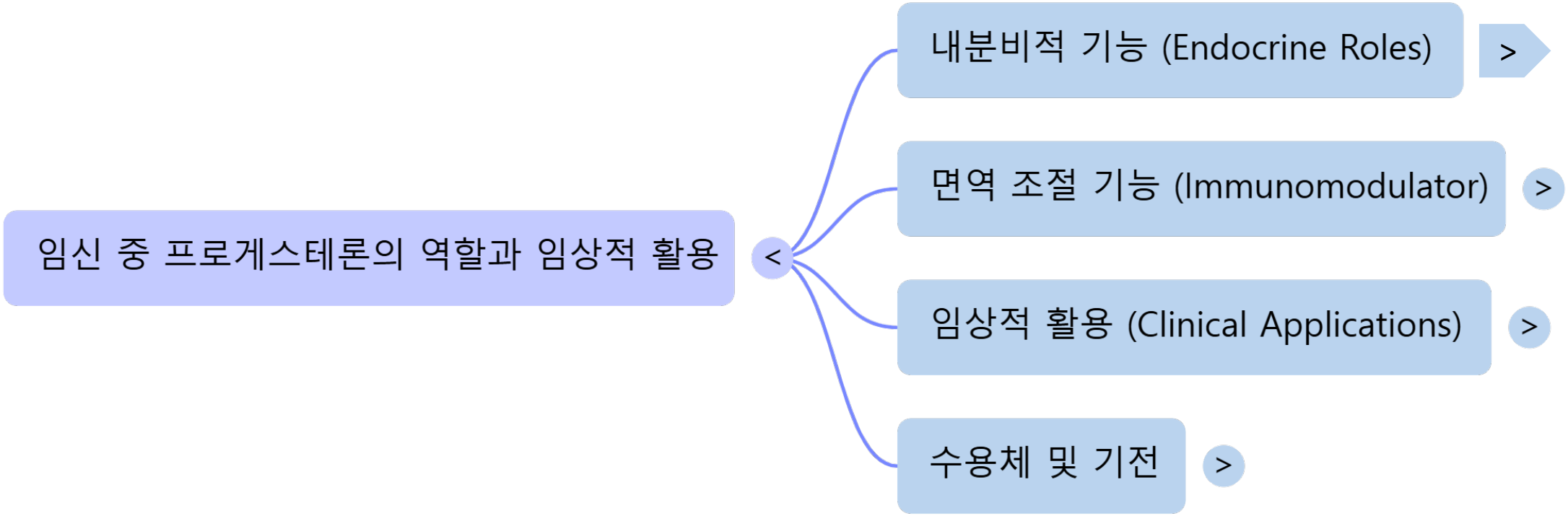
대한생식면역학회
Korean Society for Reproductive Immunology

CATHOLIC UNIVERSITY OF KOREA

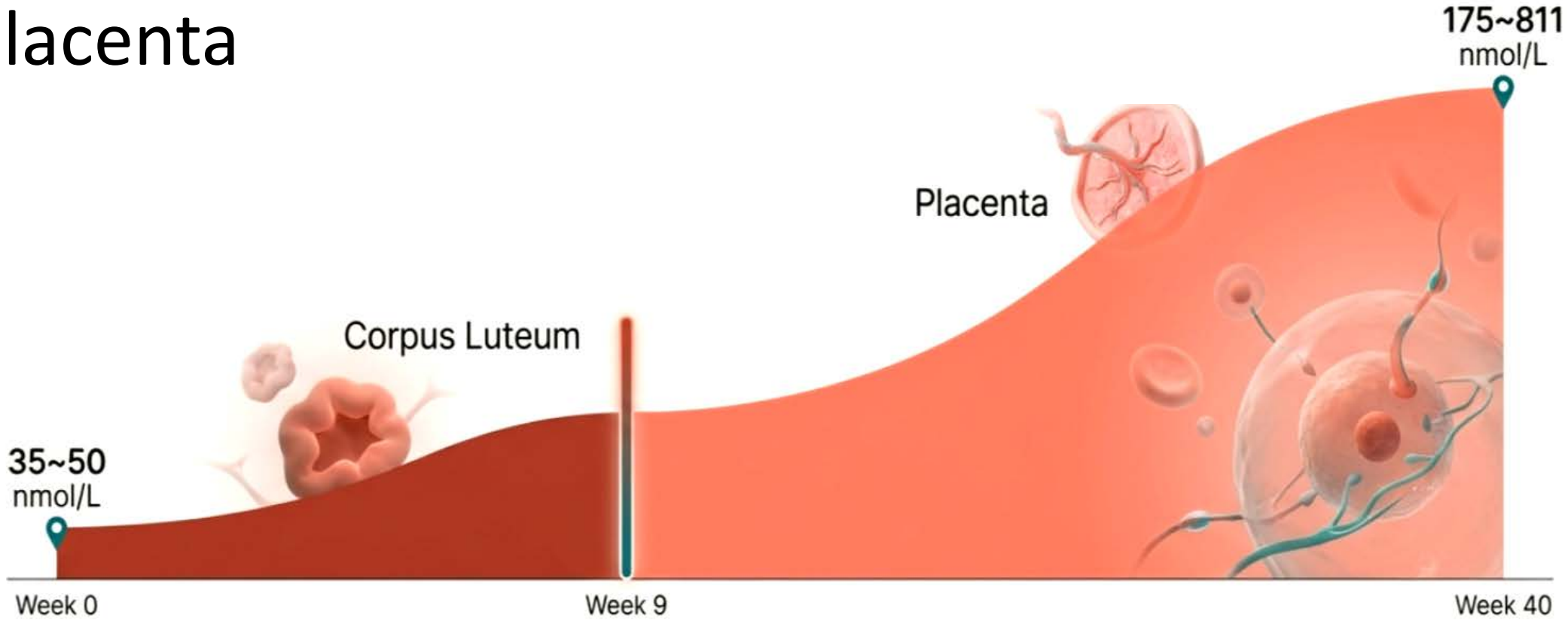
Progesterone in Obstetrics: Hormone, Immunomodulator, or Both ?

가톨릭대학교 산부인과
김연희

순서


임신 중 프로게스테론의 역할과 임상적 활용
내분비적 기능 (Endocrine Roles)
면역 조절 기능 (Immunomodulator)
임상적 활용 (Clinical Applications)
수용체 및 기전

Progesterone from Corpus luteum to Placenta



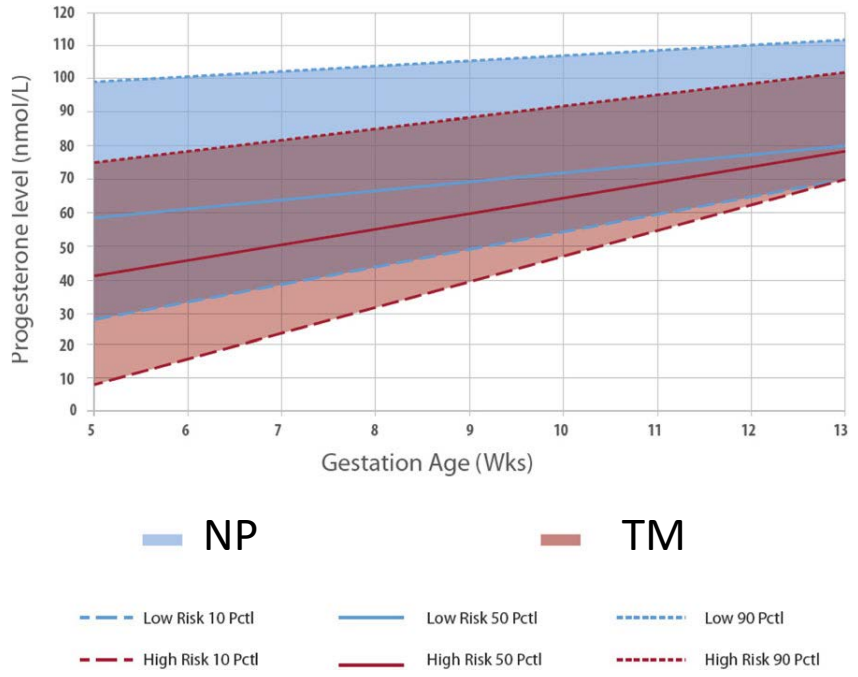
- 임신초기 : 난소 corpus luteum progesterone P4 생성
- 태반으로 이행 (9주 이후) : 태반에서 생산 증폭, 임신 제3분기에 이르러 급격히 상승

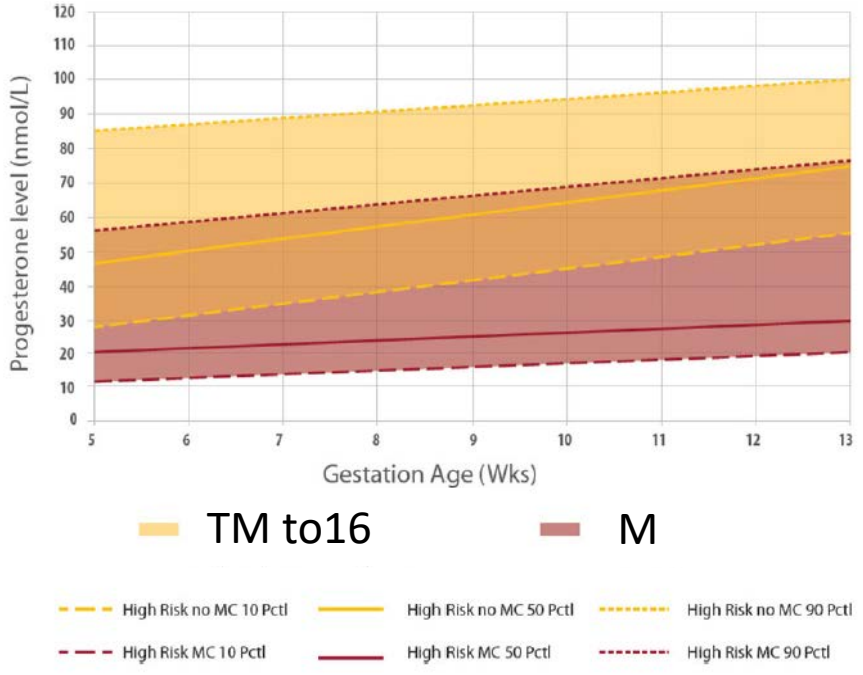
Endocrine role 1: Uterine environment

- Endometrium secretary transformation, decidualization 유도
- 배아의 histotrophic nutrient , trophoblast invasion, angiogenesis 를 위한 물리적, 생리적 토대 마련

Serum progesterone distribution in threatened miscarriage

Lower serum progesterone associated with threatened miscarriage and a subsequent complete miscarriage at 16 weeks gestation.



