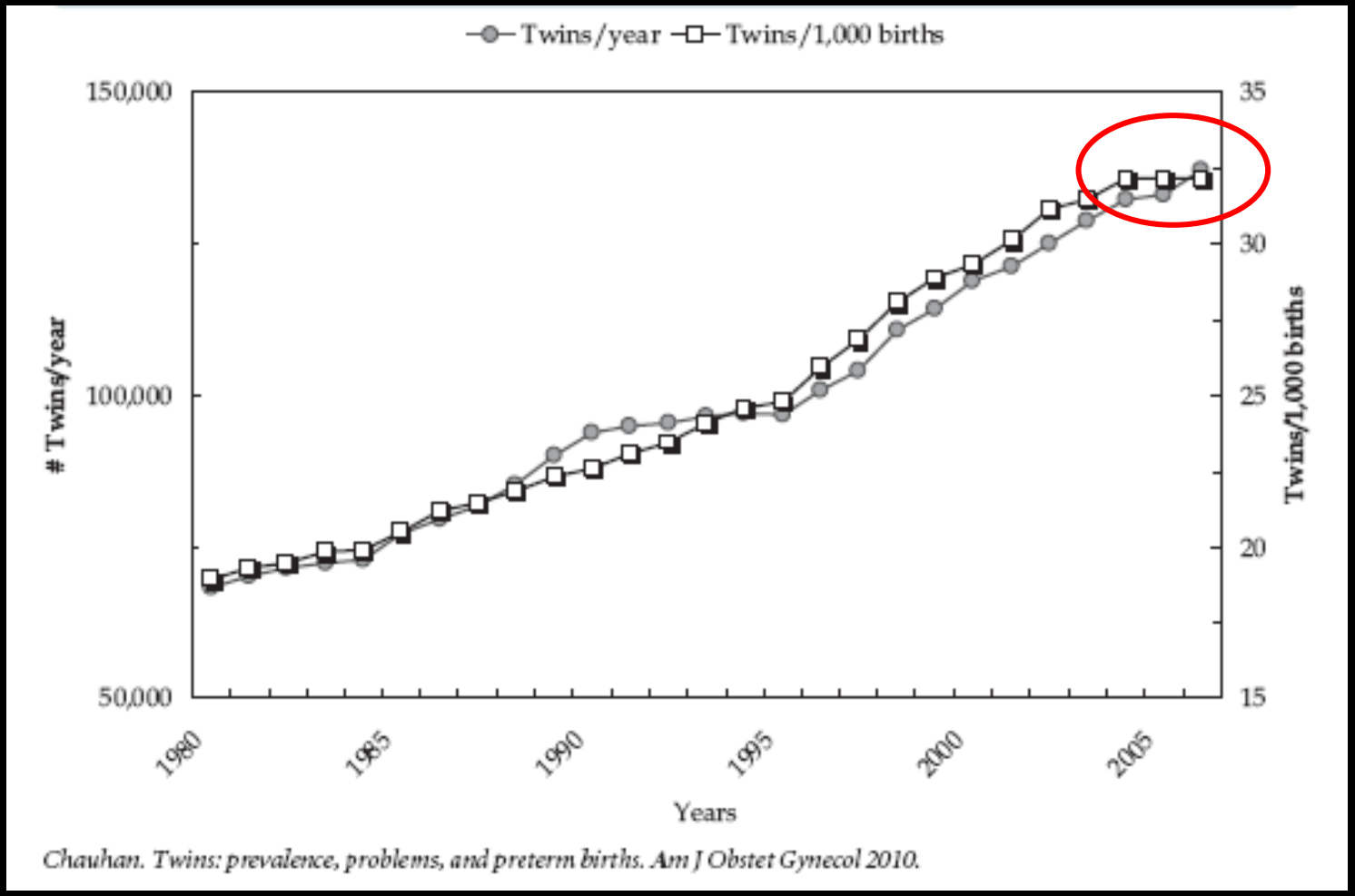
Twin deliveries and birth rate in USA



Chauhan eta al: Am J Ob Gyn,2010

ART births

Europe

Nyboe-Andersen *et al.*, 2004

twins: ~ 25%

triplets 1.5%

USA

SART and ASRM, 2004

twins: 30.8%

triplets 3.9%

High rates of MZ twins (1-5%) among ART births. **Blickstein, 1999**

Prevention of preterm birth in twins

1. **Complications twins vs. singleton**
    1. As for pregnant women
    2. As for neonates
2. **Tests in asymptomatic twins to prevent preterm birth**
    1. U/S measurement of cervical length
    2. Fetal fibronectin
3. **Treatment during pregnancy to prevent preterm birth**
    1. Tocolytics
    2. Progesterone
    3. Cervical cerclage
    4. Bed rest, home monitoring
4. **Treatment of preterm labor in twins**
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Differences in pregnancy according the number of fetuses

