Preterm labour/ birth

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Introduction

• Preterm birth is a leading cause of perinatal morbidity and mortality
• About 15 million births per year are preterm
• Prevention is an important healthcare priority
• Early identification of risk factors provides an opportunity for intervention
• However, many preterm births occur among women without risk factors
• IATROGENIC CONTRIBUTION
Early Prediction of small babies:

- Small fetuses:
  - 20% starved
  - 75% normal
  - 5% abnormal

Piramid of care: If all normal

- 12 w
- 20-24 w
- 32 w or 36 w
- 41 w
BORN TOO SOON:

- PRETERM DELIVERY:
- GLOBAL ACTION REPORT ON PRETERM BIRTH
- 15 MILLION per annum (10% of births)
- RATE IS INCREASING!!!!
- > 1 MILLION NEWBORN DEATHS per annum
PREDICTION OF PRETERM BIRTH:

- DELIVERY < 34 WEEKS 1.8%
- IATROGENIC 1/3
- SPONTANEOUS 2/3
- SINGLETONS 2%
- TWINS 15%
Prediction of spontaneous preterm birth <34 weeks

Singletons 22 w: History plus cervical length

- Height: 144 cm, 164 cm, 184 cm
- Black
- Smoker
- Oil drugs
- IVF
- Nullip
- 16-33 w x1 + Term
- 16-33 w x2 + Term
- 34-36 w
- Term

Distribution of cervical length

- n=672 (1.2%)
- n=49,203

Risk of spontaneous delivery <34w

Odds ratio (95% CI)

DR for FPR 10%

- History
- + Cx

65%

33%
PREVENTION OF PRETERM BIRTH IN TWINS:

- **BEDREST:** NO, ACTUALLY WORSENS OUTCOME SLIGHTLY

- **PROGESTERONE:**
  - 31 to 26 %
  - 25 to 20 %
  - 15 to 19 %

- **ARABIN PESSARY:**
  - DOES NOT WORK FOR TWINS!
Prevention of preterm birth in twins

vaginal silicone pessary

Randomised (n = 1,180)

- Pessary group (n = 590)
  - Lost to follow up (n=2)

- Expectant group (n = 590)
  - Lost to follow up (n = 3)

Delivery < 34 wks

Spain: Canary, Granada, Murcia
Albania, Austria, Brazil, Chile, England, Germany,
Hong Kong, Italy, Portugal, Slovenia

FMF study in twins

Total 98 (16.7%)
Spontaneous 78 (13.3%)

Total 91 (15.4%)
Spontaneous 72 (12.2%)
Early prediction of FGR and PE

History, uterine PI, MAP, PAPP-A, PLGF at 11-13wks

Algorithm for PE

Algorithm for FGR

Detection rate %

Risk 1:100 200 300

Risk 1:50 100 150 200 250

FPR

FGR

PE

97%

95%

87%

66%

97%

95%

56%

57%

57%

43%

46%

Risk >1:300 None Risk >1:300 Risk >1:200 Risk >1:100 Risk >1:150 Risk >1:50 Risk >1:200 None FPR 11% FPR 11% FPR 11% FPR 11% FPR 11% FPR 11% FPR 11% FPR 11%
Singleton pregnancies n=75,394

FGR < 32 wks 164 (0.2%)

Preeclampsia 75 (46%)

No preeclampsia 89 (54%)
Potentially effective interventions

- Progesterone
- Treat infections, eg. asymptomatic bacteruria, GBHS
- Smoking: reduce / stop if possible
- Vaginal pessary: Arabin “ring & funnel”
- ART: ↓ twinning + higher order multiples
- Cervical cerclage
- Fatigue + physical exertion
- Nutrition, eg. L-carnitine
Progesterone

- Natural
- Synthetic
Preparations

Natural

• Administration PV or oral (micronised)
• Vaginal route – high uterine bio-availability and systemic side effect profile benign; doses: 90 mg to 400 mg
• Oral preparations – sleepiness, fatigue, headache; dose: 900 mg to 1600 mg; first pass through liver, poorer bio-availability
Preparations

Synthetic

- 17-alphahydroxyprogesterone
- Intramuscular administration
- Doses of 25mg every 5 days to 100mg weekly
- Begin from 16 weeks
Progesterone - history of PTB

Interest in progesterone supplementation re-kindled in 2003:

- Meis, NEJM – 459 patients
- da Fonseca, Am J Obstet Gynecol – 142 patients

Statistically significant reduction in PTB < 34w
Progesterone – history of PTB

*Ultrasound Obstet Gynecol* 2007; 30: 687–696

Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial

Progesterone - history of PTB

- 659 with prior history of PTB
- Randomised to progesterone or placebo
- Progesterone supplementation did not reduce frequency PTB compared to placebo
- No difference in maternal or neonatal outcome
Progesterone - short cervix

- Fonseca et al, NEJM 2007
- Screened 24,620 pregnant women
- 413 (1.7%) women had short cervix (15mm or less)
- Randomised to progesterone or placebo
- Reduction in PTD < 34 weeks (19% vs 34%, 95% CI 0.36-0.86)
- Non significant reduction in neonatal morbidity
32,091 women screened

