TOCOLYTIC DRUGS IN PRETERM LABOR

PGS. TS. Đang Thi Minh Nguyet

Preterm labor

- Pathogenesis - Unclear
- Diagnosis - Difficult
- Prevention – Controversy
- Management – Unpredictable
- Cost – High

Preterm labor

In most of contries, the diagnostic of preterm labour just bases on clinical data

Excessive management:

Hospitalization

Use tocolytic

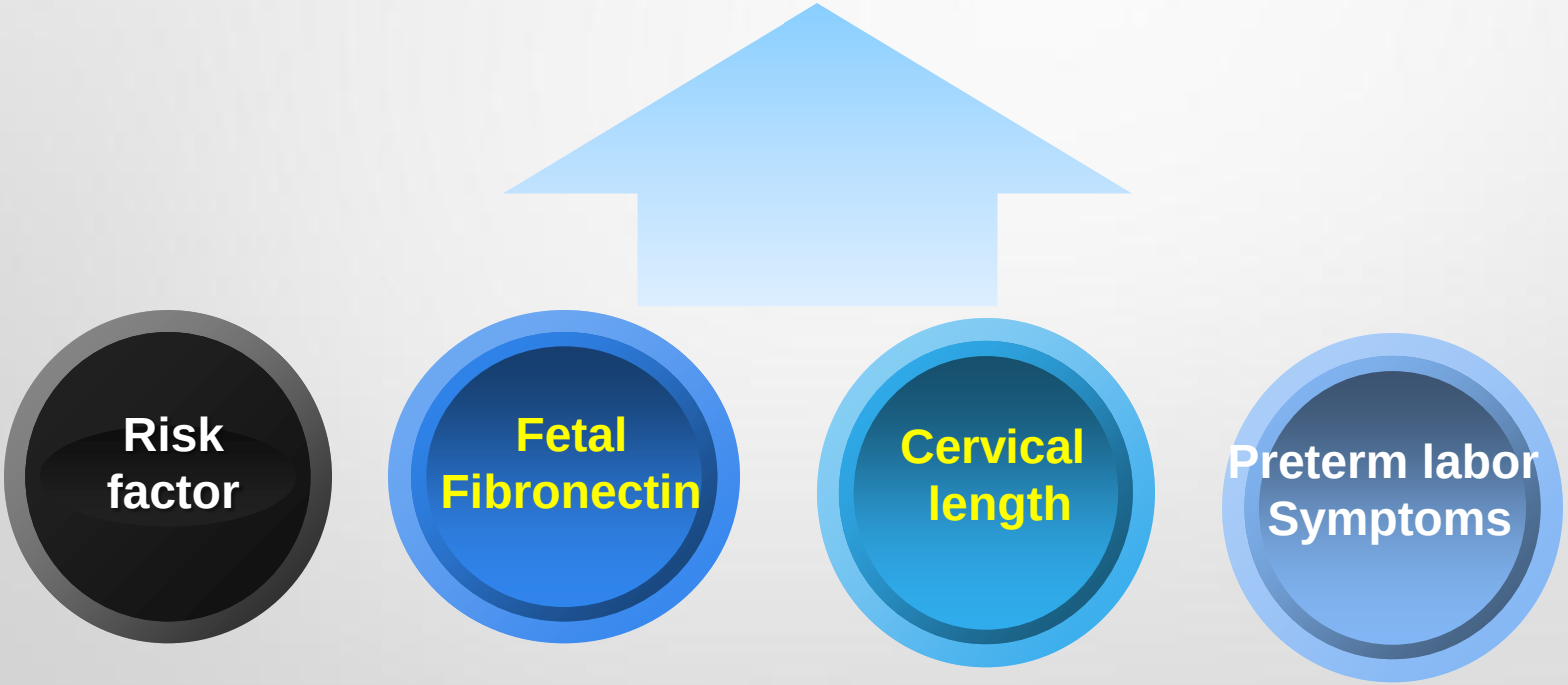
Corticosteroids

high cost

unnecessary interventions and potential negative consequences

PRETERM LABOR

How to identify subjects at risk ?