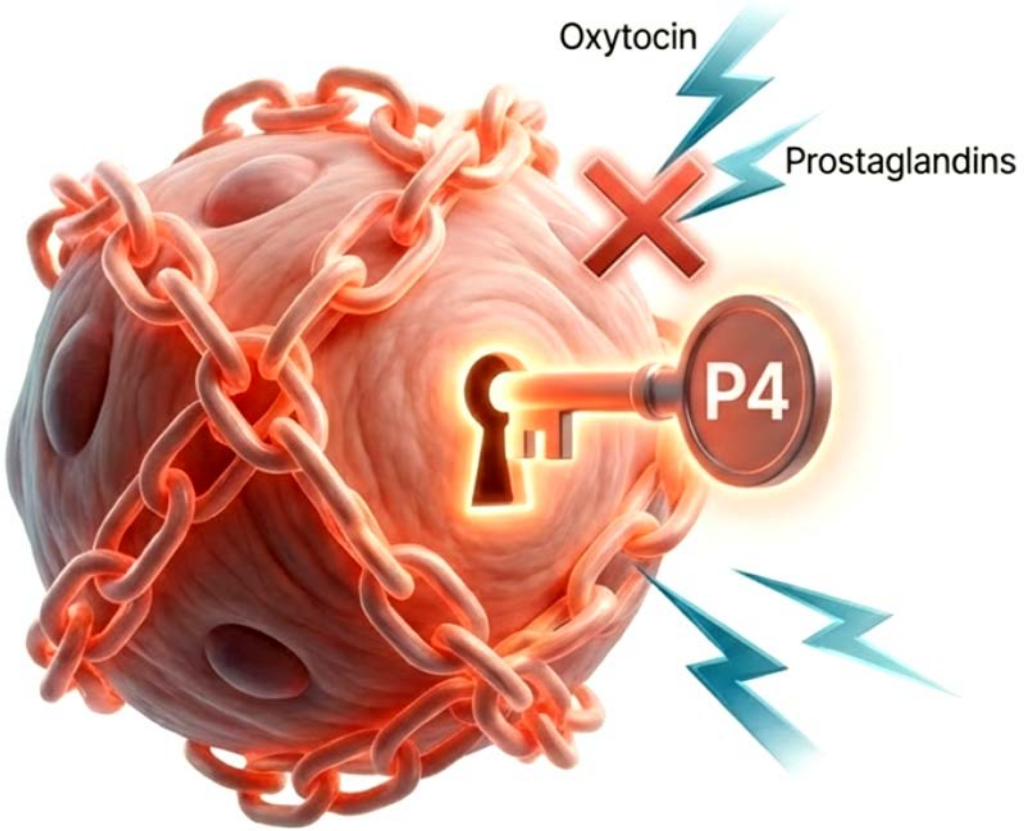


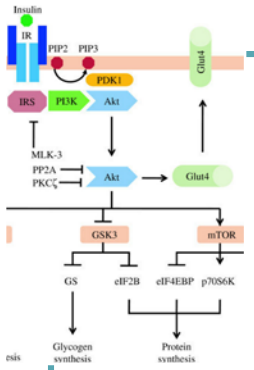
NP : normal pregnancy, TM: threatened miscarriage,

TM to16: TM ongoing to 16w GA, M: miscarriage

Ku et al. BMC Pregnancy and Childbirth (2018) 18:360

Endocrine role 2. myometrial Quiescence





Prostaglandin ↓

프로스타글란딘 합성의 간접 차단

유전자 발현 하향 조절

분만전까지 옥시토신 수용체 (OTR) , gap junction 단백질인 connexin 43, 전염증성 유전자 전사의 하향 조절

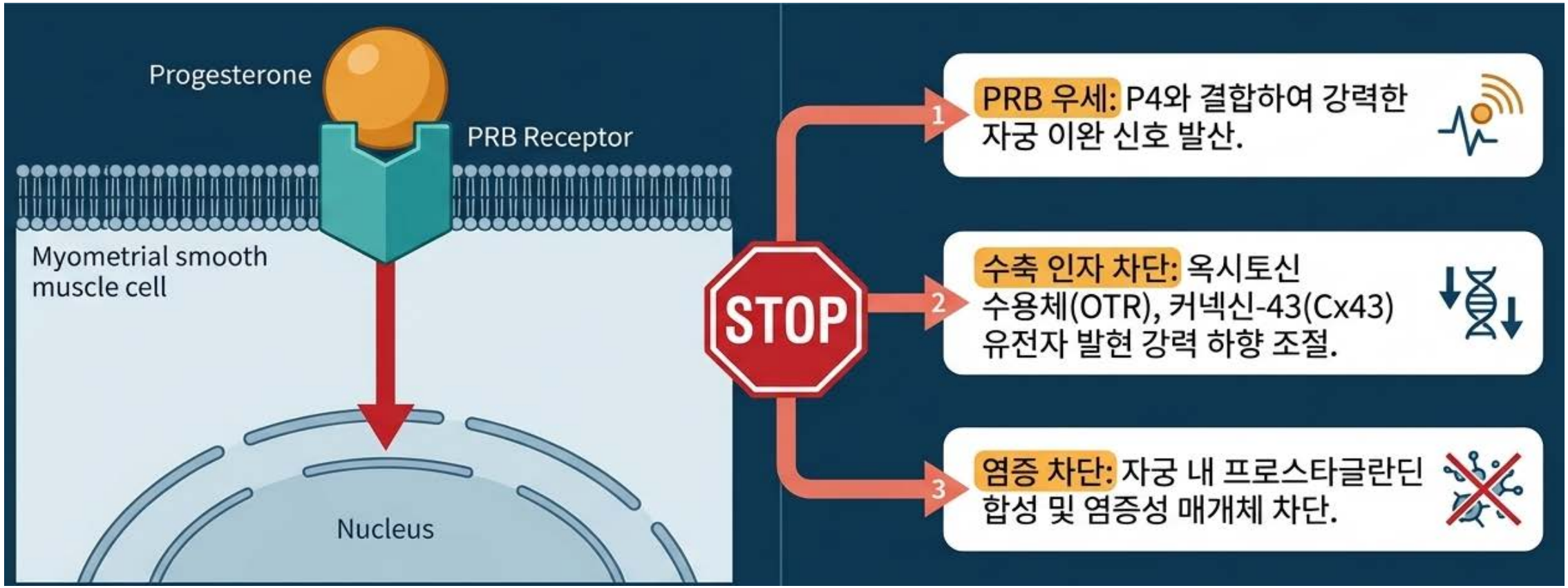
* 분만 촉진 유전자 : connexin 43, OTR, COX-2 , NF-κB2

Nuclear Receptors : PRA vs PRB

- Dominant isoform during healthy pregnancy
- Repress proinflammatory, pro-contractile genes
- Maintains absolute myometrial quiescence

- PRA : Truncated isoform, acts as a repressor of PR-B.
- Unliganded PR-A, upregulates Connexin – 43(Cx43) and Oxytocin Receptors (OTR)

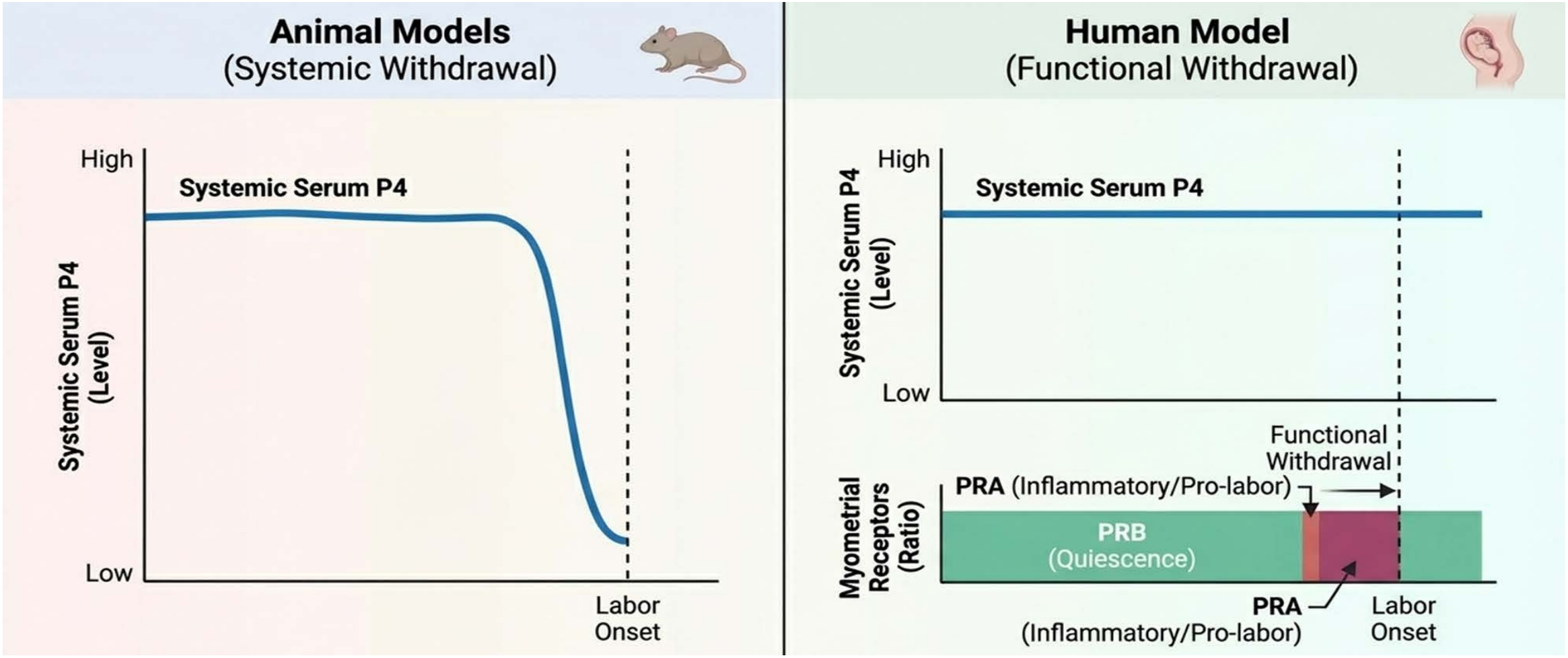
Uterine Quiescence mechanism in pregnancy