31,358 women cervical length <10 or >20 mm

733 women cervical length 10-20 mm

268 women declined to participate or had other exclusions

465 randomized with a cervical length of 10 – 20 mm

236 randomized to progesterone (intervention group)

1 lost to follow-up

235 analyzed (intent-to-treat population)

229 randomized to placebo (control group)

6 lost to follow-up

223 analyzed (intent-to-treat population)
Short cervix

*Ultrasound Obstet Gynecol* 2011

Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo controlled trial

Sonia S. Hassan, MD1,2; Roberto Romero, MD1,3; Dommeti Vidyadhari, MD, DGO, MBBS4; Shalini Fusey, MD, DGO, MBBS5; Jason Baxter, MD, MSCP6; Meena Khandelwal, MD7; Jaya Vijayaraghavan, MD, DGO, MBBS8; Yamini Trivedi, MD, DGO, MBBS9; Priya Soma-Pillay, MBChB, FCOG10; Pradip Sambarey, PhD, MD, MBBS11; Ashlesha Dayal, MD12; Valentin Potapov, MD, PhD13; John O’Brien, MD14; Vladimir Astakhov, MD, PhD15; Oleksandr Yuzko, MD, PhD16; Wendy Kinzler, MD17; Bonnie Dattel, MD18; Harish Sehdev, MD19; Liudmila Mazheika, MD, PhD20; Dmitriy Manchulenko, MD21; Maria Teresa Gervasi, MD22; Lisa Sullivan, PhD23; Agustin Conde-Agudelo, MD, MPH1; James A. Phillips, DrPH24; and George W. Creasy, MD25, for the PREGNANT Trial
Cervical length technique

- Empty bladder
- Prepare condom covered vaginal probe
- Guide probe into anterior fornix of vagina
- Sagittal long-axis view of endocervical canal
- Withdraw probe until image is blurred then reapply just enough pressure to restore image
- Measure cervical length (3 measurements)
- Fundal pressure for 15 seconds, re-measure
Progesterone - short cervix

- 45% reduction in PTB before 33 weeks
  (8.9% vs 16%; p=0.02; CI 0.33-0.92)

- PTB < 35 weeks
  (14% vs 23%; p=0.02; CI 0.42-0.92)
Progesterone - short cervix

- Respiratory distress syndrome
  3% vs 7.6%; p=0.03; CI 0.17-0.92
- Any neonatal morbidity or mortality event
  7.7% vs 13.5%; p=0.04; CI 0.33-0.99
- Birth weight <1500g
  6.4% vs 13.6%; p=0.01; CI 0.26-0.85
Progesterone - short cervix

Numbers needed to treat

• 14 patients to prevent 1 preterm birth

• 22 patients to prevent 1 case of RDS
Implications

Universal screening of women with a short cervix identifies patients at risk and can now be coupled with intervention.
Progesterone – acute PTL

Progesterone supplementation associated with:

• less shortening of the cervix
• reduced rate of preterm delivery
• fewer complications of prematurity
• higher birth weight
Progesterone – not beneficial

- Twin gestations
- Triplet pregnancies
- Fetal fibronectin positive pregnancy
- Preterm premature rupture of membranes
Cerclage
Cerclage – history of PTB

- Elective cerclage based only history may be justified in women with 3 or more 2nd trimester losses. (MRC/RCOG RCT of cervical cerclage; BJOG 1993)
- In such a population cerclage will reduce risk of PTB <33 weeks from 32 to 15%
Prior cerclage

- Once a cerclage, not always a cerclage. (Fejgin 1994)

- Prior cerclage: to repeat or not to repeat? That is the question. (Pelham 2008)

Prior cerclage not an indication for repeat cerclage
Cerclage – short cervix

- Meta-analysis (4 trials); Berghella 2005
- Cerclage beneficial in women with cervical length <25mm before 24 weeks only if they had a prior PTB
- Birth <35 weeks reduced from 39% without cerclage to 23% with cerclage (RR 0.61; CI 0.40 – 0.92)
- No difference in perinatal mortality
Cerclage – short cervix

- Vaginal Ultrasound Trial Consortium
- 302 patients
- Short cervix and history of preterm birth
- Significant benefit only in women with cervical length <15mm (RR 0.23; CI 0.08-0.66)
Cerclage or progesterone

- Not enough evidence comparing the 2 treatment modalities
- Small study of 79 patients cerclage superior to 17-alpha hydroxyprogesterone if cervical length <15mm
- No difference if cervical length <25mm
Algorithm for short cervical length

Cervical length < 25mm

- Multiple Gestations
  - Expectant Management
  - Cerclage plus Indomethacin
- Singleton Gestation
  - Prior PTB
    - Progesterone
  - No Prior PTB
    - Progesterone
Conclusion

- A short cervix on TVU is the best predictor of imminent preterm labour. Universal screening in the midtrimester.
- Successful management of these patients depends on the understanding that short CL is the final pathway of various causes of preterm labour.
- There probably isn’t one management technique that could be used across the board in all patients.
- Therapy tailored to each unique clinical situation.
- TLC also plays an important role in preventing PTB.