Prediction of preterm labor: measure cervical length (CL)

- CL >2.5 cm → **low risk of preterm labor**
- CL <1.5 cm → high risk of **preterm labor**

Evaluation of a novel placental alpha microglobulin-1 (PAMG-1) test to predict spontaneous preterm delivery

- Subject of reseach is 101 singleton pregnancies, 20w- 36 6/7 w, had symptoms of threatened preterm, iclinica Intact membrane and minimal cervical dilatation (<3cm)
- A positive PartoSure test in pregnancy with symptoms of preterm labor, intact membranes, and minimal cervical dilatation (≤3 cm) indicated spontaneous preterm delivery will occur within 7 days with a high degree of accuracy. A negative result indicated that spontaneous preterm delivery within 14 days is highly unlikely.

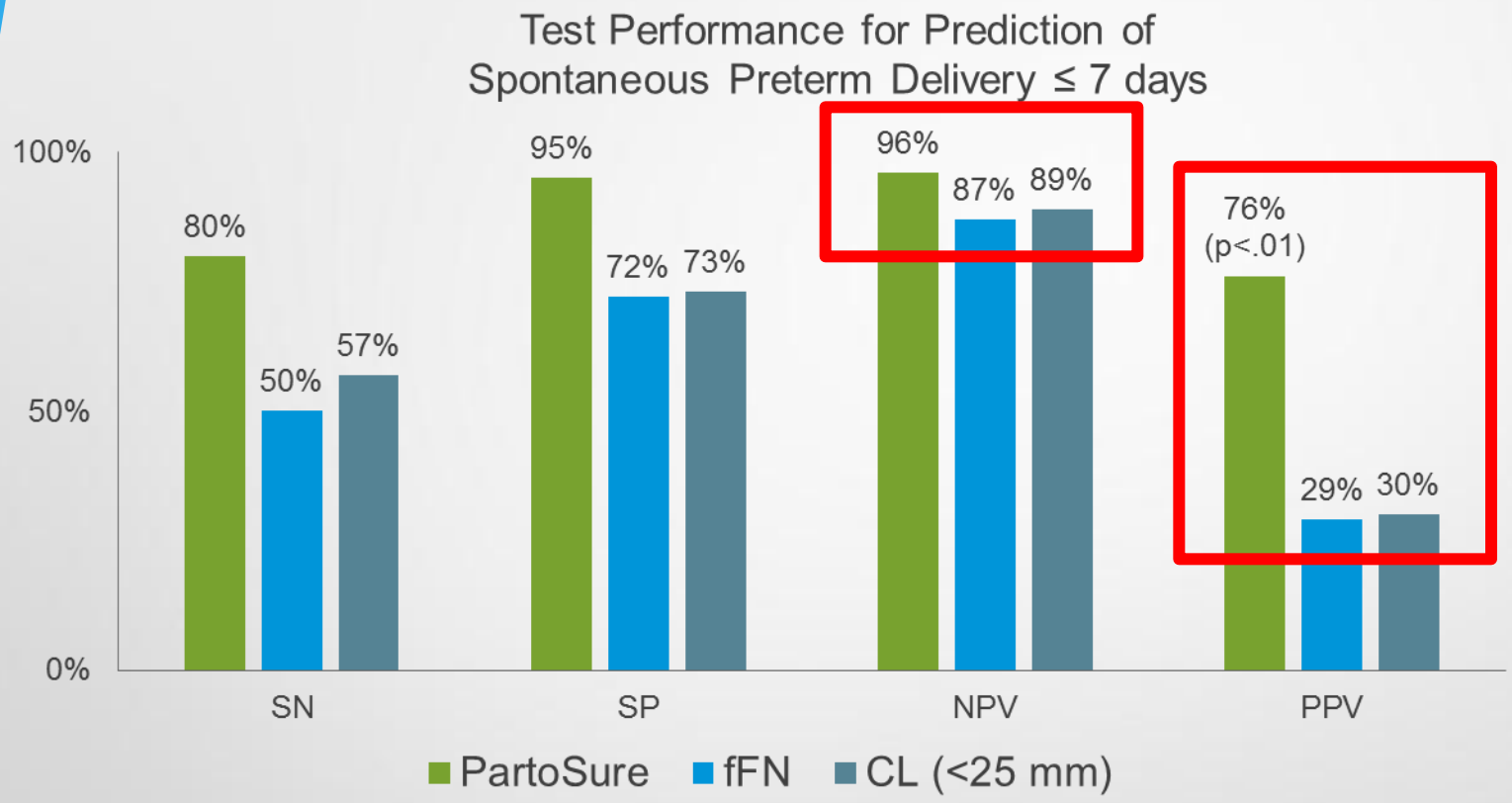
Table 2 PartoSure™ time-to-delivery (TTD) test performance metrics.

