

# Cervical Pessary for Prevention of Preterm Birth?

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Sheri Jenkins, MD  
Maternal-Fetal Medicine  
University of Alabama, Birmingham

# Disclosures

- I have no relevant financial relationships to disclose or conflicts of interest to resolve
- This presentation includes discussion of “off-label” use of pessaries for prevention of preterm delivery

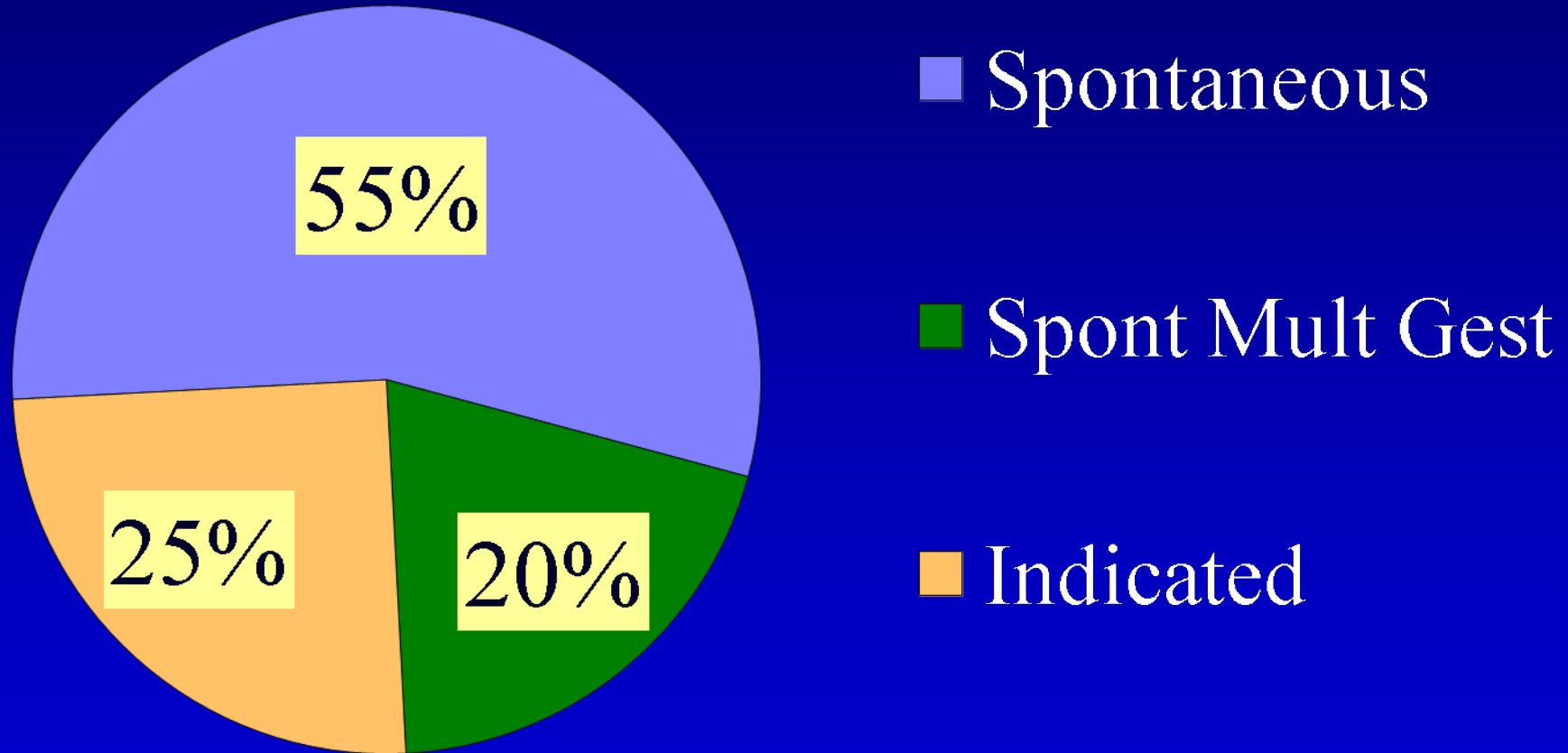
# Educational Objectives

1. To examine how pessaries might work to prevent spontaneous preterm birth (PTB)
2. To review the literature regarding pessaries for prevention of PTB in singleton and twin gestations
3. To examine ongoing pessary trials

# Preterm Birth

- Scope of the PTB problem:
  - 6-10% of pregnancies
  - Leading cause of perinatal morbidity & mortality
  - Massive financial burden
  - PTB rates are rising

# Preterm Birth



# Preterm Birth

- Preventing PTB is a key goal of perinatal medicine
- Initial therapies were directed at those with prior PTB
  - Small effect on overall rate of prematurity
- How can we identify others at risk for PTB?

