Preterm Labor Management: From Principle to Practice

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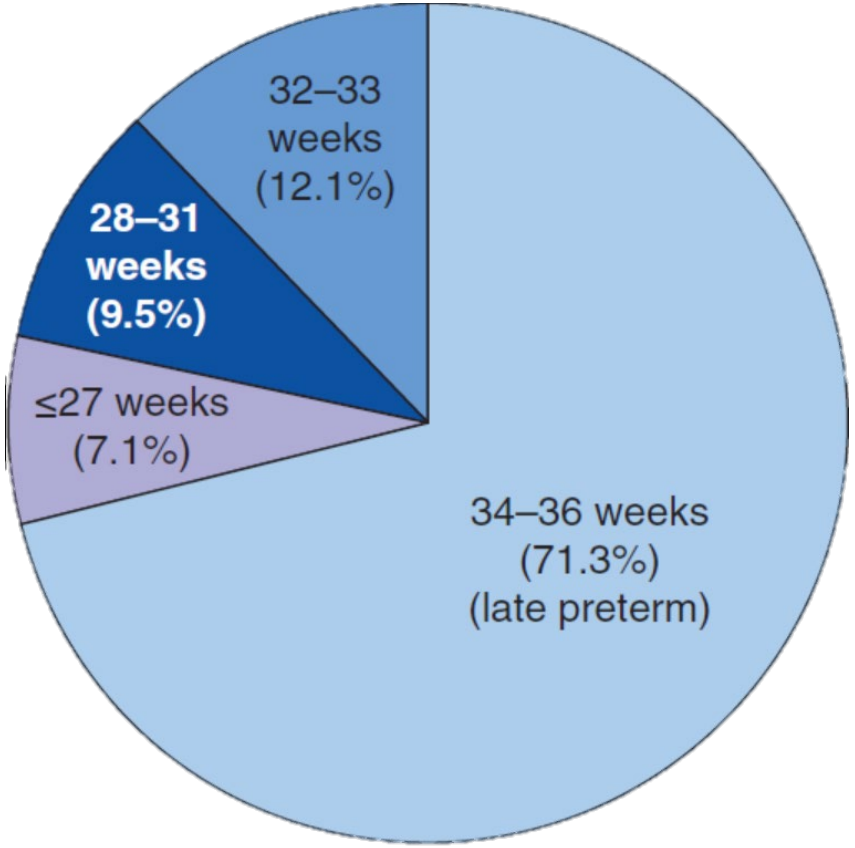
Outline

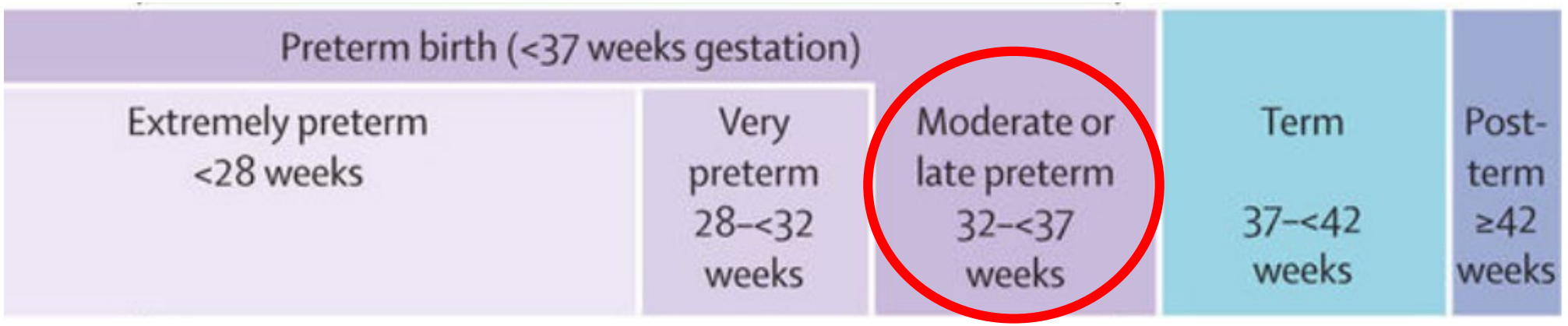
- Background
- Assessment
- Current guidelines
- Case Sharing
- Take home message

Background

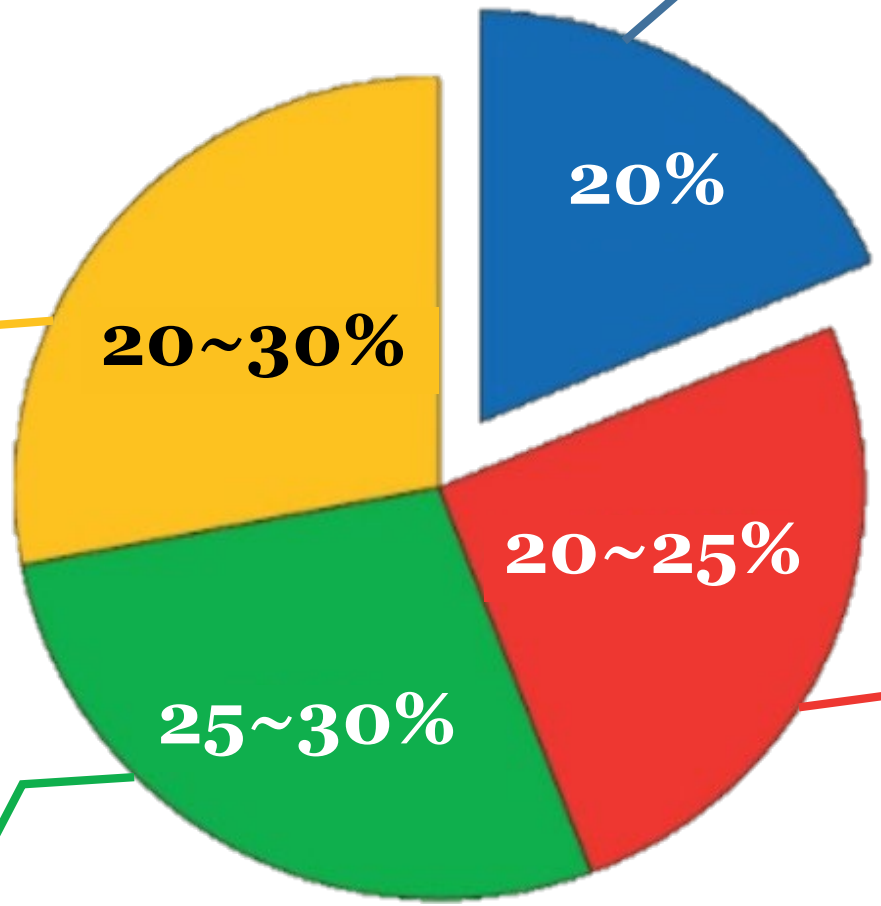
- Definition:

