دکتر ریحانه پیرجانی

پریناتولوژیست
دانشیار دانشگاه علوم پزشکی تهران

Cervical insufficiency

- **Obstetrical history-based diagnosis** — We make an obstetrical history-based diagnosis of cervical insufficiency in women with a classic history of ≥2 consecutive prior second-trimester pregnancy losses/extremely preterm births (ie, <28 weeks) associated with no or minimal mild symptoms.

- **Ultrasound-based diagnosis** — In asymptomatic women with a past history of a preterm birth associated with no or minimal mild symptoms and those in whom a history-based diagnosis is uncertain, we perform serial transvaginal ultrasound (TVU) examinations and make a diagnosis of cervical insufficiency when cervical length is <25 mm before 24 weeks
- TVU screening is discontinued at 24 weeks of gestation, as cerclage is rarely performed after this time
- The presence of risk factors for structural cervical insufficiency supports the diagnosis.

- **Physical examination-based diagnosis** — We make a diagnosis of physical examination-based cervical insufficiency in women 14 through 27 weeks of gestation with a dilated and effaced cervix on physical examination and no contractions or weak irregular contractions that appear inadequate to explain the cervical dilation and effacement. The membranes may be prolapsed or ruptured.

CERCLAGE PLACEMENT

- Cerclage is not indicated in multiple gestations, given that the body of evidence shows no improvement in pregnancy outcome compared with appropriate controls without cerclage.

CERCLAGE PLACEMENT

- **Obstetrical history-based cervical insufficiency** —

- We suggest cerclage placement (called history-based or history-indicated cerclage) at 12 to 14 weeks of gestation in women with this diagnosis.
- Structural weakness of the cervix can be treated effectively with structural support from a cerclage

CERCLAGE PLACEMENT

- At 16 weeks of gestation, begin hydroxyprogesteronecaproate weekly and continues it until 36 weeks of gestation [
- However, the routine use of hydroxyprogesteronecaproate is controversial, in part because no randomized trials have evaluated the efficacy of combination therapy (both history-indicated cerclage and hydroxyprogesteronecaproate) in this patient population.

CERCLAGE PLACEMENT

- Reasonable alternative approaches are to limit use of hydroxyprogesteronecaproate to women with previous preterm deliveries ≥20 weeks of gestation or to avoid progesterone supplementation unless the cervical length falls to ≤25 mm and then begin vaginal progesterone supplementation

CERCLAGE PLACEMENT

- **Ultrasound-based cervical insufficiency** — We suggest cerclage placement (called ultrasound-based or ultrasound-indicated cerclage) in women with one prior spontaneous preterm birth and cervical length <25 mm before 24 weeks in the current pregnancy.

- Women with a prior spontaneous preterm birth are prescribed hydroxyprogesteronecaproate beginning at 16 to 20 weeks of gestation (which may be before or after cerclage placement) and continued through 36 weeks.

CERCLAGE PLACEMENT

- **Physical examination-based cervical insufficiency** — For women with physical examination-based cervical insufficiency before 24 weeks of gestation, we consider cerclage placement a reasonable option (called physical examination-based cerclage, physical examination-indicated cerclage, rescue cerclage, or emergency cerclage)

- We administer indomethacin (usually 50 mg orally every 6 hours for 48 hours total, starting before the cerclage) and antibiotics (usually one dose of cefazolin 1 to 2 g intravenously preoperatively depending on weight

- Most clinicians avoid placing a cerclage after approximately 24 weeks of gestation since the procedure may cause accidental rupture of the fetal membranes leading to early preterm delivery of a viable infant, with its attendant high risk of neonatal morbidity and mortality.

- However, each case must be individualized, weighing the risks of the procedure against the likely outcome with expectant management

Women with no prior second-trimester pregnancy loss/extremely preterm birth, but risk factors for cervical insufficiency

- Although a minority of these women develop cervical insufficiency, most do not; therefore, we believe the pregnancy course and outcome need to be evaluated before making this diagnosis.
- Perform a single transvaginal cervical length measurement at 18 to 24 weeks of gestation (usually at approximately 20 weeks, with the anatomic survey ultrasound) in women with singleton gestations and with no prior preterm birth, and treats those with a short cervix (<25 mm) with vaginal Progesterone supplementation

- However, in women with transvaginal ultrasound cervical length <10 mm, a cerclage may be helpful

- In women with no previous preterm birth and a short cervix ≤20 mm before 24 weeks, we begin natural progesterone upon diagnosis and continue the drug through 36+6 weeks of gestation.