# Preterm Birth

- There are various potential causes of PTB:
  - Cervical incompetence
  - Intraamniotic infection/inflammation
  - Premature contractions
- These causes are associated with changes in the appearance of the cervix
- How are these changes best identified?

# Preterm Birth

- Midtrimester cervical length ultrasound
  - Detects changes at internal os not perceived by digital exam
    - Funneling
    - Cervical shortening
    - Prolapsing membranes
  - One of the best predictors of spontaneous PTB
  - Singletons & twins



# Preterm Birth

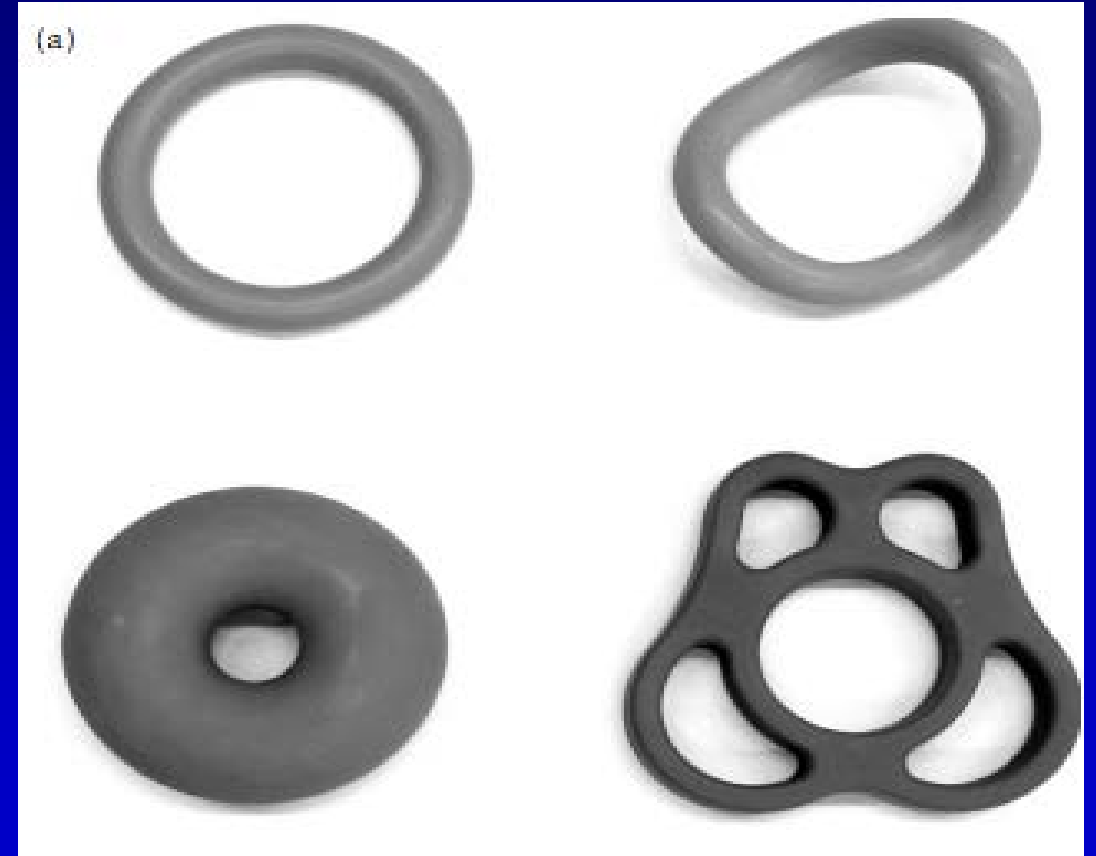
- Prevention or treatment of these cervical changes is a current strategy for lowering rates of PTB
- Options include mechanical and/or hormonal support
  - Cerclage
  - Cervical pessary
  - Progesterone

# Preterm Birth

- Cerclage
  - First used by Shirodkar & McDonald in 1950s
  - Effective for singletons with prior PTB & cervical shortening
  - Drawbacks:
    - Invasive
    - Requires anesthesia
    - Complications of bleeding, infection & pregnancy loss