P4, Maintain the uterus in a 'safety box' state without contraction before delivery

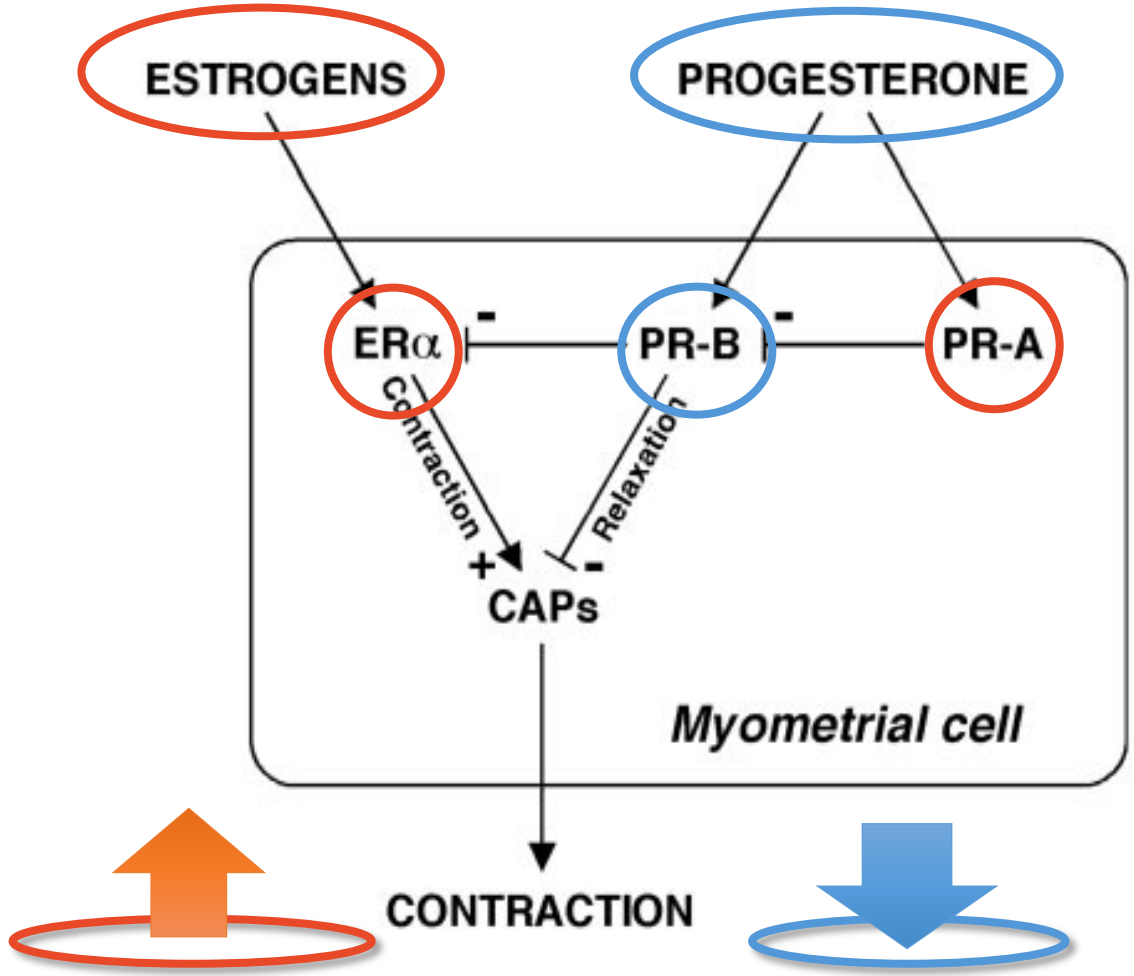
Human Labor : Functional Withdrawal

Altered PRA: PRB ratio that reactivates inflammatory pathway



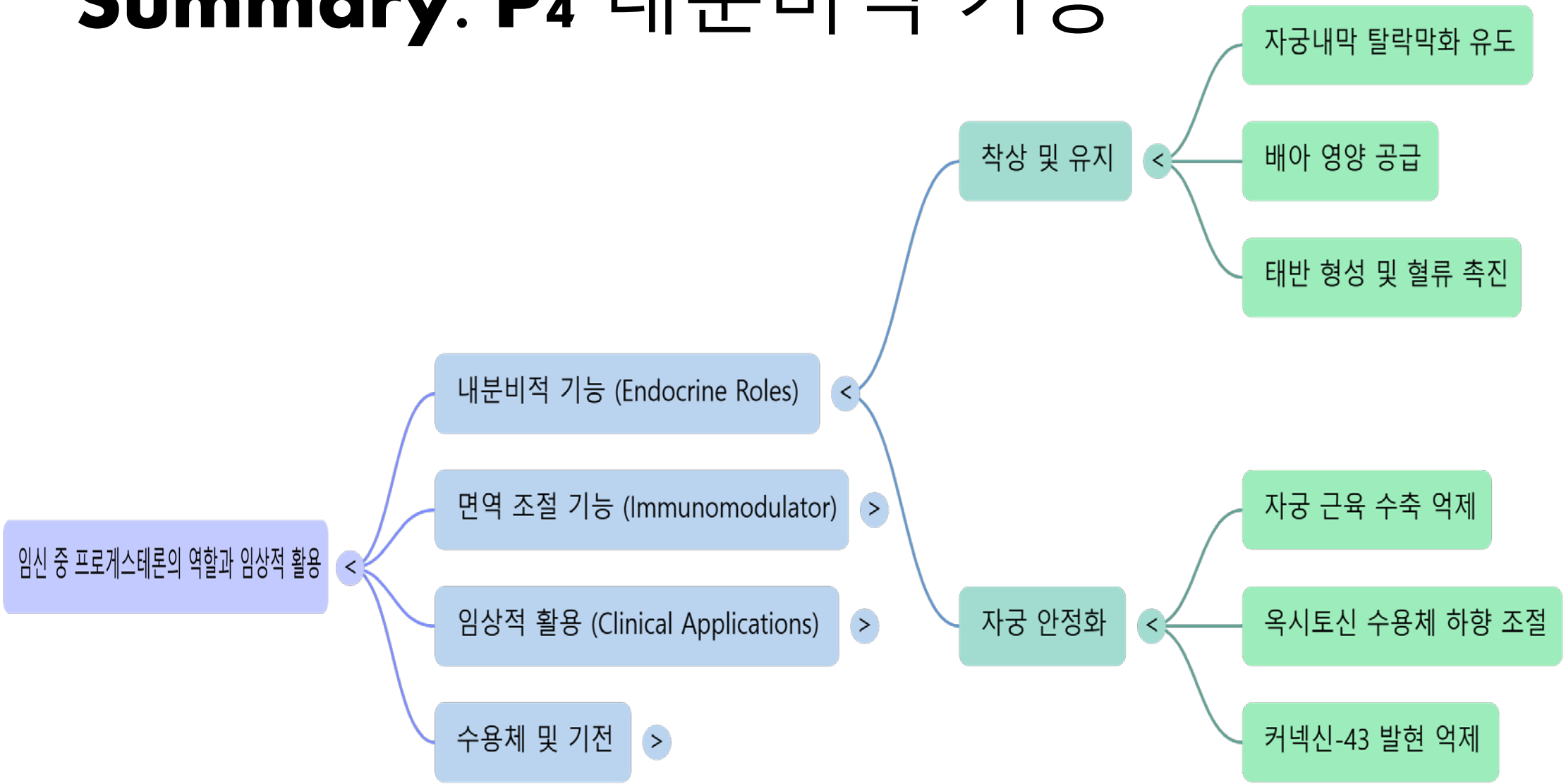
Hormonal Control

Theoretical model for the role of progesterone in the regulation of pregnancy and parturition