After preterm prelabor rupture of membranes

- Beginning supplementation is not beneficial in women who develop preterm prelabor rupture of membranes (PPROM) in Progestrones the current pregnancy.
- In a meta-analysis of randomized trials, progesterone supplementation did not prolong the latency period or increase the gestational age at delivery in singleton pregnancies with PPROM
- In contrast, women with a history of preterm birth due to PPROM appear to benefit from Progestrones supplementation in subsequent pregnancies

BEHAVIORAL COUNSELING

- Lifestyle interventions (cessation of work and exercise, abstinence from coitus, bedrest/limited activity) have not been adequately evaluated by well-designed studies.

- Clinicians should consider the available evidence and the patient's individual circumstances when making lifestyle recommendations as there are social, psychological, financial, and medical side effects associated with these interventions.

MANAGEMENT OF FUTURE PREGNANCIES FOLLOWING CERCLAGE IN INDEX PREGNANCY؟

- **Prior successful outcome after cerclage**

✓ **●Prior successful obstetrical history-indicated cerclage**

✓ **●Prior successful ultrasound-indicated cerclage**

✓ Successful pregnancy outcome after ultrasound-indicated cerclage does not establish or exclude a diagnosis of cervical insufficiency

MANAGEMENT OF FUTURE PREGNANCIES FOLLOWING CERCLAGE IN INDEX PREGNANCY?

- **Prior unsuccessful outcome after cerclage**

✓ ●**Prior unsuccessful obstetrical-history indicated cerclage**

✓ ●**Prior unsuccessful ultrasound-indicated cerclage**

INEFFECTIVE AND UNPROVEN INTERVENTIONS

- **Pessary** — We do not prescribe pessaries for women with a short cervix.

- Vaginal pessaries may work by altering the axis of the cervical canal and displacing the weight of the uterine contents away from the cervix, as well as by other mechanisms.

- By changing the angle of the cervix in relation to the uterus, the pessary also obstructs the internal os and thus may provide protection against ascending infection.
- However, the body of evidence does not support using a pessary to prolong gestation or improve neonatal outcome.

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- In a 2017 meta-analysis that evaluated the effectiveness of the Arabin cervical pessary for preventing spontaneous preterm birth (SPTB) in singleton gestations with second-trimester cervical length ≤25 mm use of the pessary did not result in statistically significant reductions in SPTB <37 weeks ,<34 weeks ,<32 weeks and <28 weeks compared with no pessary,

- no significant differences were observed in the mean gestational age at delivery, incidence of preterm premature rupture of membranes, cesarean delivery rate, or neonatal outcomes

- Two subsequent trials performed in women with singleton pregnancies, short transvaginal ultrasound cervical length, and no prior SPTB reported discordant results.

- One trial failed to show a benefit with use of a pessary compared with no pessary while a similar trial reported a benefit (SPTB <34 weeks: 7 versus 15 percent

- A noninferiority trial was unable to reject the hypothesis that use of a cervical pessary was noninferior to vaginal progestrone for preventing SPTB <34 weeks in women with a short cervix

Antenatal corticosteroid therapy

- **Reduction of RDS** -- respiratory distress syndrome

- **Reduction of IVH--** Intraventricular hemorrhage
- **Reduction of NEC--** Necrotizing enterocolitis
- **Reduction of NNM--** Neonatal mortality
- **Reduction of infection--** Systemic infection in the first 48 hours of life

GESTATIONAL AGE AT ADMINISTRATION

- all pregnant women at 23+0 to 33+6 weeks of gestation who are at increased risk of preterm delivery within the next one to seven days.

- Selection of such pregnancies is a clinical judgment based on high probability of induction/cesarean for obstetrical or medical indications (eg, preeclampsia) or high probability of spontaneous preterm labor and delivery (eg, preterm premature rupture of membranes, tocolysis for active preterm labor).

GESTATIONAL AGE AT ADMINISTRATION

- The administration of antenatal steroids at 22+0 to 22+6 weeks ?

- At 23+0 to 25 weeks of gestation?