  Any delivery occurring prior to 37 weeks
- Incidence: **12%** of live-births





Causes



Iatrogenic

-Maternal: PE
-Fetal: IUGR, nonreassuring fetal testing

Infection

Spontaneous preterm labor

PPROM

Assessment

Fetal fibronectin → QuikCheck fFN™

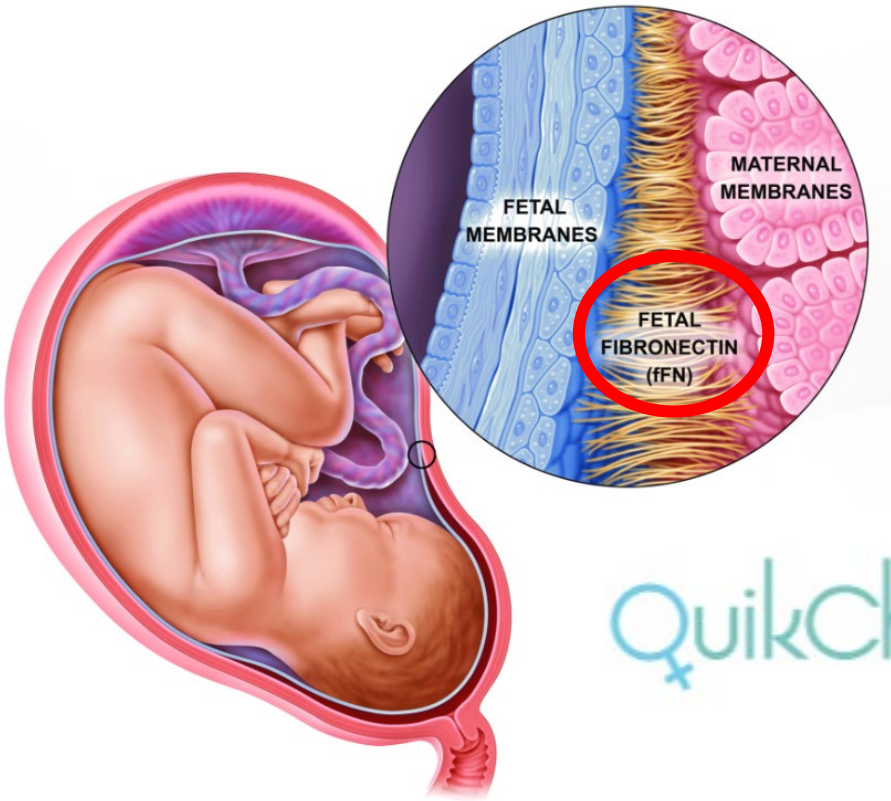
PAMG-1 → PartoSure™ Time to Delivery (TTD) Test

phIGFBP-1 → Actim® Partus

Prediction of preterm delivery in symptomatic women using PAMG-1, fetal fibronectin and phIGFBP-1 tests: systematic review and meta-analysis ; Ultrasound Obstet Gynecol 2018; 52: 442–451
Preterm Labor and Birth Management: Recommendations from the European Association of Perinatal Medicine. J Matern Fetal Neonatal Med 2017; 30: 2011–2030

Fetal fibronectin

Component of the amniochorionic extracellular matrix aiding in membrane adherence to the decidua



QuikCheck fFN™

- Positive test for **fFN (>50 ng/ml)** between GA 22~34 can be a sign that the PTB is imminent

[1] Health Technol Assess, 2013 Sep;17(40):1-138. doi: 10.3310/hta17400
[2] Predictive performance of PAMG-1 vs fFN test for risk of spontaneous preterm birth in symptomatic women attending an emergency obstetric unit: retrospective cohort study, Ultrasound Obstet Gynecol. 2018 May;51(5):644-649.

Fetal fibronectin

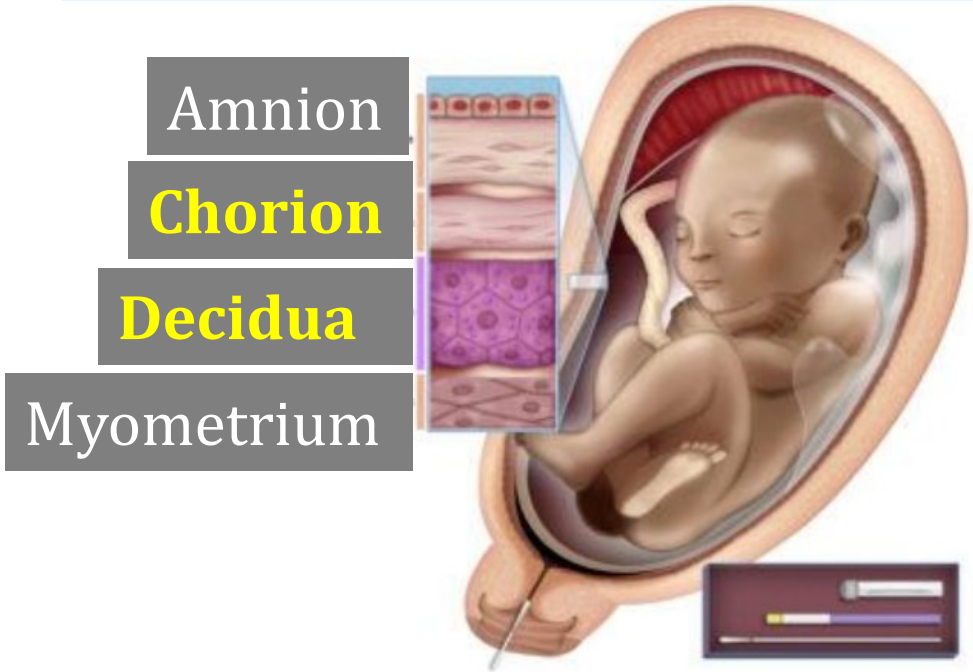
- Vaginal bleeding
- Multiple pregnancy
- Routine screening for high risk asymptomatic women

[1]Fetal fibronectin as a biomarker of preterm labor: a review of the literature and advances in its clinical use. Biomarkers in medicine. 2014;8(4):471-484
[2]The effect of blood staining on cervicovaginal quantitative fetal fibronectin concentration and prediction of spontaneous preterm birth. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2017;208:103-108
[3] The fetal fibronectin test: 25 years after its development, what is the evidence regarding its clinical utility? A systematic review and meta-analysis. The Journal of Maternal-Fetal & Neonatal Medicine. 2020;33(3):493-523
[4] Cervicovaginal fetal fibronectin for the prediction of spontaneous preterm birth in multiple pregnancy: a systematic review and meta-analysis. J Matern Fetal Neonatal Med 2010;23:1365–76.

phIGFBP-1

Actim® Partus

Produced by **decidua**
Leaks into the cervix when decidua and chorion detach



PAMG-1

PartoSure™

Time to Delivery (TTD) Test

A protein released from decidual cells into the **amniotic cavity** throughout pregnancy.

PAMG-1

Does not require a speculum examination
(Can be used after vaginal exam and coitus)

Specimens valid within 24 hours of collection
-or stored refrigerated at 2˚ ~ 8˚C: last for five days

Bloody samples may lead to false-positive results

Fetal fibronectin/PAMG-1/ phIGFBP-1

PAMG-1 ($n = 14$) (Patients, $n = 2278$)	fFN ($n = 40$) (Patients, $n = 7431$)	phIGFBP-1 ($n = 22$) (Patients, $n = 3192$)

	PAMG-1	fFN	phIGFBP-1
PPV	76.3% (95% CI, 69–84%)	34.1% (95% CI, 29–39%)	35.2% (95% CI, 31–40%)
NPV	96.6% (95% CI, 94–99%)	93.3% (95% CI, 92–95%)	98.7% (95% CI, 98–99%)

Prediction of preterm delivery in symptomatic women using PAMG-1, fetal fibronectin and phIGFBP-1 tests: systematic review and meta-analysis ; Ultrasound Obstet Gynecol 2018; 52: 442–451