TTD (days)	NPV (95% CI)[a]	PPV (95% CI)[a]	SN (95% CI)[a]	SP (95% CI)[a]
≤7	97.4% (91.0%–99.7%)	78.3% (56.3%–92.5%)	90.0% (68.3%–98.8%)	93.8% (86.2%–98.0%)
≤14	93.6% (85.7%–97.9%)	87.0% (66.4%–97.2%)	80.0% (59.3%–93.2%)	96.1% (88.9%–99.2%)

[a]The Clopper-Pearson procedure computed 95% confidence intervals (CI). NPV=negative predictive value, PPV=positive predictive value, SN=sensitivity, SP=specificity.

Nikolova T, Bayev O, Nikolova N, Di Renzo GC. Evaluation of a novel placental alpha microglobulin-1 (PAMG-1) test to predict spontaneous preterm delivery. J Perinat Med. 2014 Jul;42(4):473-7.

PartoSure in comparison with Fetal Fibronectin and Cervical length measurement



"PartoSure is the single best predictor of imminent spontaneous delivery in women with symptoms of preterm labor, compared to fFN and CL"

Nikolova T, Bayev O, Nikolova N, Di Renzo GC. Comparison of a novel test for placental alpha microglobulin-1 with fetal fibronectin and cervical length measurement for the prediction of imminent spontaneous preterm delivery in patients with threatened preterm labor. J Perinat Med. 2015 Jan 6. [Epub ahead of print]

New method to predict spontaneous preterm delivery in women with symptom of preterm labor

Stratify CL in prediction of **spontaneous preterm delivery in women with symptom of preterm labor**

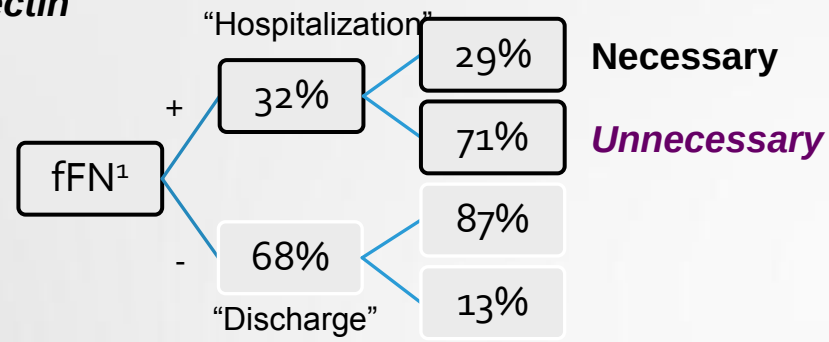
	CL < 15 mm	CL 15- 30 mm	CL > 30 mm
% population	6% (3/49)	85% (42/49)	8% (4/49)
PartoSure (PAMG-1) +	100%	2% (1/42)	0
PartoSure (PAMG-1) -	0	98% (41/42)	100%
Delivery within 7 days	67% (2/3)	2% (1/42)	0
Positive PartoSure test in patients deliver in 7 days	100%	100%	N/A

Women with CL between 15 mm - 30 mm:

- **100% patient with PartoSure (PAMG-1) (+) deliver in 7 days**
- **100% patient with PartoSure (PAMG-1) (-) not deliver in 7 days**