# Preterm Birth

- Cervical pessary
  - An alternative to cerclage developed in late 1960s
  - Various shapes & sizes
  - Made from silicone
  - Not extensively studied in pregnancy until recently



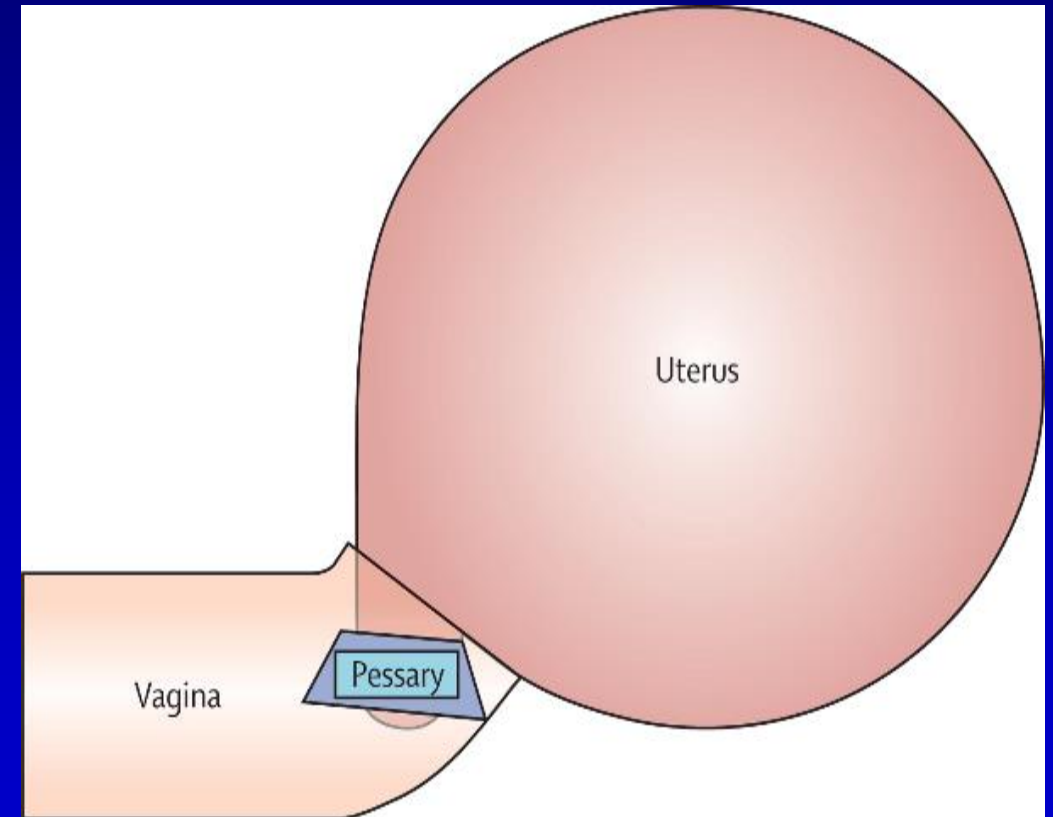
# Preterm Birth

- Dr. Arabin developed current design in 1970s



# Pessary Design

- How might a cervical pessary prevent PTB?
  1. Compress the cervical canal
  2. Displace the cervix posteriorly
    - Uterine weight applied to posterior vaginal wall & pelvic floor
  3. Prevent deterioration of the cervical mucus plug



# Potential Indications for Pessary

- History of PTB
- Cervical length ultrasound findings
- Physical exam findings

# Pessary Contraindications

- Lethal fetal abnormality
- Chorioamnionitis
- Membrane prolapse into vagina
- Regular painful contractions
- Vaginal bleeding

# Advantages of Pessary

- Relatively non-invasive
- Safe & low cost
- Outpatient & requires no anesthesia
- Can be placed at any GA
- Easily removed when necessary



# Disadvantages of Pessary

- Patient discomfort
- Increased vaginal discharge
- Rare cervical damage:
  - Edema
  - Erosions
  - Lacerations

# Initial Pessary Studies

# Early Pessary Research

<u>Author, Yr</u>	<u>Type</u>	<u>N</u>	<u>Controls</u>	<u>Helpful?</u>
• Cross, '59	Ring	13	Hx	Y
• Vitsky, '63	Smith	5	Hx	Y
• Oster, '66	Hodge	35	Hx	Y

# Later Pessary Research

<u>Author, Yr</u>	<u>Type</u>	<u>N</u>	<u>Study-Cntrl</u>	<u>Helpful?</u>
. Quaas, '90	Arabin	107	Case series	?
. Gmoser '91	Stutz	300	RCT-No Rx	Y
. Arabin, '03	Arabin	70	Cohort-No Rx	Y
. Antczak, '03	?	57	Cohort-Cerc.	N
. Acharya, '06	Arabin	32	Case series	?
. Sieroszewski, '09	Arabin	54	Case series	?
. Kimber, '10	Ring	56	Case series	?