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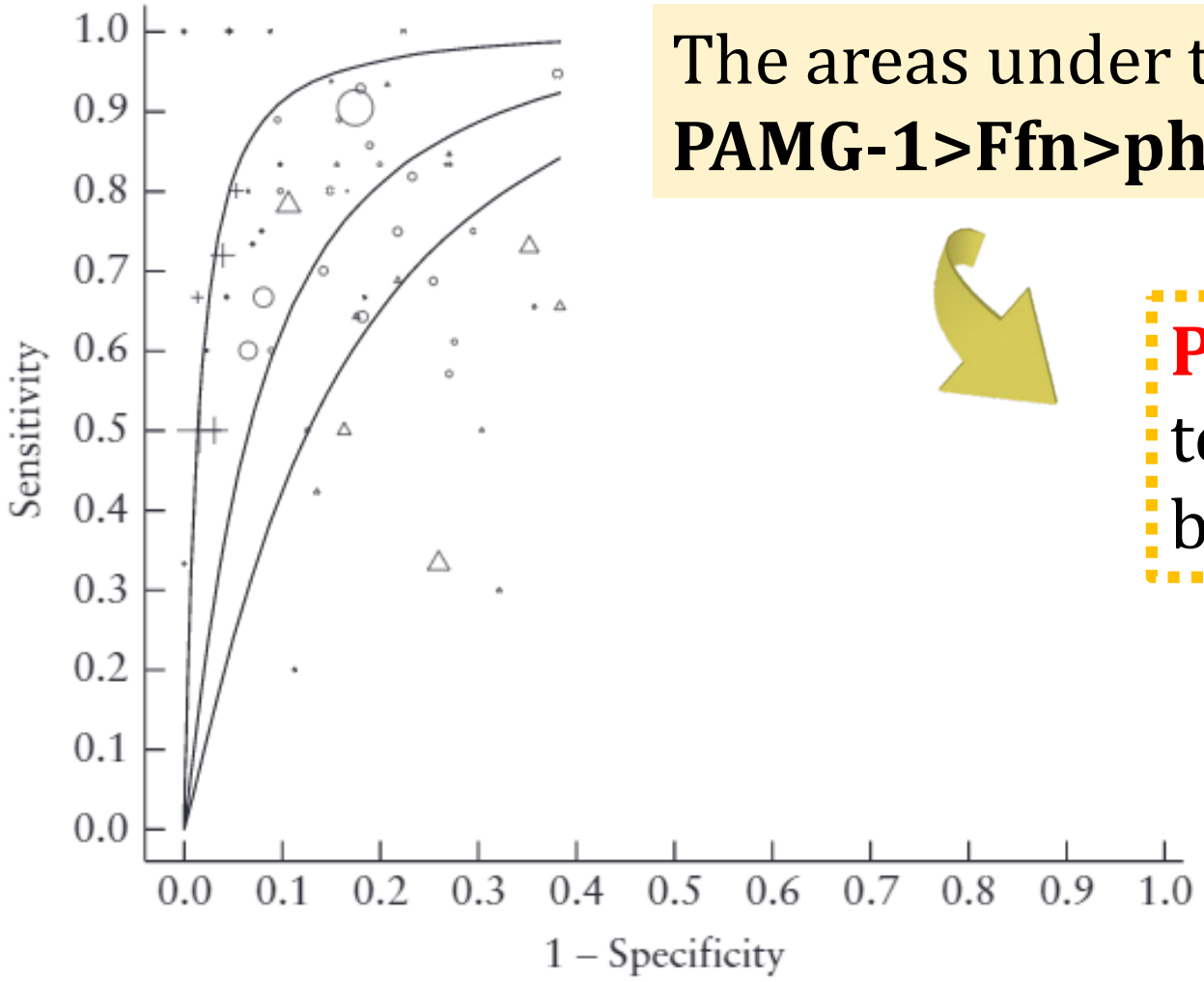
sPTB within 7 days of testing in women with signs and symptoms of preterm labor, the PPV of **PAMG-1** was significantly higher.

Fetal fibronectin/PAMG-1/ phIGFBP-1



The areas under the ROC curves
PAMG-1>Ffn>phIGFBP-1

PAMG-1 test is the most accurate test to be used in women with a CL between 15 and 30 mm

Prediction of preterm delivery in symptomatic women using PAMG-1, fetal fibronectin and phIGFBP-1 tests: systematic review and meta-analysis ; Ultrasound Obstet Gynecol 2018; 52: 442–451

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

PRACTICE BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN–GYNECOLOGISTS

NUMBER 171, OCTOBER 2016

(Replaces Practice Bulletin

Reaffirmed 2018

Management of Preterm Labor

Candidates?

Benefit from a 48-hour delay

- **Less than 10% born within 7days**
- **30% resolved spontaneously**
- **50% hospitalized women delivery at term**