	Initial number of fetuses		
	1	2	3
Deliveries	7650	2470	390
PIH	4,8	8,3	11,0
PPROM	3,1	7,9	13,1
Hospitalization	12,2	30,6	76,9
Cesarean Section	26,1	57,0	89,5

ESHRE Capri Group, Hum Reprod, 2000

Risks of twin pregnancies for the woman

- Twin pregnancy increases the risk for
  - Hypertension
  - Premature rapture of membranes
  - Hospitalization
  - Cesarean Section

Pregnant woman is in more danger
in twin than in singleton pregnancy !!!

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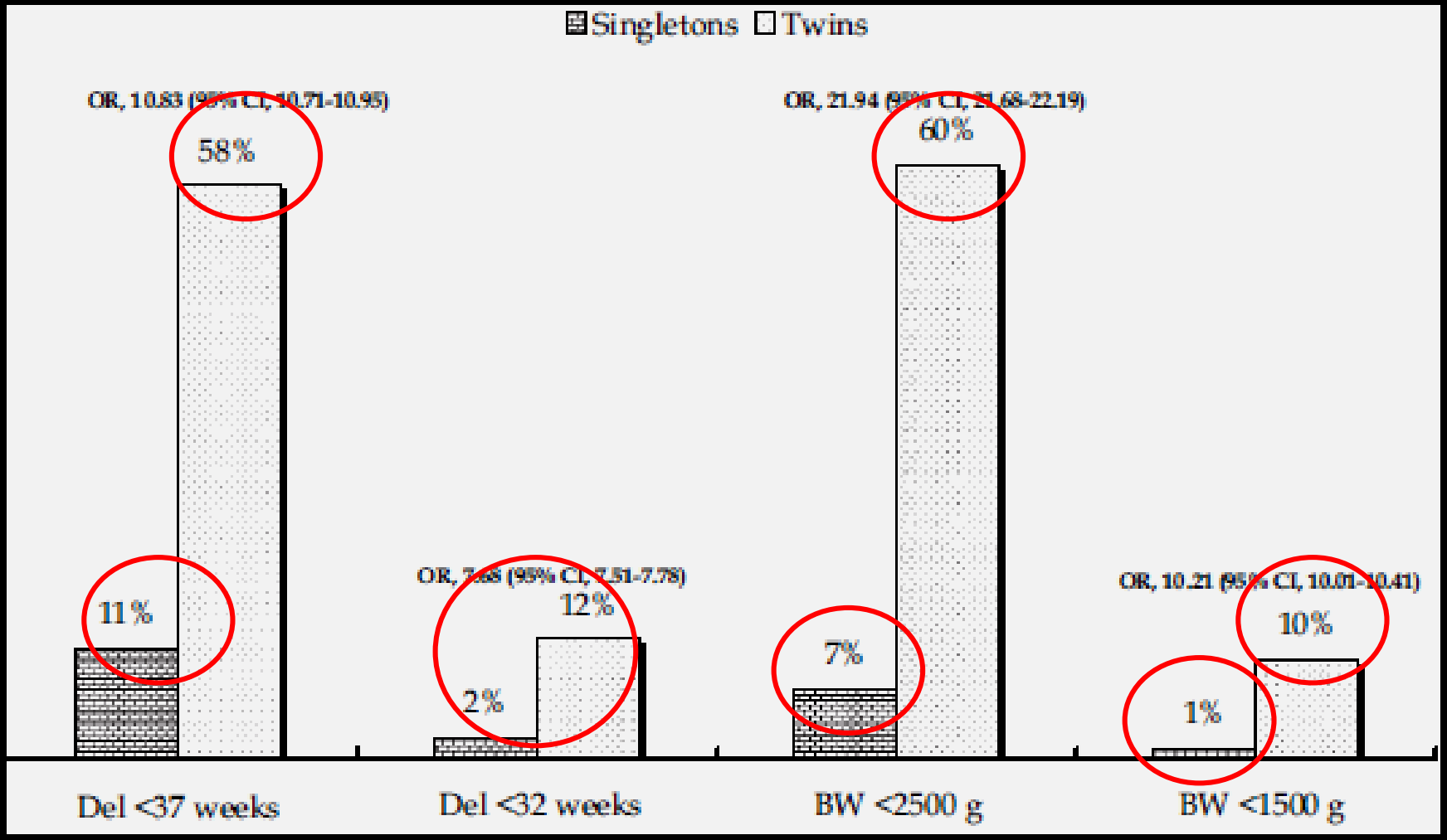
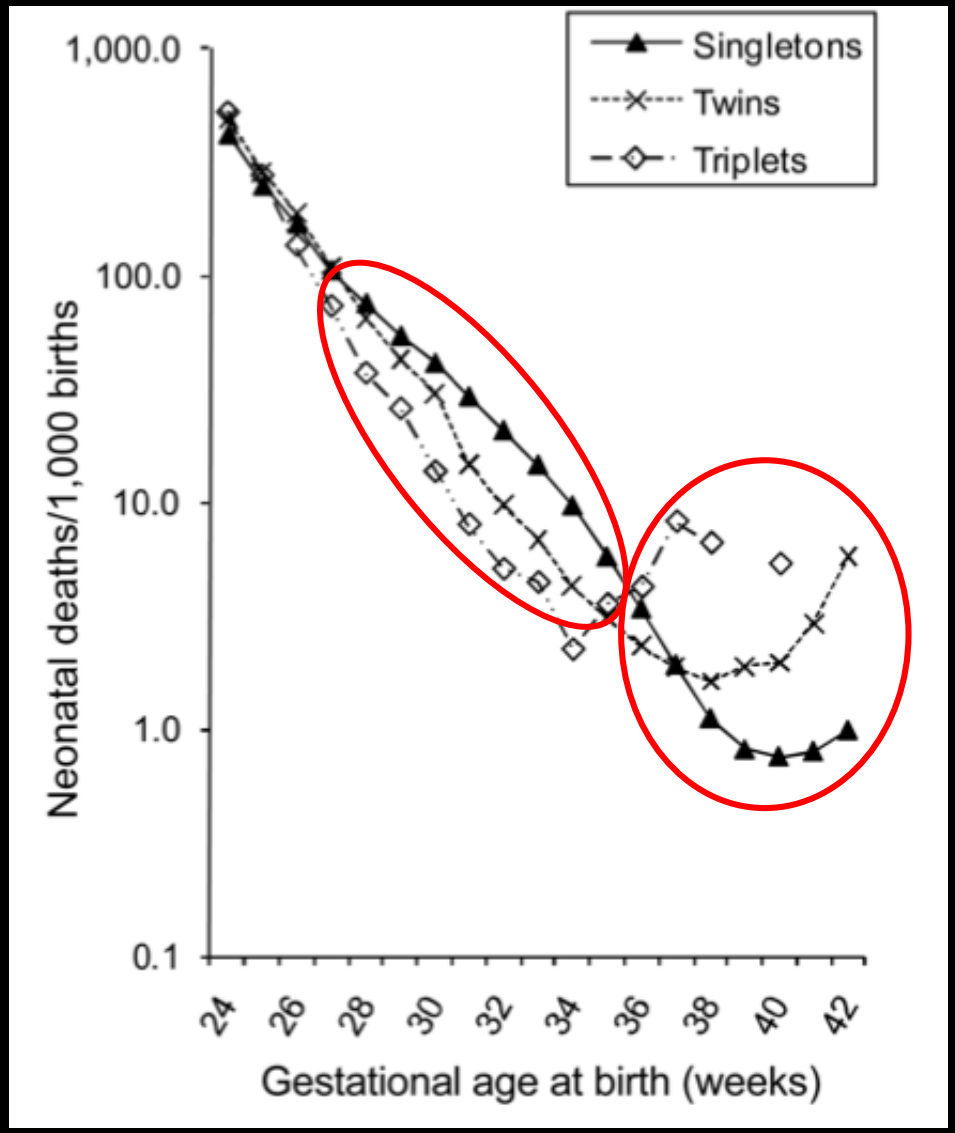
Preterm birth in 2006
Twins vs. Singletons



Martin JA,et al: Nat Statist Rep, 2009

Gestational-age-specific neonatal mortality rates in singletons, twins, and triplets