- **34+0 or more weeks** ?

34+0 or more weeks ?

- Different approach:
- Up to date
- The Society for Maternal-Fetal Medicine Specialists
- The American College of Obstetricians and Gynecologists
- The NICE guideline

34+0 or more weeks ? Up to date

- For women scheduled for cesarean delivery at ≥37+0 to 38+6 weeks, a course of steroids can be discussed but not necessarily encouraged. We inform women who have not received a prior course of steroids

- For women scheduled for cesarean delivery at 34+0 to 36+6 weeks, we believe offering a first course of antenatal corticosteroids

- For women in whom vaginal delivery at ≥34+0 weeks is expected, we would not administer a first course of steroids as respiratory problems are less common after labor and vaginal birth

Other approaches

The Society for Maternal-Fetal Medicine

- recommends a two-dose course for women at 34+0 to 36+6 weeks of gestation at high risk for preterm birth within seven days, with the following caveats:
- •For women with symptoms of preterm labor, cervical dilation should be ≥3 cm or effacement ≥75 percent before treatment and tocolysis should not be used to delay delivery for completion of the course of steroids.
- •For women with potential medical/obstetric indications for early delivery, steroids should not be administered until a definite plan for delivery has been made.

34+0 or more weeks ?The American College of Obstetricians and Gynecologists

- women with a singleton pregnancy at 34+0 to 36+6 weeks of gestation at imminent risk of preterm birth within 7 days, with the following caveats:
- •Antenatal corticosteroid administration should not be administered to women with chorioamnionitis.
- •Tocolysis should not be used to delay delivery in women with symptoms of preterm labor to allow administration of antenatal corticosteroids. Medically/obstetrically indicated preterm delivery should not be postponed for steroid administration.
- •Antenatal corticosteroids should not be administered if the patient has already received a course antenatal corticosteroids.
- •Newborns should be monitored for hypoglycemia.

34+0 or more weeks ? The NICE guideline

- recommends considering maternal corticosteroids for women between 34+0 and 35+6 weeks of gestation who are in suspected, diagnosed, or established preterm labor, are having a planned preterm birth, or have preterm prelabor rupture of membranes

Evidence

- **Efficacy at 37+0 to 39+6 weeks of gestation**
- **Efficacy at 34+0 to 36+6 weeks of gestation**

Evidence

Efficacy at 37+0 to 39+6 weeks of gestation

- A 2018 meta-analysis of four randomized trials of antenatal corticosteroids administered 48 hours before planned cesarean delivery at ≥37 weeks of gestation found:

- reductions in neonatal respiratory morbidity compared with placebo or no treatment

- A trend toward reduction in need for mechanical ventilation w

- Neonatal hypoglycemia and long-term outcomes in offspring were not reported

Evidence

Efficacy at 34+0 to 36+6 weeks of gestation

- A 2016 meta-analysis found statistically significant reductions in severe RDS and transient tachypnea of the newborn

- No data are available about the long-term neurodevelopmental outcomes of children exposed to corticosteroids between 34+0 and 36+5 weeks of gestation

TIMING BEFORE DELIVERY

- Maximum efficacy appears to occur when delivery occurs two to seven days after administration of the first dose of antenatal corticosteroids
- Efficacy is incomplete <24 hours from administration and appears to decline after 7 days
- Observational data suggest neonatal benefits begin to accrue within a few hours of corticosteroid administration Infants who received one dose but delivered before the second dose was given, had better outcomes than infants who did not receive any antenatal corticosteroids
- Laboratory data also support an early physiologic effect as early as 6 hours following the first injection

- Antenatal corticosteroid therapy should be administered when indicated unless imminent delivery is anticipated .

- Therapy should not be withheld if delivery is anticipated prior to completion of the second dose of the first course of medication.

- We suggest this liberal approach to treatment because the minimal interval between drug administration and delivery required to achieve neonatal benefits has not been clearly defined and the hour of delivery cannot be predicted accurately.