Only preterm contraction without cervical change

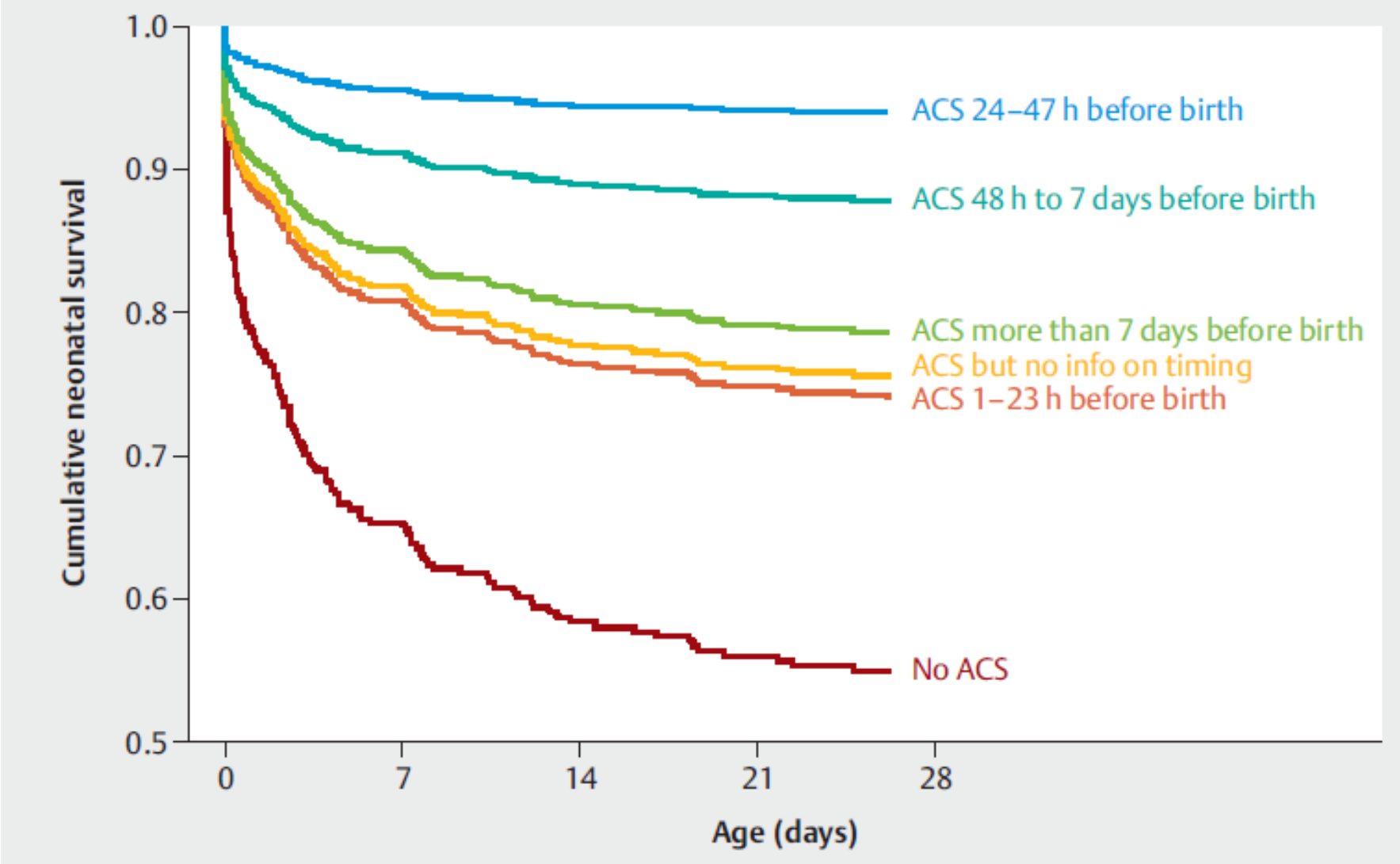
Prophylactic tocolytic therapy

Antenatal corticosteroids

23+0~33+6 weeks of gestation

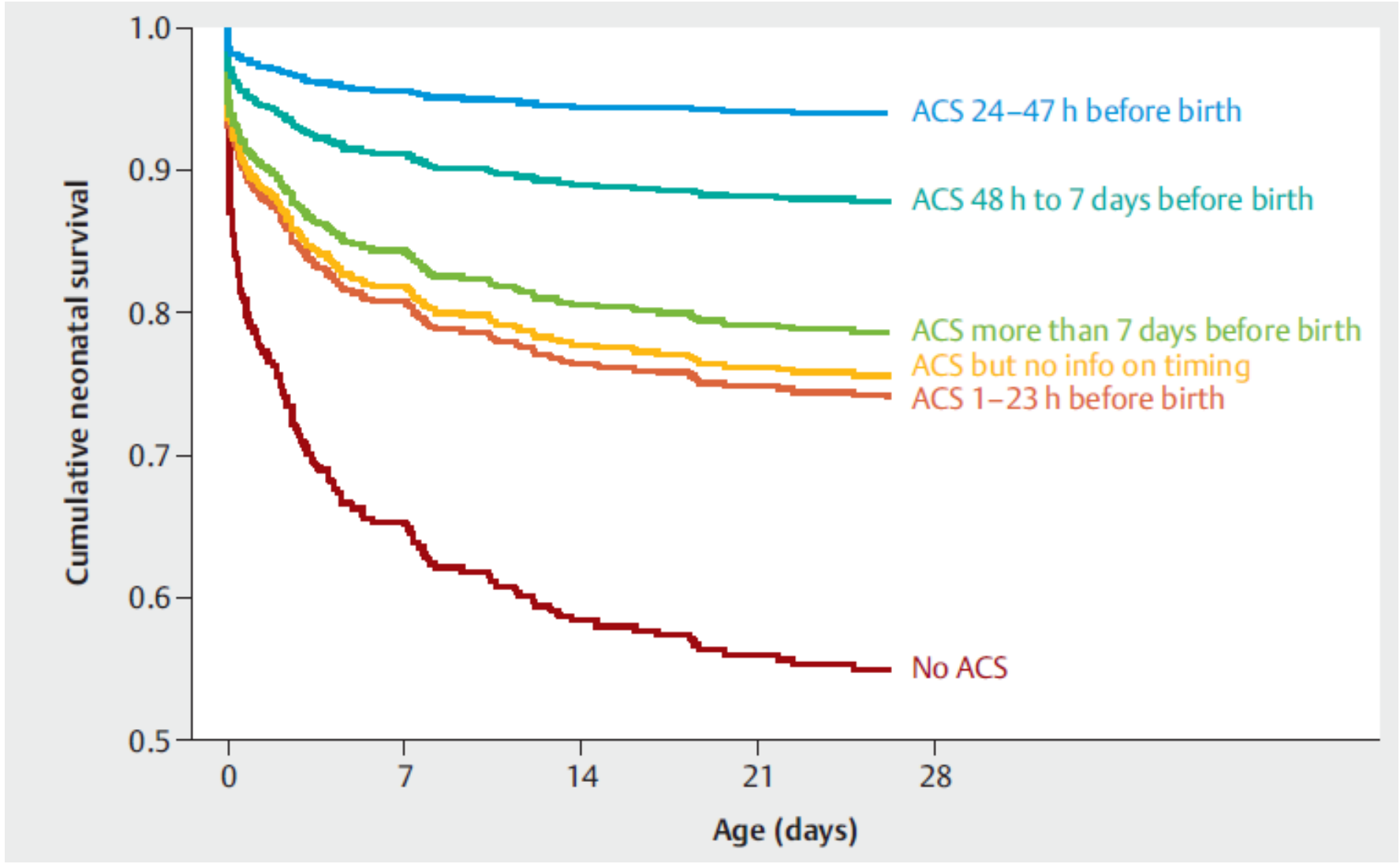
Regiment

- Betamethasone(12mg QD*2days)
- Dexamethasone (6mg Q12H*2days)



Survival of very immature infants (< 26th week of gestation) according to the timing of antenatal steroid administration

Timing of antenatal corticosteroid administration and survival in extremely preterm infants: a national population-based cohort study. BJOG 2017; 124: 1567–1574



24-47hr > **48hr~7day** > **>7 days** > **1-23hr** > **No**

Antenatal corticosteroids
-A single repeated course

ACOG

< 34+0 weeks of gestation and in risk of preterm delivery within 7 days and the prior course was administered **14 days** previously. (Rescue course could be administered as early as 7 days)

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< 34+0 weeks of gestation and in risk of preterm delivery within 7 days and the prior course was administered **14 days** previously.
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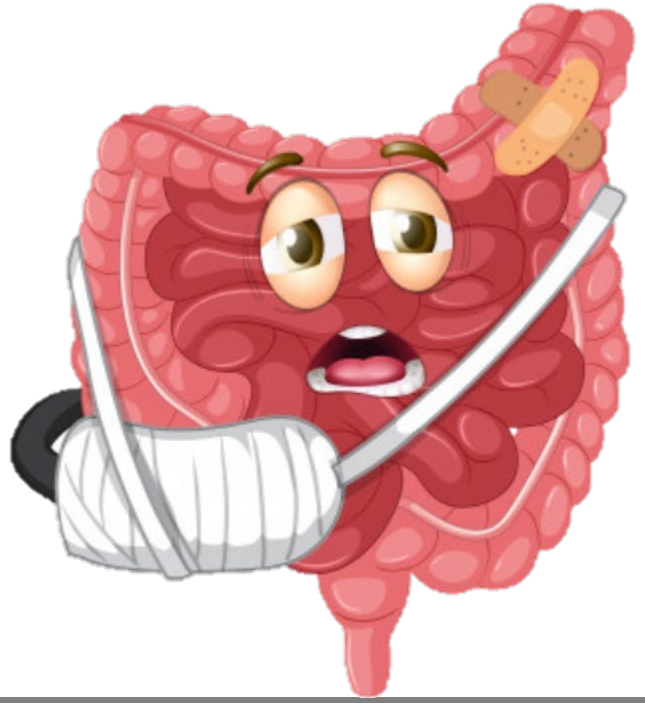
EUROPEAN GUIDELINE

Administered to women before the **29 + 0 week** of gestation
+ administered more than **7 days** previously

Antenatal corticosteroids
-Rapid maturation

Administration of a second dose of betamethasone after just **12h** rather than after 24 h, **should be avoided** as this significantly increases the risk of **necrotizing enterocolitis.**



02 $MgSO_4$

< 32 weeks of gestation
Improved the neurological outcomes

None of the trials demonstrated pregnancy prolongation

Magnesium sulphate for preventing preterm birth in threatened preterm labour. Cochrane Database Syst Rev 2014; (8): CD001060
Management of preterm labor, ACOG Practice bulletin, Number 171, Oct 2016

03 Antibiotics

PPROM(+)

→Prolong pregnancy & reduce newborn infections

<34+0 weeks' gestation: h
2 days of ampicillin+erythromycin(IV) followed by amoxicillin+erythromycin(PO) for 5 days

Amoxicillin–clavulanic acid(Augmentin) has been associated with increased rates of necrotizing enterocolitis and it is **not** recommended

03 Antibiotics

PPROM(+)

→Prolong pregnancy & reduce newborn infections

PPROM(-)

NO effect on pregnancy prolongation or on the improvement of newborn outcomes

Antibiotics in NTUH

PPROM (+)

- < 34+0 weeks' gestation:
  2 days of Cefmetazone (1g IV q8h)+Zithromax (1g PO stat) followed by amoxicillin (500mg q8h PO) for 5 days.

Tocolytics

EUROPEAN GUIDELINE

- Indicated between GA22+0 ~ GA33+6
- Administered if spontaneous, regular, **preterm contractions of ≥ 4/20 min** with **shortening of the functional cervical length** (transvaginal measurement) and/or opening of the cervix.
- Delay the birth by 48 h in 75–93% of cases and by 7 days in 62–78% of cases.

Adverse drug reactions to tocolytic treatment for preterm labour: prospective cohort study. BMJ 2009;338: b744
New WHO recommendations to improve the outcomes of pretermbirth. Lancet Glob Health 2015; 3: e589–e590

Tocolytics

EUROPEAN GUIDELINE

- Combining different tocolytics
  → **Significantly increased** rates of maternal side effects
  → **No** data confirming any increase in efficacy

Combining different tocolytics should be avoided

- Tocolytics should **not** be administered in combination with **oral/vaginal progesterone** ("adjunctive tocolysis")
  -Insufficient data.