Basso O: Epidimiol, 2010

Mortality and morbidity in multiples till infancy

	1	2	3	4
Cerebral palsy	0	x4	x17	
Infant mortality	0	x7	x20	
Major handicap	0	0	20%	50%
NICU admission	<2%	x12	x38	x50
Birth weight	3500	2347	1687	1309
Gestational age	39.5	35.5	32.2	29.5

Norwitz , 2005

Risk associated with a twin pregnancy. Offspring

	Twins	vs.	Singletons
Stillbirth rate	14.2	vs.	4.4
Early neonatal mortality rate	22.8	vs.	2.9
Late neonatal mortality rate	3.9	vs.	0.8
Post-natal mortality rate	6.3	vs.	2.4
Infant mortality rate	33.0	vs.	6.1

Doyle, 1996

- **Risk of cerebral palsy**

Odd ratio: 10.2 compared with singletons

Petridou et al., 1996

Twins complications as for fetuses and neonates

- Increasing of prematurity
  - < 37 & <32 weeks
  - <2500 & <1500 grams
- In twins it is increased:
  - Fetal death
  - Neonatal death
  - Infant death
  - Cerebral palsy
  - Risk of fetal anomalies
- The probability to have a serious illness till the age of 2 is increasing .

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Interventions used to diagnose and prevent preterm birth

- Perinatal care
- Risk scoring
- Cervical cerclage
- Quit of smoking and alcohol using
- Psychological support
- Dietological interventions
- Ca & Mg
- Aspirin
- Progesterone

- Education in preterm labor manifestations
- Home monitoring
- Tocolytic therapies
- Bed rest
- Hydration
- Prenatal examinations for infections
- Antibiotics in premature contractions

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Tests to diagnose preterm birth in asymptomatic twin pregnancies

Variable	Gestational week <28	<30	<32	<34	<37
Negative fetal fibronectin level: 135 births, %	2.1	2.9	4.5	<11.5	46
Negative fetal fibronectin level and transvaginal cervical length ≥20 mm: 120 births, %	1.6	2.4	4.2	10.3	43
Either positive fetal fibronectin level or transvaginal cervical length <20 mm: 24 births, %	13.3	9.5	8.3	26.1	77.3
Positive fetal fibronectin level and transvaginal cervical length <20 mm: 11 births, %	50	33.3	54.5	54.5	100
P value	< .001	.001	< .001	< .001	< .001

Routine use of diagnostic tests can ascertain which pregnancy will be delivered prematurely, but should NOT be expected to decrease the preterm birth rate!!!

Fox NS et al: Am J Ob Gyn, 2009

Cervical length in asymptomatic twin pregnancies as a predictor of PTD

- Cervical shortening between 22 and 27 weeks
- Single cervical length (CL) measurement at 22

- The performance of cervical shortening for the prediction of preterm delivery of asymptomatic twins before 34 weeks ***does NOT differ*** from that of CL measurements at 22 or 27 weeks.

Leveque C: J Matern Fetal Neonatal Med. 2015

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Treatments during pregnancy to prevent preterm birth in twins

- Prophylactic use of oral betamimetics
  - 😐 Birth <37 weeks of gestation (RR,0.85), <34 weeks of gestation (RR,0.47)
  - 😐 Birthweight <2500 grm (RR,1.19)
  - 😐 Neonatal mortality (RR, 0.80) **Yamasmit W et al: Cohr, Syst Rev, 2012**

The use of prophylactic tocolysis should not be undertaken to prevent preterm birth in twins !!!

Combs, Am J Obst Gynecol, 2011

- Bed rest
  - ☹ Birth <34 weeks of gestation (RR,1.84) **Crowther CA et al: Cohr, Syst Rev, 2001**
- Home monitoring
  - ☹ Not beneficial in prevention of PTB **Colton T et al: Obstet Gynecol, 1995**

Progesterone and risk of preterm delivery in twins with cervical length <30mm and history of PTD

Table 3 Maternal and infant outcomes according to treatment with progesterone ($n = 17$) or placebo ($n = 30$) in women with twin pregnancy and cervical length ≤ 30 mm