CHOICE OF DRUG AND INITIAL DOSE

- **Betamethasone and dexamethasone** —
- Both are effective for accelerating fetal lung maturity; either drug is acceptable for antenatal corticosteroid therapy

- These steroids are preferred over other steroids because they are less extensively metabolized by the placental enzyme

- A course of therapy consists of:
- ●Betamethasone two doses of 12 mg given intramuscularly 24 hours apart
- ●Dexamethasone four doses of 6 mg given intramuscularly 12 hours apart

- We prefer betamethasone because:

1. long-term follow-up data of fetuses exposed only to dexamethasone are limited and do not clearly demonstrate equivalence or superiority of dexamethasone over betamethasone for both short- and long-term outcomes.

2. Use of betamethasone also requires fewer injections than use of dexamethasone.

SAFETY AND SIDE EFFECTS OF A SINGLE COURSE THERAPY

- Administration of a single course of antenatal corticosteroid therapy before 34+0 weeks of gestation appears to be safe for the fetus/infant and mother, but has some side effects.

- The safety of administration later in pregnancy is less clear

Potential fetal side effects

- Fetal heart rate and biophysical parameters
- Doppler flow studies
- Potential adverse effects on infants
- Potential long-term effects in children and adults
- Maternal side effects

USE OF REPEATED COURSES OF THERAPY

- Up to date
- The American College of Obstetricians and Gynecologists (ACOG)

USE OF REPEATED COURSES OF THERAPY

up to date:

- A single repeat dose of betamethasone 12 mg to pregnancies up to 34 weeks of gestation with all of the following characteristics:

✓ Clinically estimated to be at high risk of delivery within the next one to seven days

✓ Prior exposure to antenatal corticosteroids at least 14 days earlier

✓ Initial course of antenatal corticosteroids administered at ≤28 weeks of gestation.

USE OF REPEATED COURSES OF THERAPY

up to date:

- A single dose rather than a two-dose course

- A single repeat course of therapy using the two-dose betamethasone or four-dose dexamethasone regimen is also reasonable and commonly used.

USE OF REPEATED COURSES OF THERAPY

ACOG:

- A single repeat course of antenatal corticosteroids should be considered in women who:
- are less than 34+0 weeks of gestation
- have an imminent risk of preterm delivery within the next 7 days,
- whose prior course of antenatal corticosteroids was administered more than 14 days previously.

- Rescue course corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario"

NONSTANDARD DOSING REGIMENS

- Higher dose
- Shorter dosing interval
- Intravenous administration
- Oral administration

When is fetal lung maturity testing performed?

- Fetal lung maturity testing before delivery is rarely performed.

- It is not useful as a component of delivery timing decision-making in pregnancies with:

When is fetal lung maturity testing performed?

- well-documented gestational age ≥39 weeks
- pregnancies less than 32 weeks of gestation
- when delivery is obstetrically/medically indicated
- If a pregnancy is suboptimally dated (no ultrasound examination before 22+0 weeks), timing of delivery should be based on the best clinical estimate of gestational age and standard indications for intervention; fetal lung maturity testing is not recommended as a component of decision-making.

When is fetal lung maturity testing performed?

- A test for fetal lung maturity may be performed before semielective but medically indicated births <39 weeks when this information significantly impacts assessment of the balance between the maternal-fetal risks of continuing the pregnancy versus the maternal-fetal risks of preterm birth.

  - This is an infrequent occurrence.

Fetal maturity tests

- Fetal lung maturity can be assessed by testing for components of fetal lung secretions in amniotic fluid.
- No test performs significantly better than another,
- all are better at predicting the absence, rather than the presence, of respiratory distress.

- **Lamellar body count**
- **Phosphatidylglycerol**
- **Lecithin/sphingomyelin ratio**

Fetal maturity tests

- The choice of test should be based upon availability, presence or absence of contaminants, and physician preference.
- The lamellar body count is the test generally used for assessing fetal lung maturity in the United States. The other tests may be available in some hospital laboratories.

Fetal maturity tests

- Fetal lung maturity can be assessed by testing for components of fetal lung secretions in amniotic fluid.
- No test performs significantly better than another,
- All are better at predicting the absence, rather than the presence, of respiratory distress.
- It is suggested performing only one test for fetal lung maturity on an amniotic fluid sample.

- Blood or meconium in amniotic fluid affects some test results

- Oligohydramnios, polyhydramnios, and source of amniotic fluid (vaginal pool versus amniocentesis) can also affect results.

- The same threshold value for lung maturity can be used for both nondiabetic and diabetic patients (pregestational or gestational diabetes).