Prevention of preterm delivery with vaginal progesterone in women with preterm labour (4P): randomised double-blind placebo-controlled trial. BJOG 2015; 122: 80–91
Adverse drug reactions to tocolytic treatment for preterm labour: prospective cohort study. BMJ 2009; 338: b744
Combination of tocolytic agents for inhibiting preterm labour. Cochrane Database Syst Rev 2014; (7):CD006169

Tocolytics

- Could use **Nifedipine, NSAID, β-adrenergic receptor agonist** for tocolytics.

- Maintenance therapy with tocolytics
  → Most are **ineffective**
  → Only **Atosiban** showed superiority than placebo as maintenance therapy

Tocolytics-Atosiban

Atosiban is at least **as effective** as standard of care in delaying delivery

Incidence of maternal and fetal adverse events are **significantly lower** with Atosiban than usual care

Tractocile® ATOSIBAN

Nifedipine versus atosiban for threatened preterm birth (APOSTEL III): a multicentre, randomised controlled trial. Lancet. 2016 May 21;387(10033):2117-2124.

ATOSIBAN (MOA)
(THE UTEROSPECIFIC TOCOLYTIC)

Binds to Oxytocin Receptors

Block calcium concentration

↓

Decrease in frequency and tone of myometrial contractions

↓

Relaxed uterus

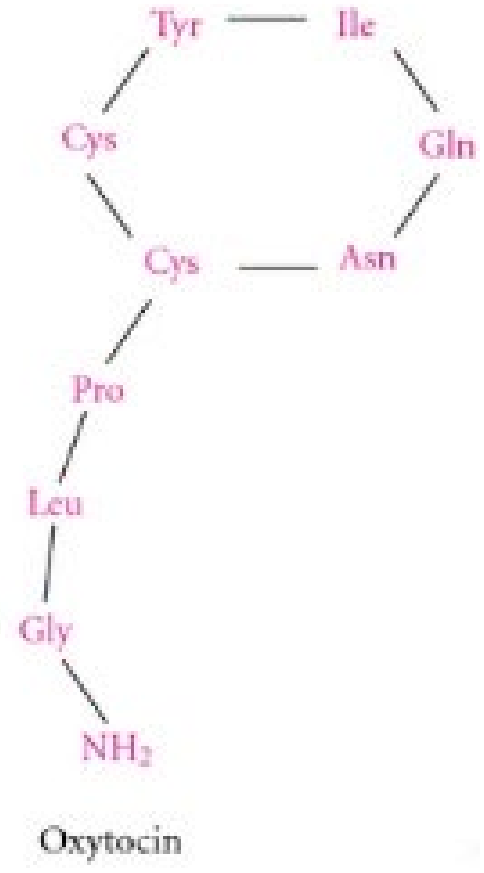
Avoid activating Vasopressin V_{1A}

↓

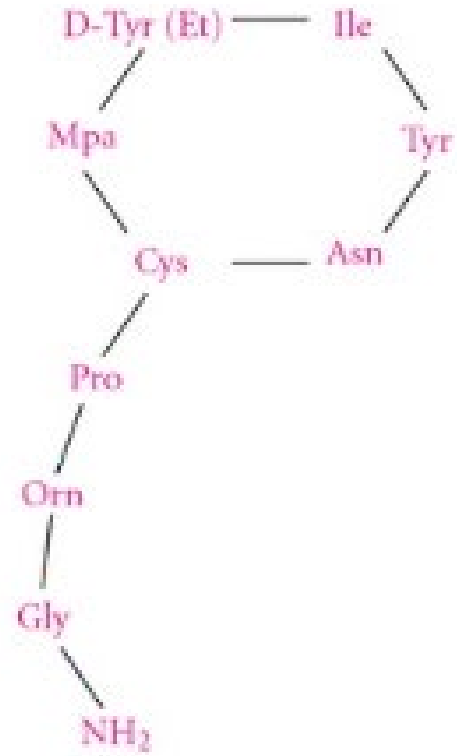
No uterine contraction & No vasoconstriction

↓

Relaxed uterus



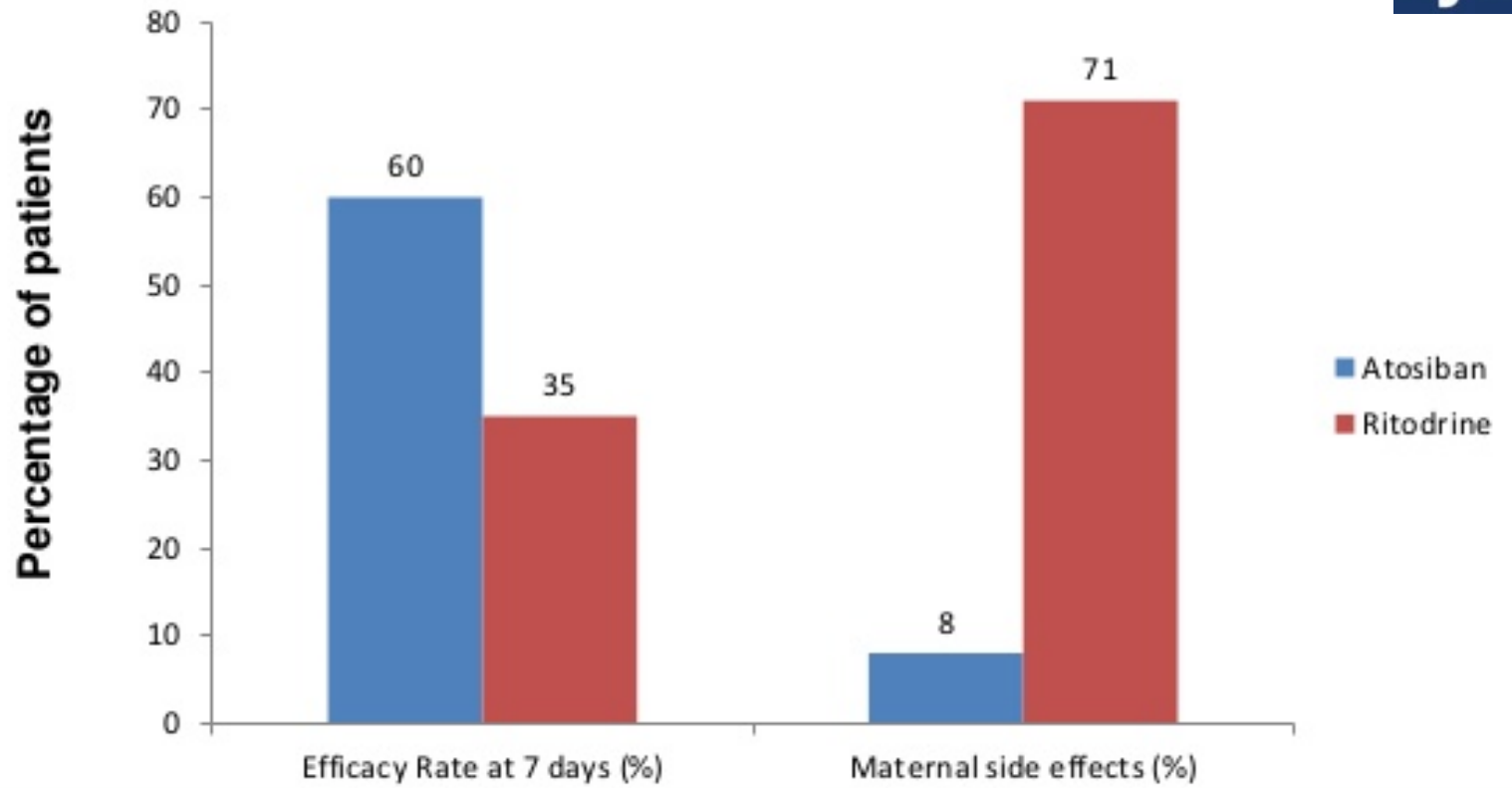
Oxytocin



Atosiban

- Atosiban doesn't alter uterine nor fetal arterial blood flow pattern.
- Hemodynamic cardiac activity in fetuses remains unaffected.