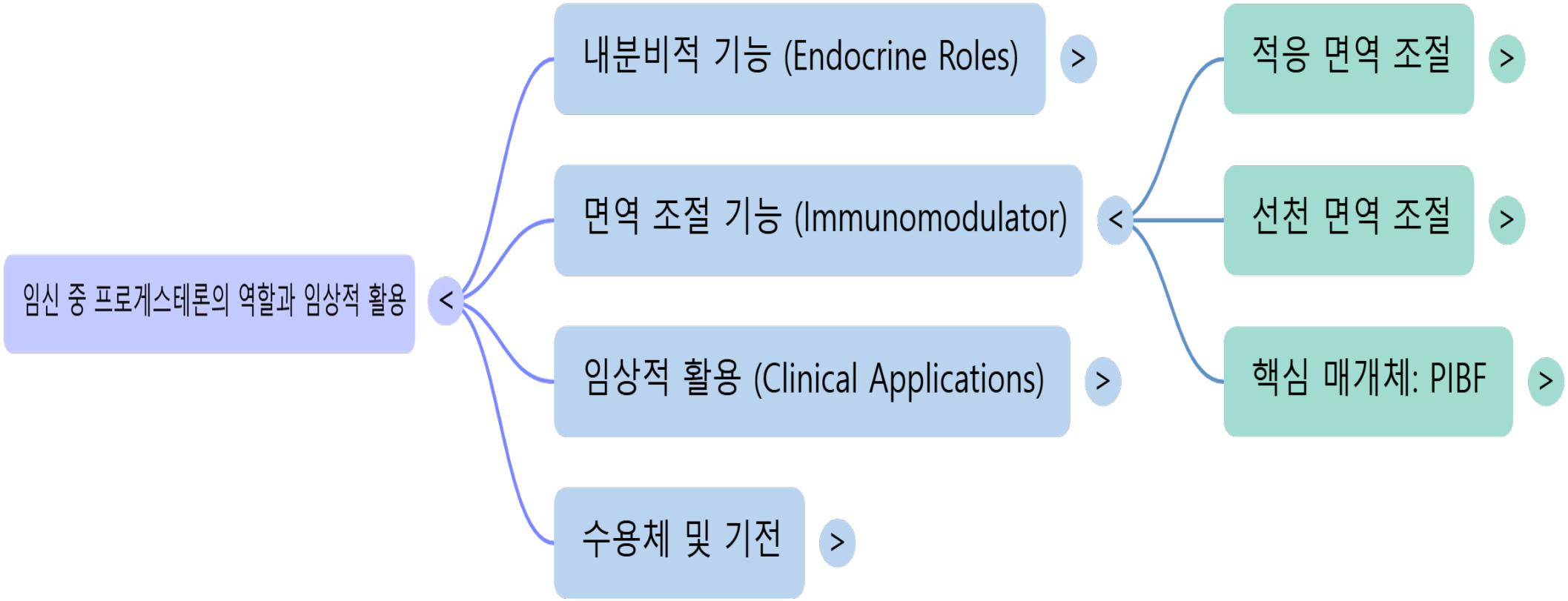


Mesiano et al. *J Clin Endocrinol Metab 2002;* **87***: 2924-2930*

Summary. P4 내분비적 기능



프로게스테론 면역조절자 기능



임신 후 모체의 면역계의 어려움

태아

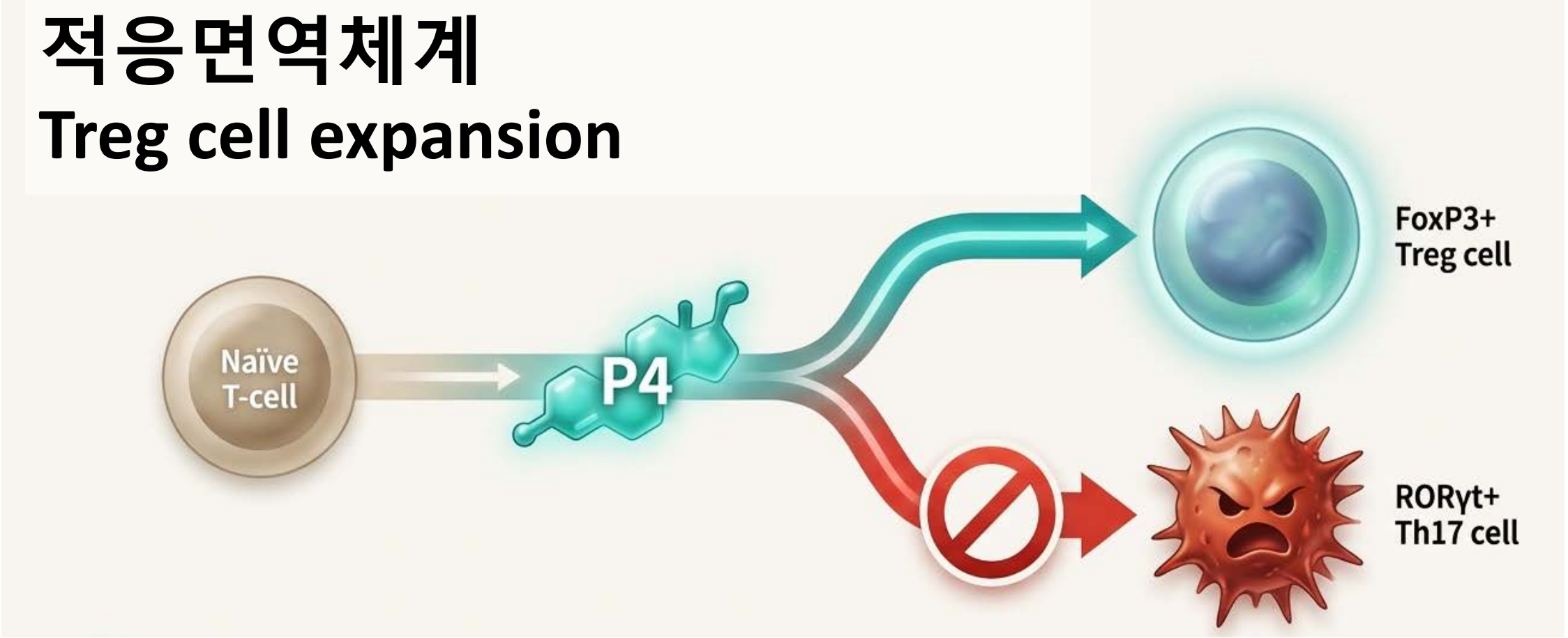
paternal antigen, Semi allograft

모체면역계: 외부 이물질로 간주,
거부반응 일으킬 수 있음

프로게스테론: maternal fetal interface

‘Forced Immune Tolerance’

적응면역체계
Treg cell expansion



Treg 세포강화 (Regulatory T cells)
P4 에 의해 조절 T 세포 (Tregs) 증식과 기능강화 (FoxP3 발현) → 모체면역계로부터 태아보호

Th17 분화차단: 자가면역반응과 염증 유발 Th17 세포로의 분화 차단: 임신유지 적응면역 환경

Mjösberg J, et al . FOXP3+ regulatory T cells and T helper 1, T helper 2, and T helper 17 cells in human early pregnancy decidua. Biol Reprod. 2010 Apr;82(4):698-705

적응면역체계

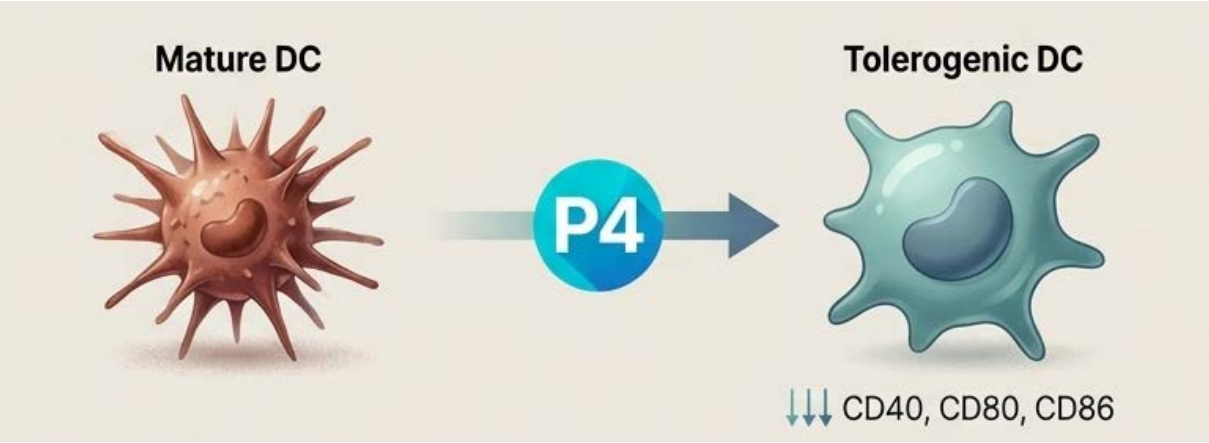
Treg cell expansion

성공적인 임신 유지 위해 T helper cells 의 분화 방향 역전

Cytotoxic Tcell(CD8+) 기능억제
Th1/Th17 cell 경로와 cytokine 억제

Th2 cell 경로 촉진: 면역 관용과 항체생성
출산 후 '조절적 면역기억'