# Pessary vs. Cerclage

- Little head-to-head comparative data
  - Von Forster 1986
    - Quasi-randomized trial, 242 patients
    - Cerclage vs. pessary
    - Indication: some prophylactic, some therapeutic
  - Alfirevic 2013
    - Retrospective cohort
    - Cerclage vs. Arabin pessary vs. vaginal progesterone
    - Indication – prior PTB & short cervix
- Cerclage = pessary

# Limitations of Initial Pessary Research

- . Retrospective
- . Non-U.S. data
- . Case series with no control group
- . Patients' prior pregnancies used as controls
- . Patient characteristics not reported
- . Inclusion/exclusion criteria unclear
- . Inconsistent outcomes

# Recent Pessary Studies

*Singletons*

# Singleton Studies

- Goya 2012 Spain, PECEP study
  - RCT pessary vs no treatment
  - 385 pts with CL  $\leq$  25mm at 18-22 wks
  - Results:
    - Pessary decreased PTB < 34 wks, 6 vs 27%, OR 0.18 (.08-.37)
    - Later GA at delivery, 37.7 vs 34.9 wks
    - Improved neonatal composite outcome, 3 vs 16%, OR 0.14 (.04-.39)



# Singleton Studies

- Hui 2012 China
  - RCT pessary vs no treatment
  - Women with CL < 25mm at 20-24 wks
  - Target sample size 1120 women (reduction in PTB from 8 to 4%)
  - Slow enrollment – 100 patients over 29 months
  - Conducted an interim analysis at 108 patients

# Singleton Studies

- Study terminated early due to small effect size & publication of results from larger Goya trial
- Results:
  - No difference in PTB at 34 wks, 9.4 vs 5.5%, RR 1.04 (.94-1.12)
  - EGA at delivery, 38.1 vs 37.8 wks
  - NICU admission, 40 vs 32%, RR 1.13 (.85-1.5)

# Singleton Studies

- Nicolaides 2016 Europe, South America, Australia
  - RCT pessary vs no treatment
  - Primary outcome = PTB < 34 wks
  - Targeted sample size 1600 patients to show 50% benefit in pessary group
  - Study terminated early due to slow enrollment

# Singleton Studies

- 935 pts with CL  $\leq$  25mm at 20-24 wks
- 423 pts had CL  $\leq$  15mm; vaginal progesterone was added
- Results showed no differences in:
  - PTB rate, 12 vs 10.8%, OR 1.12 (.75-1.69)
  - Adverse neonatal events, 6.7 vs 5.7%, OR 1.18 (.69-2.03)

# Singleton Study Issues

- Conflicting results
- Goya trial
  - High rate of PTB < 34 wks in controls
    - 27% vs typical 6-11%
    - Had higher BMI, smoking rate & history of PTB
  - Limits generalizability

# Singleton Study Issues

- Hui trial
  - Terminated after interim analysis due to slow recruitment & publication of Goya trial
  - Likely underpowered
- Nicolaides trial
  - Terminated early due to slow recruitment
  - 24% of pessaries were discontinued at < 34 weeks
  - 45% received vaginal progesterone as an additional intervention

# Recent Pessary Studies

*Multiple Gestations*

# Background

- Twins represent 2-3% of pregnancies but 25% of PTB's
- Prevention of PTB in multiples is a major goal of obstetrics
- Effectiveness of hormonal and mechanical interventions has been limited



# Multiples Studies

- Liem 2013 Netherlands, ProTWIN study
- RCT pessary vs no treatment
- 813 pts with multiples at 16-20 wks
- 1<sup>o</sup> outcome – composite perinatal morbidity and mortality
- Results:
  - No difference in perinatal outcome, 13 vs 14%, RR .98 (.69-1.39)
  - Similar GA at delivery, 36.7 vs 36.4 wks