BJOG An International Journal of Obstetrics and Gynaecology



ATOSIBAN vs. RITODRINE

- The efficacy and safety of atosiban in the treatment of preterm labour were superior to those of ritodrine.

Multicentre, parallel group, randomised, single-blind study of the safety and efficacy of atosiban versus ritodrine in the treatment of acute preterm labour in Korean women. BJOG: An International Journal of Obstetrics & Gynaecology, 2006, 113: 1228-1234

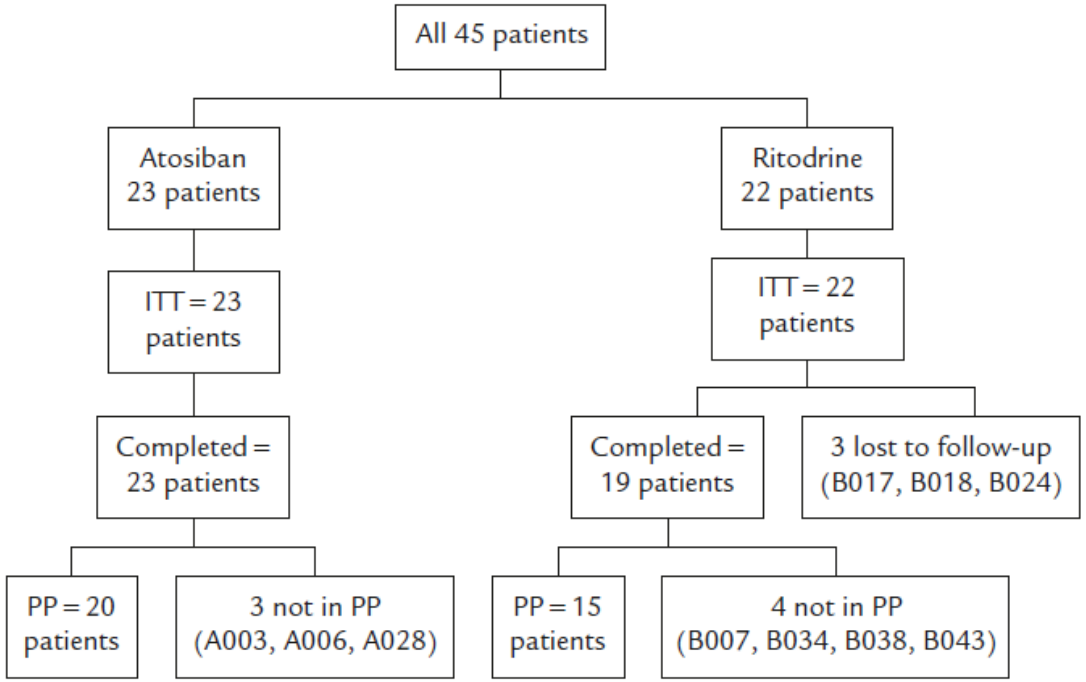


Table 2. Tocolytic efficacy of atosiban and ritodrine for patients without alternative tocolytic therapy who had not delivered at 2 and 7 days, and patients with initial treatment success*

	Atosiban ($n = 23$)	Ritodrine ($n = 22$)	95% CI	p
Tocolytic efficacy				
No delivery at 2 d	19 (82.6)	19 (86.4)	0.7–0.9	1.000
No delivery at 7 d	18 (78.3)	19 (86.4)	0.7–0.9	0.700
Initial treatment success	19 (95)	16 (72.7)	0.7–0.9	0.096

**Data presented as n (%). CI = confidence interval.*

Randomized trial of oxytocin antagonist atosiban versus beta-adrenergic agonists in the treatment of spontaneous preterm labor in Taiwanese women. J Formos Med Assoc. 2009;108(6):493-501.

Table 4. Summary of maternal adverse events (AEs) in relation to treatment drugs*

	Atosiban	Ritodrine
Total no. of women with AEs	3	4
Total no. of AEs	4	5
Relation of AE to treatment		
Unknown	1 (25)	0 (0)
None	1 (25)	0 (0)
Possible	1 (25)	0 (0)
Probable	1 (25)	2 (40)
Highly probable	0 (0)	3 (60)
Severity of AE		
Mild	1 (25)	1 (20)
Moderate	3 (75)	4 (80)
Severe	0 (0)	0 (0)

*Data presented as n (%).

Table 5. Proportion of patients with tachycardia or heart rate > 100 bpm at first treatment

	Atosiban		Ritodrine		*p*
	n/total *n*	%	*n*/total *n*	%	
Heart rate > 120 bpm (tachycardia)	0/22	0	4/22	18.2	0.1080
Heart rate > 100 bpm	3/22	13.6	20/22	90.9	< 0.0001*

*$p < 0.05$.

- Atosiban is an effective tocolytic drug without the conventional cardiovascular side effects often seen with beta-agonist treatment.

>>Twin pregnancy, hyperthyroidism

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International preterm labor guidelines

Countries	Guidelines and organizations	Treatment
UK	Royal College of Obstetricians and Gynaecologists (RCOG)	If tocolytics are to be used, atosiban or nifedipine is preferable. Atosiban is licensed and nifedipine is not. β_2-agonists should not be used.
Germany	German Society of Gynecologists & Obstetricians (DGGG)	No first-line recommendation. Atosiban, fenoterol, and nifedipine are equivalent. Atosiban has less side effects.
Austria	Austrian Society for Gynecology and Obstetrics (OEGGG)	β-Agonists or atosiban. Atosiban first line for certain patient groups.
Switzerland	No national guidelines	Not applicable
Belgium	GGOLFB and VVOG	GGOLF: Atosiban first-line treatment (48 h) with options of 3× repetitive treatments. VVOG: Atosiban is preferred treatment of choice.
The Netherlands	Dutch Gynecology Society (NVOG)	Both Atosiban and nifedipine are at 'first place' position.
France	SPTL guidelines College National des Gynecologues et Obstetriciens Francais (CNGOF)	Atosiban, β_2-agonists, and nifedipine first line of treatment. In multiple pregnancies, recommended first-line atosiban or nifedipine
Italy	SIGO	No first-line recommendation. Ritodrine and nifedipine are equivalent. Atosiban first line for 'risk patient'.
Norway	Norwegian Society of Obstetrics and Gynaecology (NGF)	(1) Atosiban; (2) nifedipine; (3) indomethicin; (4) terbutaline
Denmark	Danish Society of Obstetrics and Gynecology (DSOG)	Recommendation of atosiban as first line of treatment
Sweden	No national guidelines. Work in progress	80% of the guidelines at level III hospitals are recommending atosiban as first line.
Spain	SPTL guideline No. 10 Spanish Society of Gynecology and Obstetrics (SEGO)	Atosiban to be used as first choice

International preterm labor guidelines and tocolytic treatment recom- mendations from a selection of Western European countries (Presented at Ninth World Conference in Perinatal Medicine. Symposium on Uterine Contractility [Berlin] 2009).

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Atosiban is recommended as 1st line treatment

International preterm labor guidelines and tocolytic treatment recom- mendations from a selection of Western European countries (Presented at Ninth World Conference in Perinatal Medicine. Symposium on Uterine Contractility [Berlin] 2009).