선천면역조절 : Tolerogenic shift



- **Dendritic cells**

P4 inhibits DC maturation

⇒ Reduce expression of CD 40/CD80/ CD86

⇒ Favor a tolerogenic phenotype

⇒ Preventing T cell priming

- **Macrophages**

Drives differentiation to tissue repairing anti-inflammatory M2 phenotype

선천면역조절 : **NK cells suppression**

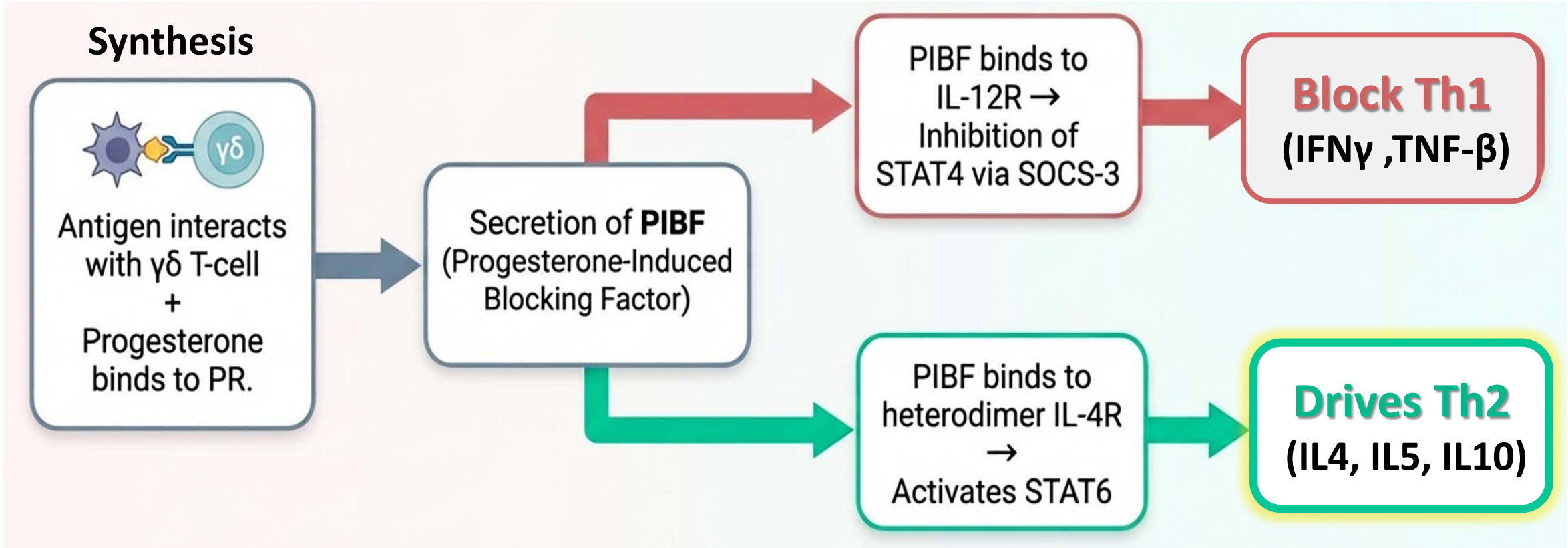
Decidual NK cells lose cytotoxicity

P4, 프로게스테론 수용체와 nGR 을 통해 degranulation과정 차단

⇒ Perforin release과 cytotoxicity 활성을 억제

⇒ 국소적 태아세포 파괴 방지

PIBF (progesterone induced blocking factor)



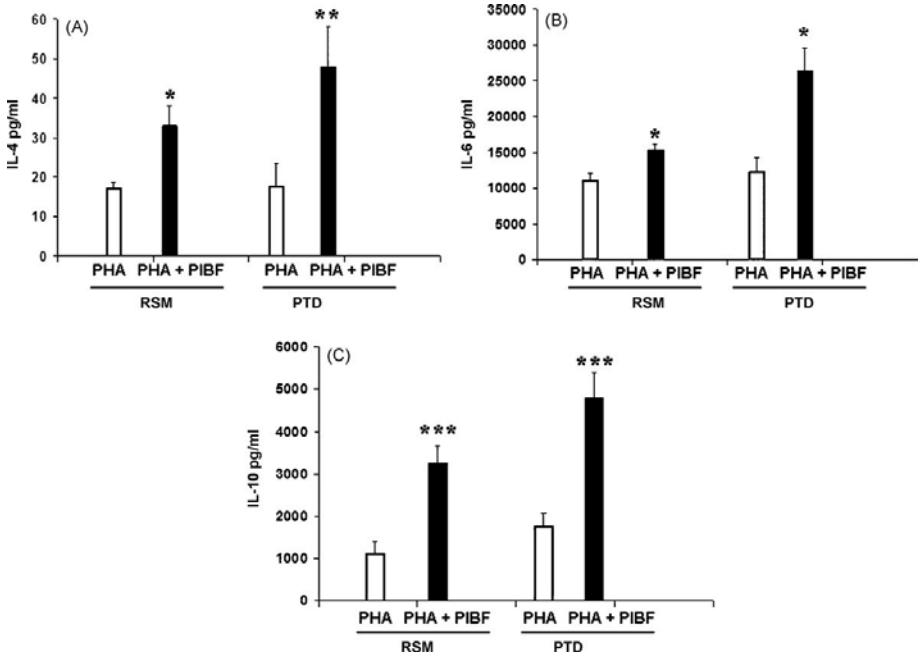
- **Clinical marker**

After dydrogesterone, decreased IFN-γ & TNF-α / higher level of PIBF in recurrent miscarriage group

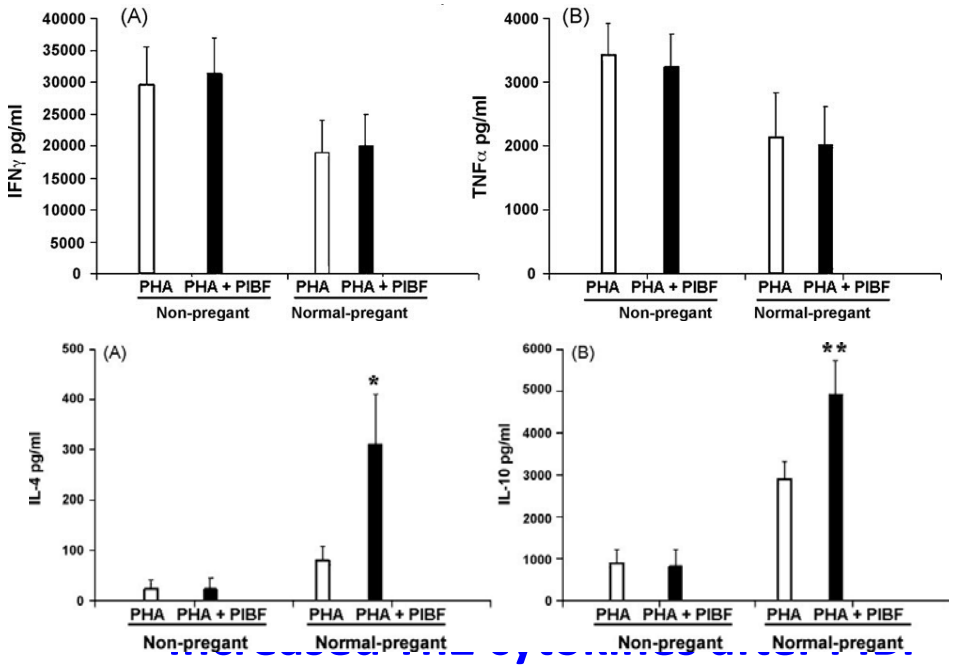
Kalinka, J.; Szekeres-Bartho, J. The impact of dydrogesterone supplementation on hormonal profile and PIBF concentrations in women with threatened abortion. Am. J. Reprod. Immunol. 2005, 53; Hudic, I.; et al. Dydrogesterone and pre-term birth. Horm. Mol. Biol. Clin.Investig. 2016, 27, 81–83

PIBF in RM and PTD

The 4 groups : non preg, normal preg, recurrent miscarriage, Preterm delivery
Measurement : Th1(IFN-γ, TNF-α), Th2 (IL-4, IL-6, IL-10) **after PIBF**



Th2 (IL-4, IL-6, IL-10) increased after PIBF



No change of Th1, but shift towards Th2 cytokines

R. Raghupathy et al. Progesterone-induced blocking factor (PIBF) modulates cytokine production by lymphocytes from women with recurrent miscarriage or preterm delivery Journal of Reproductive Immunology 80 (2009) 91–99