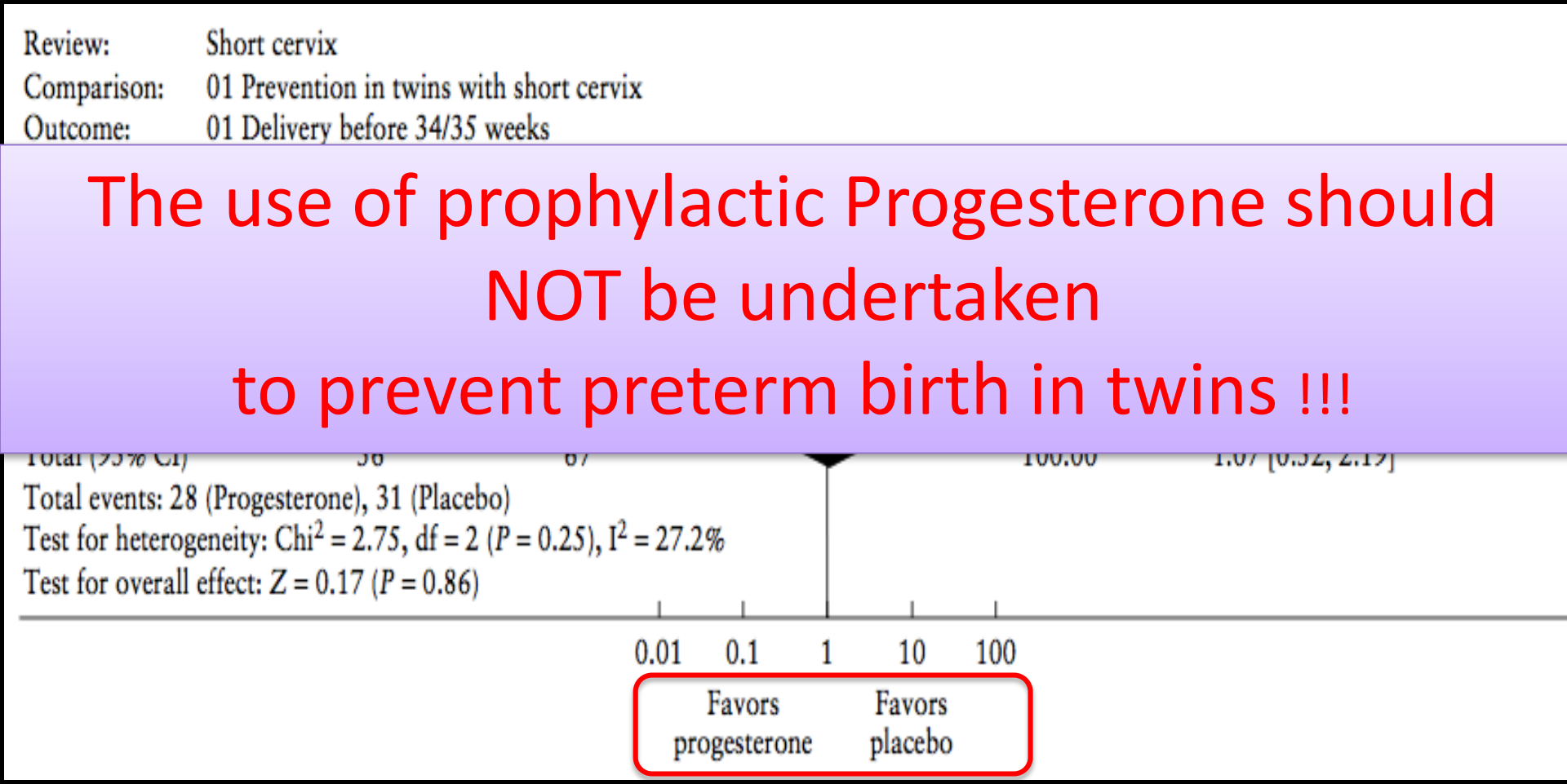
Outcome	*Progesterone group* (n (%))	*Placebo group* (n (%))	*Odds ratio* (95% CI)	P†
Gestational age at delivery				
< 32 weeks	4 (23.5)	5 (16.7)	1.54 (0.35–6.73)	0.57
< 34 weeks	5 (29.4)	12 (40.0)	0.63 (0.18–2.23)	0.47

Table 4 Maternal and infant outcomes according to treatment with progesterone ($n = 10$) or placebo ($n = 18$) in women with a history of spontaneous preterm delivery before 34 weeks or miscarriage after 12 weeks

Outcome	*Progesterone group* (n (%))	*Placebo group* (n (%))	*Odds ratio* (95% CI)	P†
Gestational age at delivery				
< 32 weeks	3 (30.0)	3 (16.7)	2.14 (0.34–13.42)	0.42
< 34 weeks	3 (30.0)	4 (22.2)	1.50 (0.26–8.64)	0.65