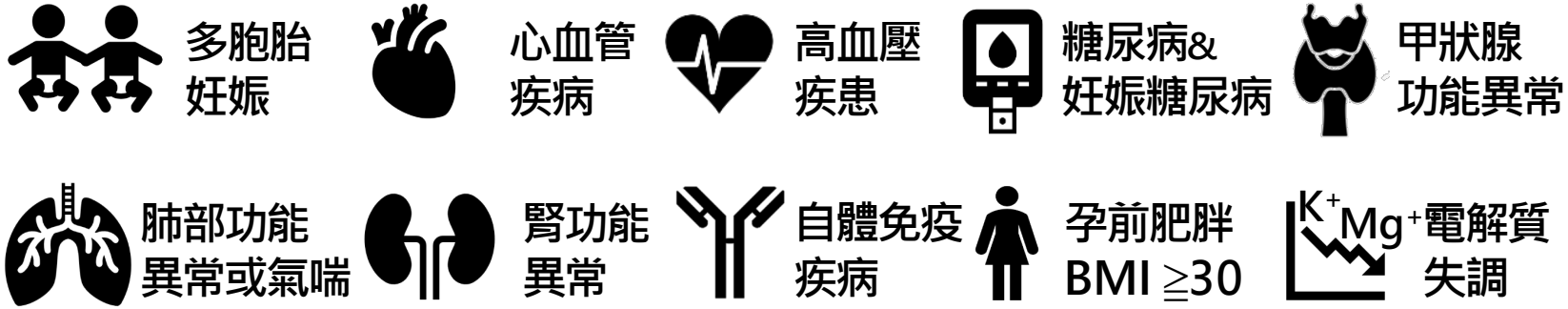
Tractocile® (atosiban) 健保給付規定

- 18歲以上且妊娠週數:24至33週
- 規律宮縮至少持續30秒，頻率≥每30分鐘4次
- 子宮頸擴張1至3公分(初產婦0至3公分)和子宮頸展平(cervical effacement) ≥50%
- 胎兒心律正常

第一線使用時機

屬易出現嚴重副作用的高危險群孕婦，無安胎禁忌症者

(指符合下列任1項高風險條件)



第二線使用時機

經使用ritodrine療效不彰及無法耐受其副作用

完整藥品給付規定請見健保署網站公告

Tractocile® (atosiban)健保給付規定

- 療程劑量：
  - 一次療程時間以48小時為上限，總劑量上限為330mg。
  - 每次懷孕以一次療程為限。

48小時內完成每次療程

步驟1 靜脈注射，1分鐘

1min

- 泡製：直接抽取 0.9 毫升
- 劑量：6.75毫克
- 速率：> 1 分鐘

步驟2 靜脈滴注，3小時

3hrs

- 泡製：1:10稀釋
- 劑量：54毫克
- 速率：24毫升/小時

步驟3 靜脈滴注，至多45小時

Max 45 hrs

- 泡製：1:10稀釋
- 劑量：270毫克max.
- 速率：8毫升/小時

每次療程：最多給予330毫克 = 8.8 vials Tractocile濃縮輸注液

健保給付價格

- 37.5mg/5mL每支2,017元
- (

Tractocile濃縮輸注液

採用下列溶液之一稀釋

- NS 0.9%(w/v) 等張生理鹽水
- LR 林格氏乳酸溶液
- D5W 5%(w/v) 等張葡萄糖溶液

Clinical practice?

947 women with threaten preterm labor were enrolled.
First-line tocolysis was administered to 822 (**86.8%**) patients.
→Beta-agonists were used most frequently (510/822, 62.0%), followed by magnesium sulfate (183/822, 22.3%), calcium channel blockers (91/822, 11.1%), and atosiban (38/822, 4.6%).
→Of the 822 women with first-line tocolysis, second-line tocolysis were required in 364 (44.3%), 199 had third-line tocolysis (37.4%).
→Antibiotics were administered to 29.9% of patients (284/947) with **single** (215, **22.7%**), **dual** (26, 2.7%), and **triple** combinations (43, 4.5%).

Practice patterns in the management of threatened preterm labor in Korea: A multicenter retrospective study. Obstet Gynecol Sci. 2015;58(3):203-209.

	Patient number of tocolysis	Discontinuation of tocolytic therapy[a)]	Side effects	Poor tolerance	Insufficient efficacy
First line tocolysis					
Beta-agonist	510	176 (34.5)	67 (13.1)	22 (4.3)	87 (17.1)
Magnesium sulfate	183	54 (29.5)	3 (1.6)	7 (3.8)	44 (24.0)
Atosiban	38	4 (10.5)	0 (0.0)	0 (0.0)	4 (10.5)
Calcium channel blocker	91	44 (48.4)	1 (1.1)	0 (0.0)	43 (47.3)
Second line tocolysis					
Beta-agonist	109	56 (51.4)	16 (14.7)	1 (0.9)	39 (35.8)
Magnesium sulfate	85	25 (29.4)	2 (2.4)	3 (3.5)	20 (23.5)
Atosiban	163	26 (16.0)	0 (0.0)	0 (0.0)	26 (16.0)
Calcium channel blocker	7	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Third line tocolysis					
Beta-agonist	23	6 (26.1)	1 (4.3)	0 (0.0)	5 (21.7)
Magnesium sulfate	6	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)
Atosiban	101	16 (15.8)	0 (0.0)	0 (0.0)	16 (15.8)
Calcium channel blocker	6	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Overall tocolysis					
Beta-agonist	642	238 (37.1)	84 (13.1)	23 (3.6)	131 (20.4)
Magnesium sulfate	274	80 (29.2)	5 (1.8)	10 (3.6)	65 (23.7)
Atosiban	302	46 (15.2)	0 (0.0)	0 (0.0)	46 (15.2)
Calcium channel blocker	104	44 (42.3)	1 (1.0)	0 (0.0)	43 (41.3)

- **Side effects** were most frequently found in **beta-agonists** (84/642, **13.1%**) including maternal tachycardia, chest discomfort, dyspnea, tremor, pleural effusion, pulmonary edema, dizziness, uncontrolled blood glucose, tingling sensation in extremities, and elevated liver enzymes.
- Among the tocolytic agents, calcium channel blockers showed the most insufficient efficacy (43/104, 41.3%)
- Management of TPL in Korea were **quite various**.

Practice patterns in the management of threatened preterm labor in Korea: A multicenter retrospective study. Obstet Gynecol Sci. 2015;58(3):203-209.

Clinical practice?

Prospective multicenter registry study
October 2013~April 2015

309 women were included.

- A median of **2 cycles** of tocolytic therapy per patient (IQR 1–3) with a median duration of **2 days** per cycle (IQR 2–5). Repeat tocolysis was administered in **41.7%** of women, resulting in up to six tocolysis cycles
- **40.8%** of the first tocolysis cycles were maintenance tocolysis
- **25.6%** of women received one single 48-h tocolysis cycle in which they received antenatal corticosteroids for fetal lung maturation in accordance evidence-based recommendations.

Differences between evidence-based recommendations and actual clinical practice regarding tocolysis: a prospective multicenter registry study. BMC Pregnancy Childbirth 18, 446 (2018).