Summary. P4 면역조절기능

- **프로게스테론 임신 중 면역조절 역할**

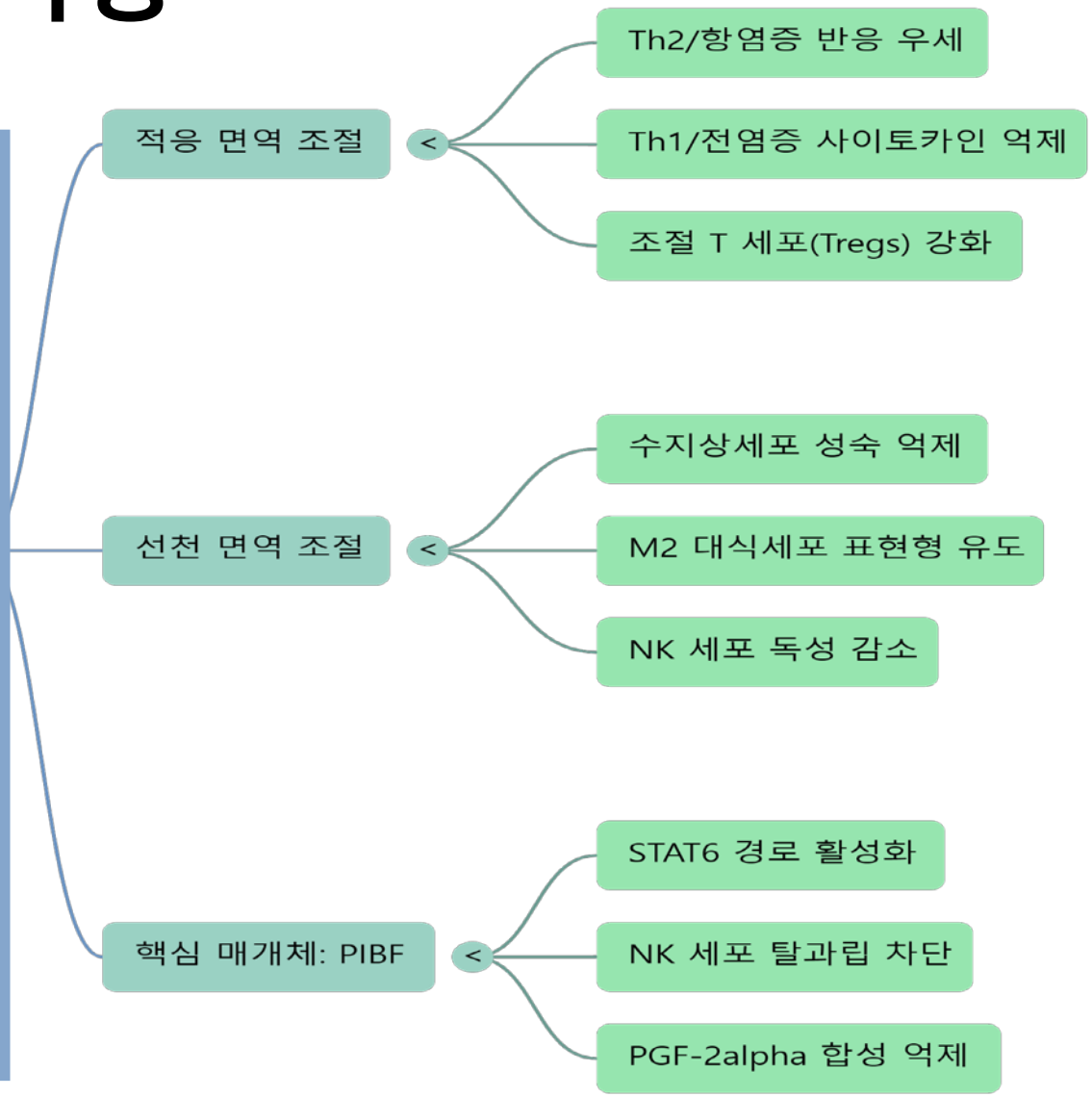
선천 면역과 적응면역 전반에 걸쳐

면역억제 네트워크 환경을 형성

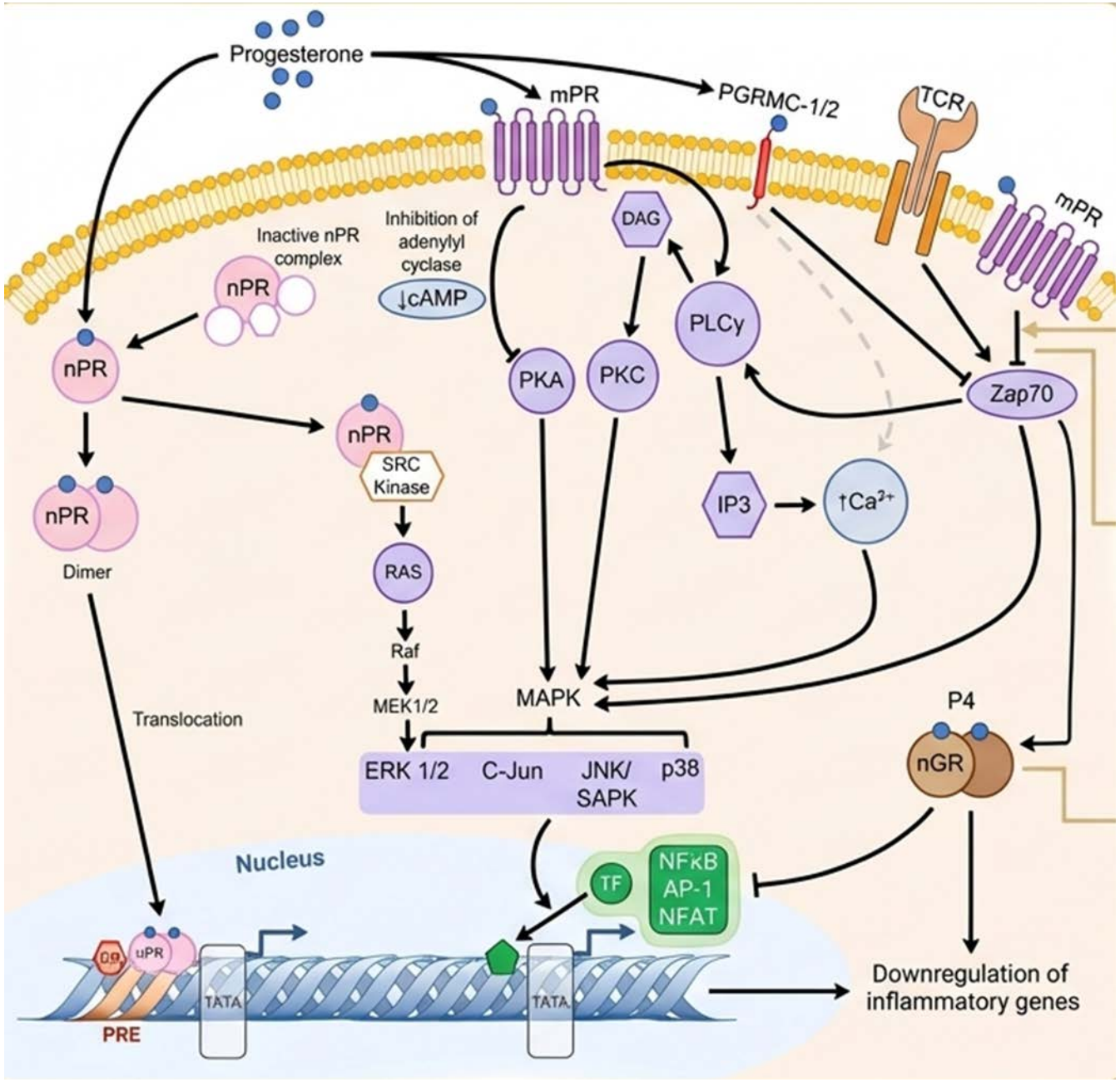
염증성 세포는 하향 조절

관용성 복구형 세포집단 상향 조절

태아보호 환경 구축



Shah NM, Lai PF, Imami N and Johnson MR (2019) Progesterone-Related ImmuneModulation of Pregnancy and Labor. Front. Endocrinol. 10:198



P4 Multi-receptor network

Classical Genomic (nuclear PR)

- Direct DNA binding at P4 response elements (PREs)
- Slow, long-term tissue remodeling

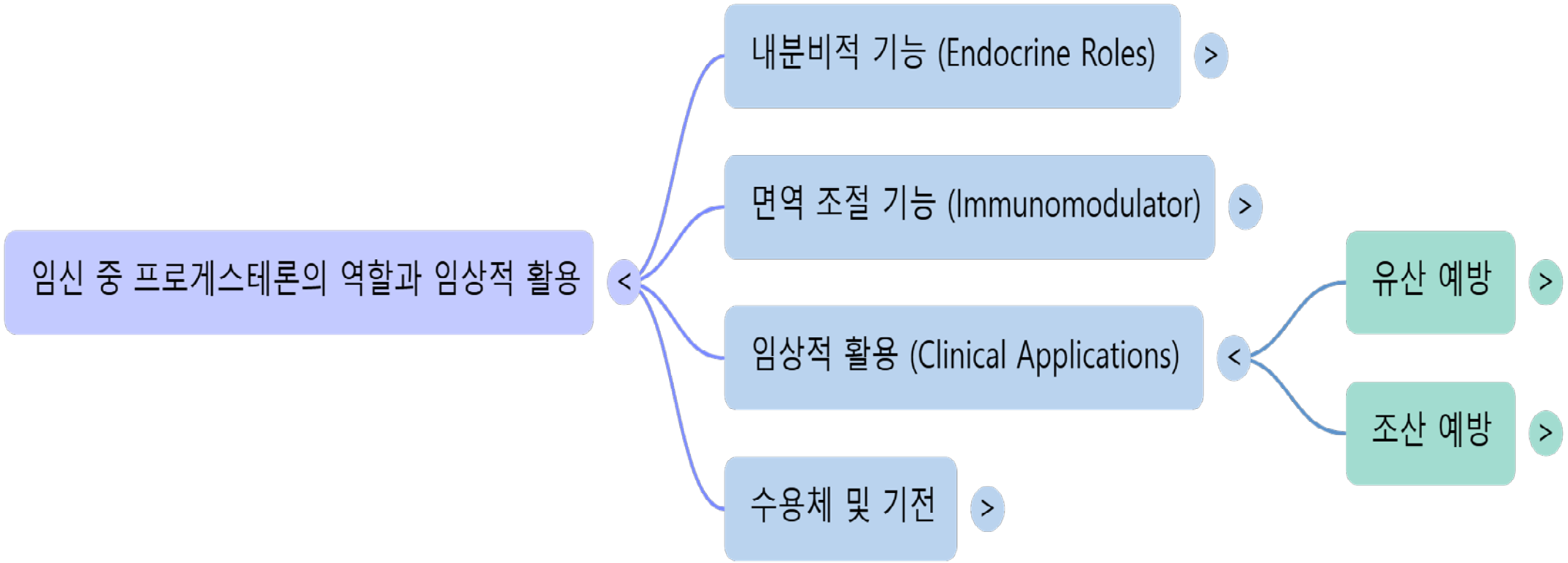
Non classical membrane (mPR/ PGRMC1)

Rapid signal, Ca 2+ flux 제어,
Reduces Zap70 phosphorylation,
T cell receptor 활성 즉각적 억제

Glucocorticoid Receptor (nGR)