Unnecessary hospitalization

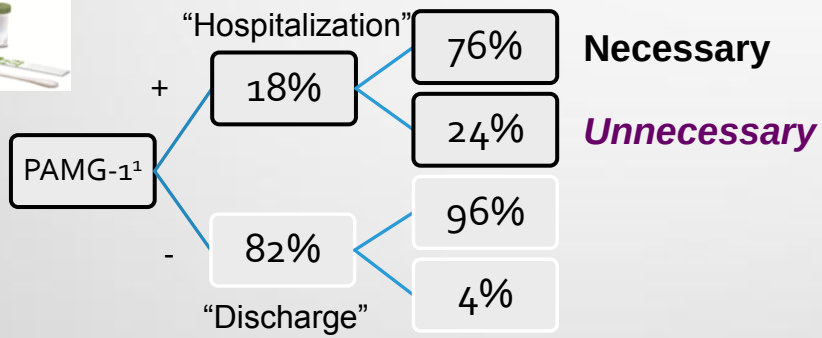
Fetal Fibronectin (fFN)



Necessary

Unnecessary

PartoSure



Necessary

Unnecessary

Key points

- The average cost for an unnecessary hospitalization estimates **$20,372 USD** [2]
- PartoSure can reduce 80 % of unnecessary hospitalization

"The statistical studies showed the outstanding efficence of PartoSure test in compairison with fFN and cervical length in specificity and positive predictive value (P<0.01), have provided evidence to improve clinical practice to reduce the unnecessary hospitalisation and excessive treatment with potentially harmful effects for women as well as to reduce the health burden"

(1) Di Renzo et al. JPM 2015. (2) Lucovnik et al. AJOG 2013

REASONABLE USE OF TOCOLYSIS

Indication of Tocolysis

- **Main target**
  - Delay delivery to use glucocorticoids to reduce respiratory distress syndrome and/or in-utero transfer to an NICU
- **Secondary target**
  - Prolonging pregnancy so the foetus can develop in oder to reduce perinatal mortality or morbidity

Suitable drugs in obstetric

- There are many drugs with no licensed during pregnancy, still frequently used in clinic
- There isn’t a powerful system to evaluate the safety of drugs.
- These make consultantcy with patients become difficult.

Contraindications

When the risks of prolonging pregnancy for mother and foetus or the risks of using tocolysis are higher than these risks related to preterm birth.

- In-utero fetal death
- Lethal fetal anomalies
- Fetal distress
- Severe preeclampsia or eclampsia
- Maternal bleeding with hemodynamic instability
- Chorioamnionitis
- Contraindications with tocolysis

Cyclo-oxygenase (COX) inhibitors

- Indomethacin is a nonspecific COX inhibitor,
- In a 2005 systematic review of randomized trials comparing any COX inhibitor with placebo for treatment of preterm labor, COX inhibitors reduced the risk of delivery within 48 hours of initiation of treatment (relative risk [RR] 0.19, 95% CI 0.07-0.51; two trials, n = 70) and within seven days (RR 0.44, 95% CI 0.26-0.74; two trials, n = 70), with no increase in any adverse neonatal outcome. COX inhibitors also reduce the risk of labor within 48 hours better than beta agonist (RR = 0.27 ; 95 % CI = 0.08 - 0.96).
- Thus , Indomethacin is the most effective tocolysis.

Cyclo-oxygenase (COX) inhibitors

❖ Fetal side effects: constriction of the ductus arteriosus and oligohydramnios. Premature ductal constriction have been reported in pregnancies in which the duration of indomethacin exposure exceeded 48 hours. However, this complication has not occurred in more than 500 fetuses exposed to shorter durations of indomethacin treatment .

❖Ductal constriction appears to depend upon both gestational age and duration of exposure. It has been described at gestations as early as 24 weeks, but is most common after 31 to 32 weeks. So, indomethacin is not recommended after 32 week. Before 32 week, fetal echocardiography is recommended to monitor the ductus arteriosus if duration of treatment exceeds 48 hours.