Maintenance Tocolysis with Atosiban

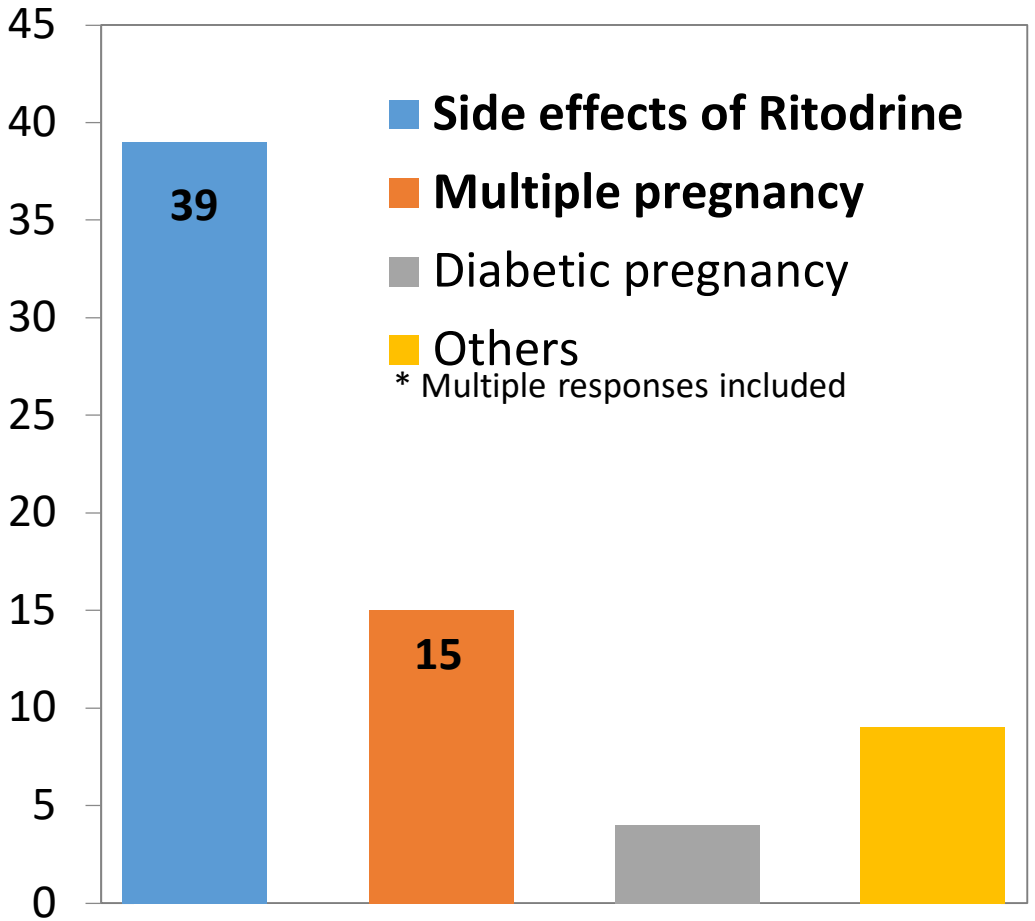
AJOG American Journal of Obstetrics & Gynecology

- N=513(Atosiban: 261, placebo: 252)
- Median time from the start of maintenance treatment to the first recurrence of labor was 32.6 days with atosiban and 27.6 days with placebo (P =0.02)

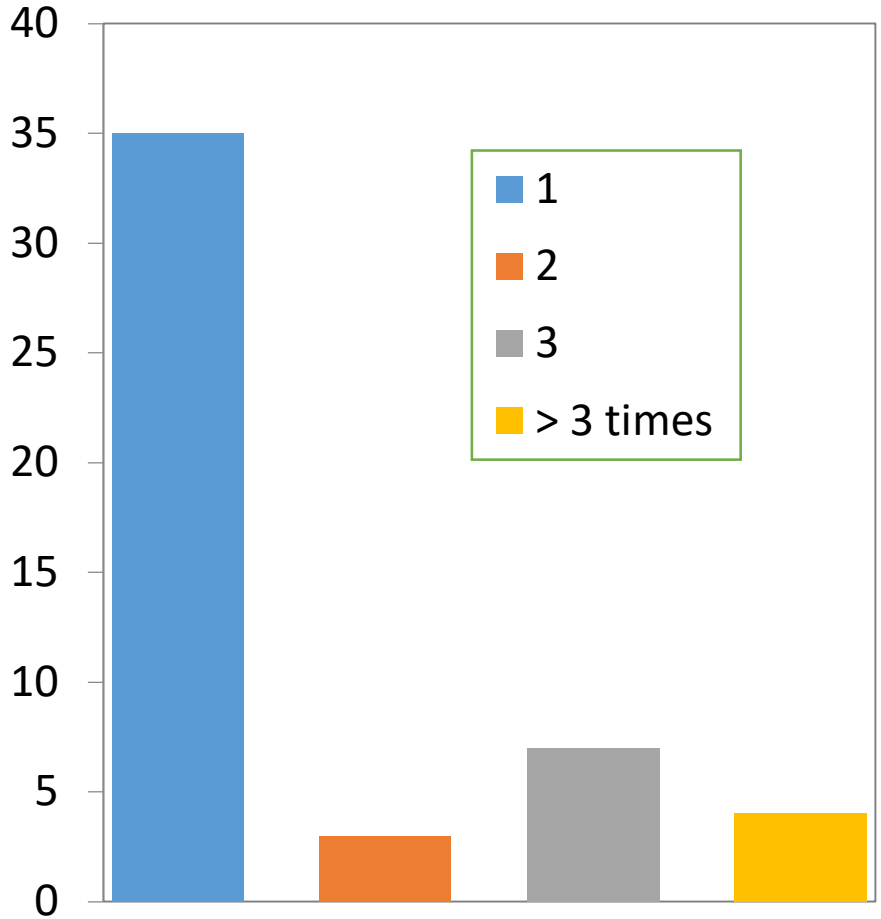
- Maintenance therapy with the oxytocin receptor antagonist atosiban **can prolong** uterine quiescence after successful treatment of an acute episode of preterm labor with atosiban

Maintenance treatment of preterm labor with the oxytocin antagonist atosiban. The Atosiban PTL-098 Study Group. Am J Obstet Gynecol. 2000;182(5):1184-1190.

Experience of Atosiban use in Korea and in Kangnam Sacred Heart Hospital



Indication for using atosiban



Number of treatments

2018

Objective	Method	Results	Conclusion
Evaluate the effect of *multiple cycle Atosiban therapy* on mother and fetus	• Retrospective, between 2021 to 2017 • **671** women with preterm labor (24-35week)	• **No report of serious maternal AEs** • All cases admitted to NICU unlikely are unlikely related to multiple atosiban treatment	The result would provide more evidence on safety of using multi-atosiban tocolytic therapy in pregnancy with preterm labor.

204 with Atosiban

17 treated with Atosiban& Ritodrine

51 treated with Atosiban& Ritodrine& Nifedipine

399 treated with Atosiban & Nifedepine

Perinatal Outcome : 627 babies
Single cycle treatment (n=249, 29.9%)
2-3 cycle treatment (n=234, 37.3%)
4-9 cycle treatment (n=143, 22.8%)
>10 cycle treatment (n=45, 7.2%)
The largest treatment cycle was up to **27 cycles**

These cases report NO serious maternal AEs

Recommendations and practices concerning maintenance and repeated tocolysis in international guidelines (2017)

	Maintenance tocolysis		Repeated tocolysis	
	Guidelines	Practices[a]	Guidelines	Practices[a]
Belgium (KCE),[31] 2014	Not recommended <28 wk: consider nifedipine maintenance (14 d) if contractions reoccur	Yes	Not specified	Yes
Denmark[32] (DSOG), 2013	≥28 wk: not recommended <28 wk: consider if contractions reoccur	Yes	Not specified	Yes
Finland, 2011	Not specified	In individual cases	Not specified	Yes
France[33] (CNGOF), 2016	Not recommended	Yes	Not specified	Yes
Holland (NVOG), 2011	Not recommended	No	Not recommended	Yes, if repeated steroids
Spain (SEGO)	Not recommended<	No	Not specified	Yes
Sweden[b]	Not recommended	In individual cases	Not recommended	In individual cases
United Kingdom (RCOG), 2011	Not recommended	No	Not specified	No

[a] Evaluation of practices comes from our respective experience, we all are clinicians and experienced training within several hospitals, where we observed that practices are often in discrepancy with guidelines.

Recommendations and practices concerning maintenance and repeated tocolysis in international guidelines(2017)

Maintenance tocolysis		Repeated tocolysis	
Guidelines	**Practices**	**Guidelines**	**Practices**
Not recommended	**Yes**	**Not specified**	**Yes**

Take home message

- **PAMG-1** has the highest PPV and NPV on detecting PTB
- Atosiban is the only effective medicine of maintenance therapy.
- Management of preterm labor were quite various between guidelines and clinical practices
- Atosiban健保給付規定:

  -18歲以上且妊娠週數:24至33週

  -規律宮縮至少持續30秒，頻率≥每30分鐘4次

  -子宮頸擴張1至3公分(初產婦0至3公分)和子宮頸展平(cervical effacement) ≥50%

  -胎兒心律正常

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Thank you