Promiscuous binding 하여
NF-kB dependent inflammation 억제
T cell 사멸유도

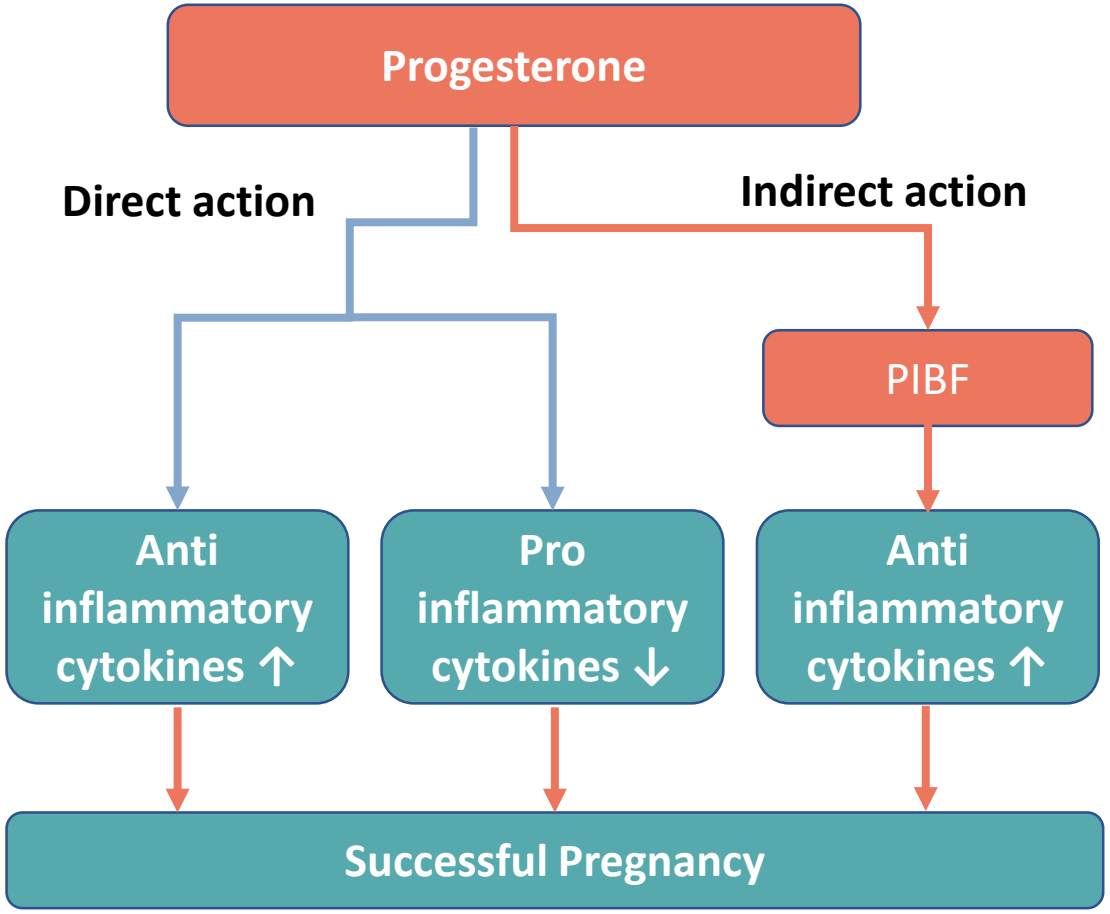
프로게스테론 임상적 활용



반복적 유산의 원인적 인자

- **Chromosomal abnormality (>50%), other genetic etiologies**
- **Luteal phase defects**
- **DM, thyroid function abnormalities**
- **Anatomic factor**
- **Infections**
- **Acquired thrombophilia (antiphospholipid syndrome)**
- **Exogenous agents**
- **Unexplained cause**

Progestogens : Therapeutic options



Int. J. Mol. Sci. 2022, 23, 1333

Micronized Progesterone

질정 형태 투약, **uterine first pass effect**

자궁내막 근육층의 국소적 조직농도를 극대화 하는 효과

Dydrogesterone

경구투여, 면역학적으로

PIBF 생성을강력 유도, Th1/ Th2 비율에서 Th2 항염증 편향으로 유도

PRISM trial
(progesterone in spontaneous miscarriage)

Multicenter, randomized, parallel-group, double-blind, placebo-controlled trial

TABLE 2
PRISM trial: vaginal micronized progesterone in women with threatened miscarriages

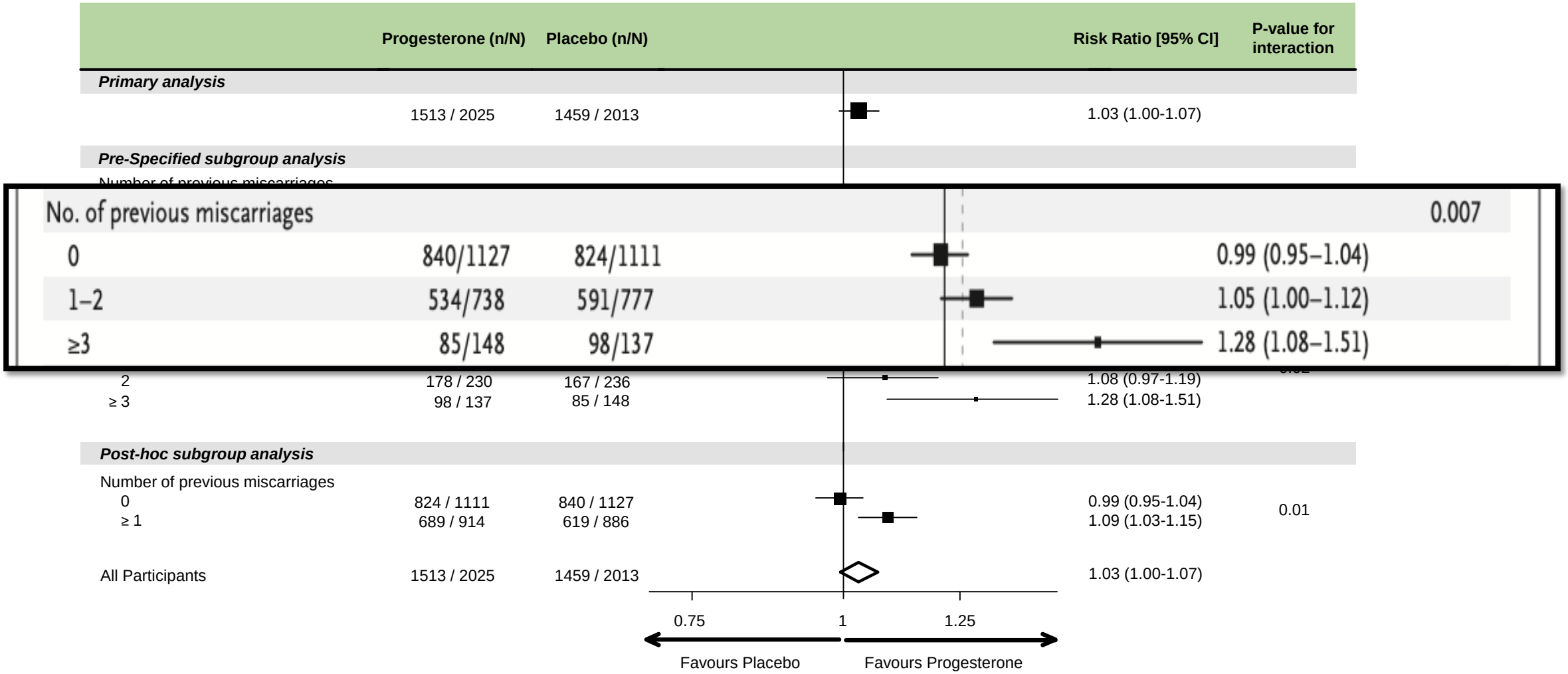
Population	Women with vaginal bleeding during the first 12 weeks of pregnancy
Intervention	400 mg of micronized progesterone taken vaginally or rectally twice daily from randomization until 16 weeks of gestation
Comparison	Placebo
Primary outcome	Live birth ≥34 weeks
Sample size and power	4153 patients randomized, 90% power to pick up a 5% difference in live births
Hospitals	48 hospitals in the United Kingdom

PRISM, PRogesterone In Spontaneous Miscarriage.

Coomarasamy, A., et al., *A Randomized Trial of Progesterone in Women with Bleeding in Early Pregnancy.* N Engl J Med, 2019. **380**(19)

Biological gradient Subgroup effect (Interaction for subgroup effect p=0.01)

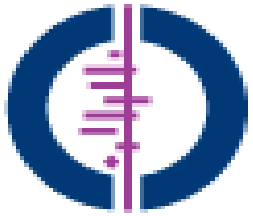
PRISM trial



Coomarasamy et al. N Engl J Med 2019; 380:1815-1824

Devall A, et al. *Best Pract Res Clin Obstet Gynaecol*: 2020; **69**: 30-39

Progestogens and preventing miscarriage: a meta-analysis



Cochrane Library

Cochrane Database of Systematic Reviews

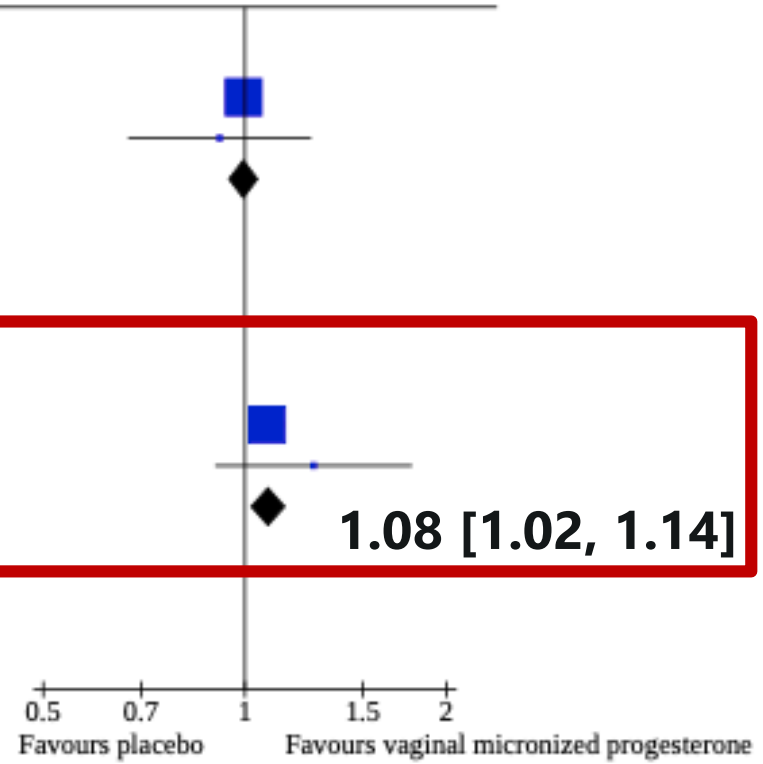
Cochrane Database of Systematic Reviews 2021, Issue 4.
Art. No.: CD013792

- Patients : threatened miscarriage, or had a history of 3 or more previous miscarriages (recurrent miscarriage)
- Four different progestogens treatments
  - vaginal micronized progesterone
  - oral dydrogesterone
  - oral micronized progesterone
  - 17-alpha-hydroxyprogesterone intramuscular injection