Klein K: UOG, 2011

Metanalysis of the preventive effect of progesterone on delivery in twins with short cervix



Klein K: UOG, 2011

Reducing the rate of preterm birth in twins by cervical circlage

- Cervical cerclage used as prophylactic for history indication
  - 😐 Prematurity 45% vs 48% without suture
  - 😐 Neonatal mortality 15% vs. 18% without suture

Dor J et al: Gynecol Obstet Invest, 1982

- Cervical cerclage of asymptomatic short cervix
  - ☹ Preterm birth <35 weeks (75% vs. 36% without suture)

Berghella et al: Obstet Gynecol, 2005

Cerclage for short cervix in twin pregnancies: Meta-analysis

- Twin pregnancies screened by transvaginal ultrasound in second trimester and where mothers had a short cervical length <25 mm before 24 weeks

Cerclage of asymptomatic short cervix must be avoided for twin gestation!!!

differences in primary (adjusted odds ratio 1.17, 95% confidence interval 0.23-3.79) and secondary outcomes

- Rates of **very low birthweight** and of **respiratory distress syndrome** were significantly ***HIGHER* in the cerclage group** than in the control group

Saccone G: Acta Obstet Gynecol Scand, 2015

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Tocolytics in the treatment of preterm labor in twins

- The use of tocolytics for the treatment of preterm labor has not been shown to decrease:
  - 😐 Delivery within 7 days
  - 😐 Neonatal death
  - 😐 Respiratory syndrome
  - 😐 Necrotizing enterocolitis Anotayanonth S: Coch Syst Rev, 2004
- Side effects
- Risk of maternal pulmonary edema

ACOG comments that tocolytics should be used judiciously once preterm labor in twins is diagnosed!!!

Results of the use of Arabin pessary in twin pregnancy with cervix <25mm

- Randomized clinical trial (Spain)

	Arabin Pessary	Expectant management	
Spontaneous delivery <28 wks	4/68 (5,9%)	9/68 (13,6%)	p<0,02
Spontaneous delivery <34 wks	11/68 (16,2%)	17/68 (25,7%)	p<0,001
Gestational age at delivery	36,4 (26-38)	35,0 (22-38)	p<0,01

Carreras E: 13th WCFM,2014

- Randomized clinical trial (FMF)

No statistical significance in preterm delivery in two groups. Trial was stopped due to the risk of possible adverse clinical effects in pessaries group

Antenatal corticosteroids (ACS) in preterm labor in twins

- The use of ACS decrease:
  - ☺ Neonatal death (RR, 0.69; 95% CI, 0.58-0.81)
  - ☺ Respiratory distress (RR, 0.66; 95% CI, 0.43-0.69)
  - ☺ Intraventricular hemorrhage (RR, 0.54; 95% CI, 0.43-0.69)
  - ☺ Necrotizing enterocolitis (RR, 0.46; 95% CI, 0.29-0.74)
  - ☺ Systemic infection (RR, 0.56; 95% CI, 0.38-0.58) **Roberts D: Cohr Syst Rev, 2006**

NIH recommends that all women in preterm labor, regardless the number of fetuses, must be given a course of ACS!!!

elapsed and delivery is likely at <33 weeks

  - ☺ Neonatal morbidity 64% vs. 42% (p<.02) **GariteTJ: AJOG, 2009**

- A single course of ACS treatment was associated with a decreased rate of RDS only when the ACS-to-delivery interval was between 2 and 7 days

Kuk JY: AJOG, 2013

Use of tocolytics in twin pregnancies should be limited

- Cervical length <25 mm
- fFN is positive
- Both of the above are present
- 48 hours have elapsed since the first dosage of corticosteroids has been administered
- The patient has been transferred to a tertiary center

IVF success rate transferring more than ONE embryo

- Twin pregnancies must be considered severe complications of ART **ESHRE Campus, 2002**
- Imposing singleton delivery as the success indicator for IVF treatment **Hazekamp et al, 2000**
- Calculate success rate as the % of singleton living full term delivery per initiated IVF cycle (BESST: Birth Emphasizing a Successful Singleton Term) to consider MP as failures **Min et al, 2004**

Summary

- Although there are diagnostic tests to identify preterm birth in twins, they do not decrease the rate of preterm birth
- There are no known treatments to decrease the rate of preterm birth
- Tocolytics should be administered when twins are in danger of preterm delivery
- Prolonged tocolytic use should be avoided

Thank you very much!!!