Cyclo-oxygenase (COX) inhibitors

❖ Neonatal effects: bronchopulmonary dysplasia, necrotizing enterocolitis, patent ductus arteriosus, periventricular leukomalacia, and intraventricular hemorrhage. These complications are still controversial.

❖ Dose: dose to inhibit labor is 50-100mg (oral or rectal) , followed by 25 mg every 4-6 hours. Fetal blood concentrations are 50 percent of maternal values, but the half-life in the neonate is substantially longer than that in the mother (15 versus 2.2 hours)

Calcium channel blockers

A system review and meta-analysis in 2014: calcium channel blockers reduces the risk of delivery within 48 hours (RR=0,3; 95%; CI=0,21-0,43).

There was no statistical reduction in this outcome compared with other classes of tocolytics (RR=0,86; 95%; CI=0,67-1,2).

However, calcium channel blockers have other benefit: serious neonatal morbidities (respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, jaundice and maternal adverse effects (RR=0,36; 95%; CI=0,24-0,52).

Calcium channel blockers

- Maternal side effects: Nifedipine is a peripheral vasodilator; thus, it may cause symptoms such as nausea, flushing, headache, dizziness, and palpitations. Arterial relaxation results in decreased total vascular resistance, which is accompanied by a compensatory rise in cardiac output (reflex increase in heart rate and increased stroke volume). These compensatory changes generally maintain blood pressure in women who have no underlying myocardial dysfunction .
- Severe hypotension have been reported in case repoerts.
- By comparison, beta-agonists are more frequently associated with adverse cardiovascular changes.

Calcium channel blockers

Calcium channel blockers are often used more than beta agonists because the drug is relatively safe, well tolerated with patient, easy to prescribe and produce less complications on infants

Dose: An optimal nifedipine dosing regimen for treatment of preterm labor has not been established. but clinically, administer an initial loading dose of 20 to 30 mg orally, followed by an additional 10 to 20 mg orally every 3 to 8 hours for up to 48 hours, with a maximum dose of 180 mg/day

The American College of Obstetricians and Gynecologists suggests a 30 mg loading dose and then 10 to 20 mg every four to six hours

Beta-agonists

✓The beta-2 agonists ritodrine and terbutaline have been studied in several randomized, placebo-controlled trials. Salbutamol and hexoprenaline have also been evaluated, but data are sparse. Although ritodrine is the only drug approved by FDA for the treatment of preterm labor, it is no longer available in the United States.

✓In a 2014 systematic review of beta-agonists for inhibiting preterm labor, beta-agonists decreased the number of women giving birth within 48h(RR 0.68, 95% CI 0.53-0.88) and within seven days (RR 0.80, 95% CI 0.65-0.98), but not before 37 weeks of gestation (RR 0.95; 95% CI 0.88-1.03). There was a trend toward reduction in respiratory distress syndrome (RR 0.87, 95% CI 0.71-1.08), but no effect on the neonatal death rate (RR 0.90, 95% CI 0.27-3.00)

Beta-agonists

Many of the maternal side effects of beta-agonists are related to stimulation of beta-1 adrenergic receptors, which increase maternal heart rate and stroke volume, and stimulation of beta-2 adrenergic receptors, which causes peripheral vasodilation, diastolic hypotension, and bronchial relaxation. The combination of these two cardiovascular effects leads to tachycardia, palpitations, and lower blood pressure. Some common side effects are: tremor (39 vs 4% with placebo), palpitations (18 vs 4%), shortness of breath (15 vs 1%), and chest discomfort (10 vs 1%), hypokalemia (39 vs 6%), hyperglycemia (30 vs 10%), and lipolysis. Myocardial ischemia is a rare complication

Warning about the use of betamimetics

Prolonged beta-agonist overstimulation during critical periods of prenatal development may induce a permanent shift in the balance of sympathetic-to-parasympathetic tone, which may lead to development of certain disease processes

Warning about the use of betamimetics

❖ The period during which this tocolysis is most harmful can be the period of maximum development of the fetal brain, from the middle or end of second trimester to at least third trimester.