# Multiples Studies

- Secondary analysis of CL < 25<sup>th</sup>% (38mm)
  - Pessary was associated with:
    - Decreased rate of PTB < 32 wks, 14 vs 29%, RR .49 (.24-.97)
    - Decreased poor perinatal outcome, 12 vs 29%, RR 0.4 (.19-.83)
    - Higher GA at delivery, 36.4 vs 35 wks

# Multiples Studies

- Nicolaides 2016 Europe, China, South America
- RCT pessary vs no treatment
- 1180 twin pregnancies at 20-24 wks
- Primary outcome = PTB < 34 wks
- Results:
  - No difference in PTB, 13.6 vs 12.9%, RR 1.05 (.79-1.4)
  - GA at delivery, 36.6 vs 36.7 wks

# Multiples Studies

- Post hoc subgroup analysis
  - 214 patients (18%) with CL  $\leq$  25 mm
  - No difference in PTB < 34 wks, 31 vs 26%, RR 1.2 (.78-1.84)

# Multiples Studies

- Goya 2016 Spain, PECEP – Twins
- RCT pessary vs no treatment
- 137 pts with twins, CL  $\leq$  25mm at 18-22 wks
- Primary outcome = PTB < 34 wks
- Results:
  - Less PTB with pessary, 16 vs 39%, RR .41 (.22-.76)
  - Higher GA at delivery, 35.3 vs 33.1 wks
  - No dif in composite neonatal morbidity & mortality, 6 vs 9%, RR .64 (.27-1.5)

# Multiples Studies

- Fox 2016 U.S.
- Retrospective study
- Twins receiving serial CL US until 28 wks
- If CL < 20 mm, vaginal progesterone
- In 2013, began offering pessary also
- Controls matched 3:1 to pessary patients by GA and CL
- Primary outcome = PTB < 32 wks

# Multiples Studies

	<u>Pessary (21)</u>	<u>Cntrl (63)</u>	<u>P</u>
• GA at CL (wks)	26	26	0.7
• CL (mm)	10.9	11.9	0.33
• Monochorionic	33%	13%	<b>0.03</b>
• IVF	33%	67%	<b>0.007</b>
• <b>PTB &lt; 32 wks</b>	<b>4.8%</b>	<b>29%</b>	<b>.05*</b>
• Birth GA (wks)	35.0	33.3	<b>.07*</b>

\* Adj for MC, IVF

# Multiples Study Issues

- Conflicting results
- Liem trial:
  - CL not obtained in 24% & not always done before randomization
  - 38 mm is extremely high to be 25<sup>th</sup>%
  - 46% of pessaries removed < 36 wks
- Nicolaides trial:
  - Pessaries placed at later gestation
  - 22% of pessaries were removed < 34 wks



# General Study Limitations

*Pessary for Preterm Birth*

# Study Limitations

- Regarding study populations:
  - Randomized at various midtrimester gestational ages
  - Selected vs unselected populations
  - Included patients with prior PTB
  - Cervical length percentiles varied by population

# Study Limitations

- Regarding pessary:
  - No training for pessary insertion
  - Unable to adequately blind the therapy
  - 1/4 to 1/2 pessaries discontinued early
- Regarding cervical length:
  - Some no training on technique
  - Some measurements taken after randomization

# Study Limitations

- Regarding therapy:
  - Other interventions still done
    - Tocolysis
    - Antibiotics
    - Steroids
    - Progesterone
    - Cerclage

# Unanswered Questions

1. How effective are pessaries for prevention of PTB?
2. What GA should pessary be placed?
3. Who are ideal patient candidates?
4. Role of pessary compared to cerclage?
5. Is there a role for pessary in cases with cervical dilation?
6. If pessaries work in twins, would they work in higher order multiples?

# Ongoing Research

- 27 registered studies of cervical pessary listed in [ClinicalTrials.gov](http://ClinicalTrials.gov)
- Current studies are further evaluating pessary for:
  - Treatment of short cervix in singletons & twins
  - Alternative or adjunctive therapy for cerclage
  - Treatment after resolution of preterm labor
  - Prevention of delivery < 36 wks with previa
  - After treatment of TTTS

# Conclusions

# Conclusions

- Cervical pessary may not prevent preterm birth in unselected singletons and twins
- However, it may be helpful in singletons and twins with a short cervix
  - May be the best (only?) therapy in twins



# Conclusions

- Cervical pessary for PTB is still investigational
  - It is not a replacement for cerclage
  - Favorable cost & risk profile compared to cerclage
- Further large, well-designed studies are needed & in progress

# References

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Questions?