❖ Besides the disorders related to autism, these drugs can increase the risk of psychiatric disorder, poor cognitive, motor retardation and blood pressure change

❖The available data show an increased risk of autism in infants exposed to high doses of this medication continuously for ≥ 2 weeks.

Oxytocin receptor agonist

In 2014, a systematic review and meta-analysis found that atosiban was as effective as beta-agonists for preventing preterm birth within 48 hours of initiating treatment (RR 0.89, 95% CI 0.66-1.22)

Oxytocin receptor agonist

❖The rate of adverse effects is lower than any other tocolysis in inhibiting preterm birth.

❖ The group treated by atosiban has less side effect on womens than the group using beta-agonist (RR=0,05; 95%; CI=0,02-0,11 This is the biggest advantage of this tocolysis.

❖ There are no absolute contraindication of atosiban.

Side effects observed after treatment of one tocolytic agent (n=1333)

Tocolysis	N	Nặng	Nhẹ
Nifedipine	543	5 (0.9%)*	8 (1.5%)*
β mimetic	158	3 (1.9%)*	4 (2.5%)*
Atosiban	576	0 (0)	1 (0.2%)

*Statistically significant difference when compared to **Atosiban**

de Heus R, et al.2009

Tocolysis

Treatment	Side effect	Benefit
1 Indomethacin	++++	++++
2 β mimetic	+++	++
3 Calcium channel blocker	++	++
4 Oxytocin receptor agonist	+	++

Mg-SO4, dẫn xuất NO không có tác dụng

Visser 2014

Magnesium sulphate

In a 2014 systematic review of randomized trials comparing magnesium sulfate with no treatment/placebo control, magnesium sulfate administration did not result in a statistical reduction in birth <48 hours after trial entry (RR 0.56, 95% CI 0.27-1.14; three trials, 182 women) or improvement in neonatal and maternal outcomes

In 33 comparative trials, magnesium sulfate was neither more nor less effective than other tocolytics (betamimetics, calcium channel blockers, cox inhibitors, prostaglandin inhibitors

Magnesium sulphate

Maternal side effects : Diaphoresis and flushing are the most common side effects; magnesium toxicity is related to serum concentration

Fetal side effects : magnesium therapy can cause fetal heart rate reduction and reduce basic cardiac fluctuation but not clinically meaningful.

Magnesium sulphate

❖ Retrospective epidemiologic studies have reported a significant increase in radiographic bone abnormalities in neonates with in utero exposure to magnesium sulfate for more than seven days, and a significant difference in the serum values of magnesium, calcium, phosphorus, and osteocalcin (a marker of bone formation) at birth between neonates unexposed to magnesium sulfate and those who were exposed.

❖Based on these and other data, in May 2013, the FDA advised healthcare professionals in the United States against using magnesium sulfate infusions for more than five to seven days to stop preterm labor

Magnesium sulphate

❖ $MgSO_4$ is a neuroprotection agent for fetus, infants and children after premature birth, which can reduce the incidence of cerebral palsy and mortality of cerebral palsy.

❖ The American College of Obstetricians and Gynecologists recommends limiting $MgSO_4$, just use in 48 hours in threatened preterm birth of 24-32 weeks.

❖ The minimum period for drug neuroprotective effect has not been studied.

Conclusion

- avoid concurrent use of tocolytic drugs because of the increased risk of side effects
- If the first-line drug does not inhibit contractions, discontinue it and begin therapy with another agent
- indomethacin as first-line therapy for labor inhibition but not used much because of its side effects.
- The second line therapy is nifedipin.

Conclusion

- Salbutamol has many maternal and fetal side effects
- $MgSO_4$ is administered in case of risk preterm birth before 32 weeks within 24 hours.
- Atosiban (Tractocile) can well inhibit the contraction, its side effects is less than any other tocolytic drugs, especially in case of contraindication of nifedipin, diabetes, multiple pregnancies...


Thank you!