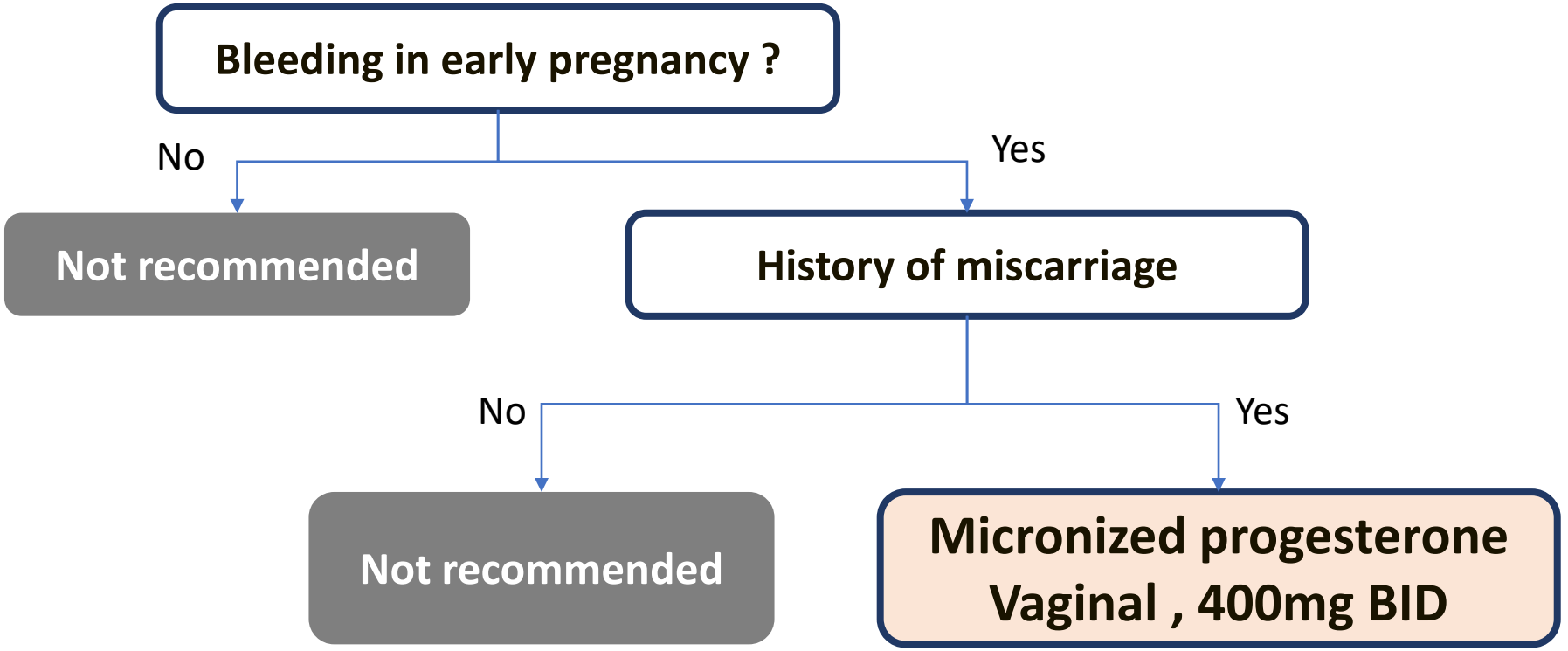
Summary : Live birth (progestogens vs placebo)

Analysis 1.8. Comparison 1: Threatened miscarriage: Vaginal micronized progesterone versus placebo, Outcome 8: Live birth (subgrouped by no previous miscarriages and one or more previous miscarriages)

Study or Subgroup	Vaginal micronised progesterone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.8.1 No previous miscarriages and early pregnancy bleeding						
Coomarasamy 2019	824	1111	840	1127	98.8%	1.00 [0.95 , 1.04]
Gerhard 1987	10	12	10	11	1.2%	0.92 [0.67 , 1.26]
Subtotal (95% CI)		**1123**		**1138**	**100.0%**	**0.99 [0.95 , 1.04]**
Total events:	834		850			
Heterogeneity: Chi² = 0.26, df = 1 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.24 (P = 0.81)						
1.8.2 One or more previous miscarriages and early pregnancy bleeding						
Coomarasamy 2019	689	914	619	886	98.3%	1.08 [1.02 , 1.14]
Gerhard 1987	13	14	11	15	1.7%	1.27 [0.90 , 1.78]
Subtotal (95% CI)		**928**		**901**	**100.0%**	**1.08 [1.02 , 1.14]**
Total events:	702		630			
Heterogeneity: Chi² = 0.84, df = 1 (P = 0.36); I² = 0%						
Test for overall effect: Z = 2.75 (P = 0.006)						
Test for subgroup differences: Chi² = 5.03, df = 1 (P = 0.02), I² = 80.1%						



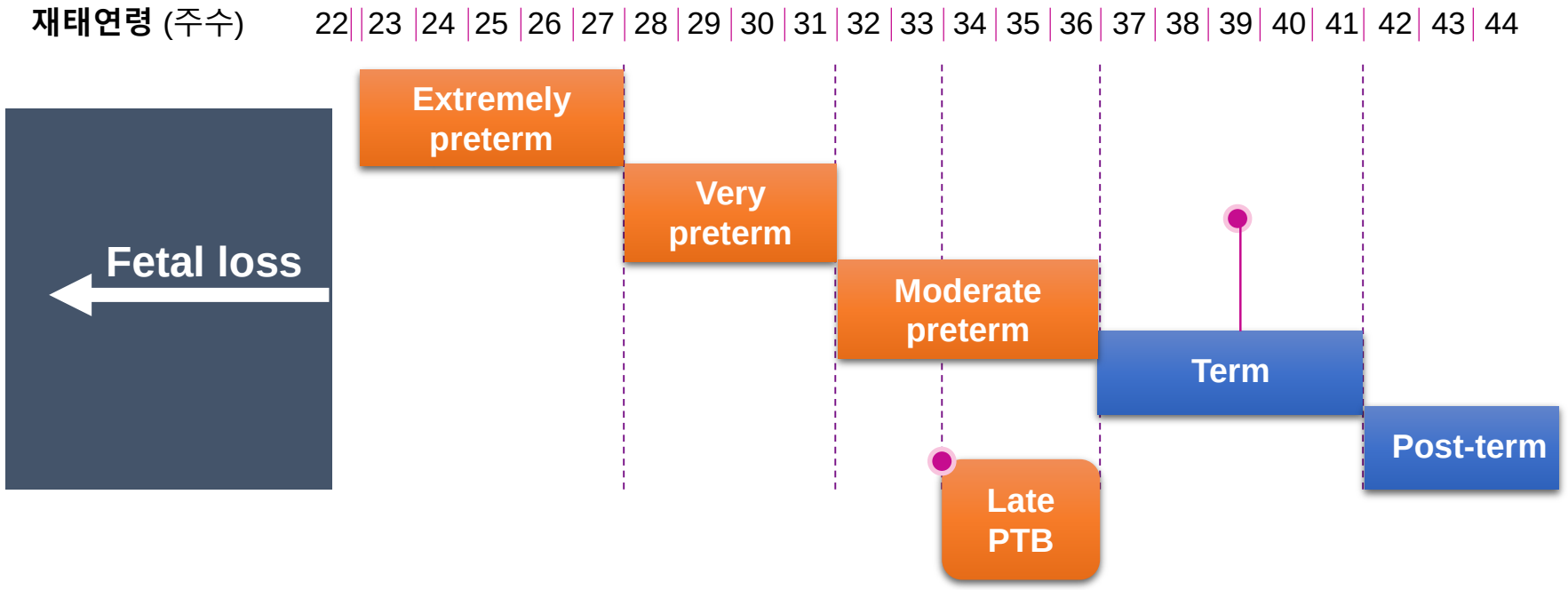
임상적 활용: 유산 예방



초음파 검사에서 태아 심박동 확인 시 임신 16주 까지 지속투여
(RCOG/ NICE/ ESHRE guideline)

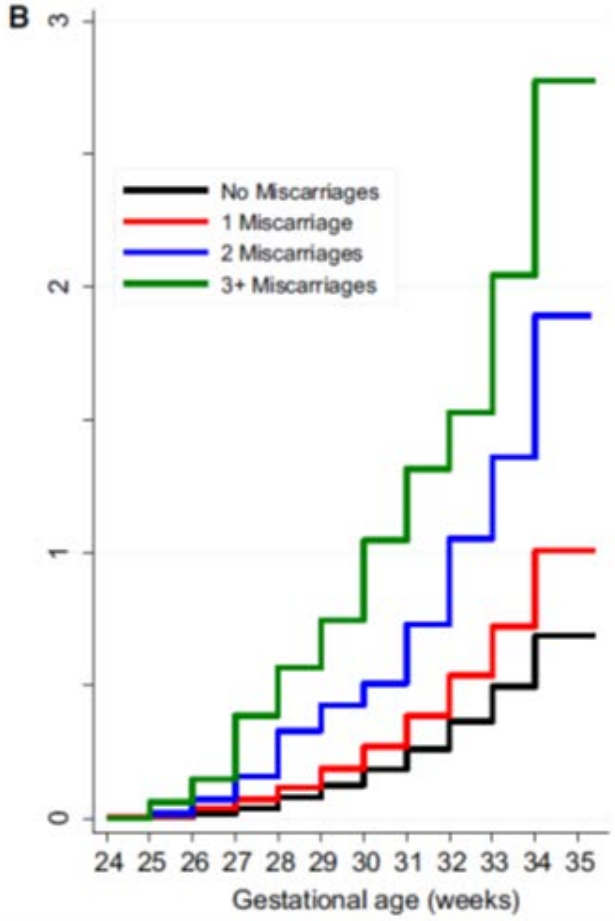
임상적 활용: 조산 예방

- 조산이란 ? 임신 37주 미만 혹은 수태 후 245일 이내 분만



WHO ICD-10: International Statistical Classification of Diseases and Related Health Problems, Tenth Revision. 2010 edition
WHO, March of Dimes. Born too Soon: The Global Action Report on Preterm Birth. 2012;

The risk of preterm birth, biological gradient with the rates of previous miscarriage

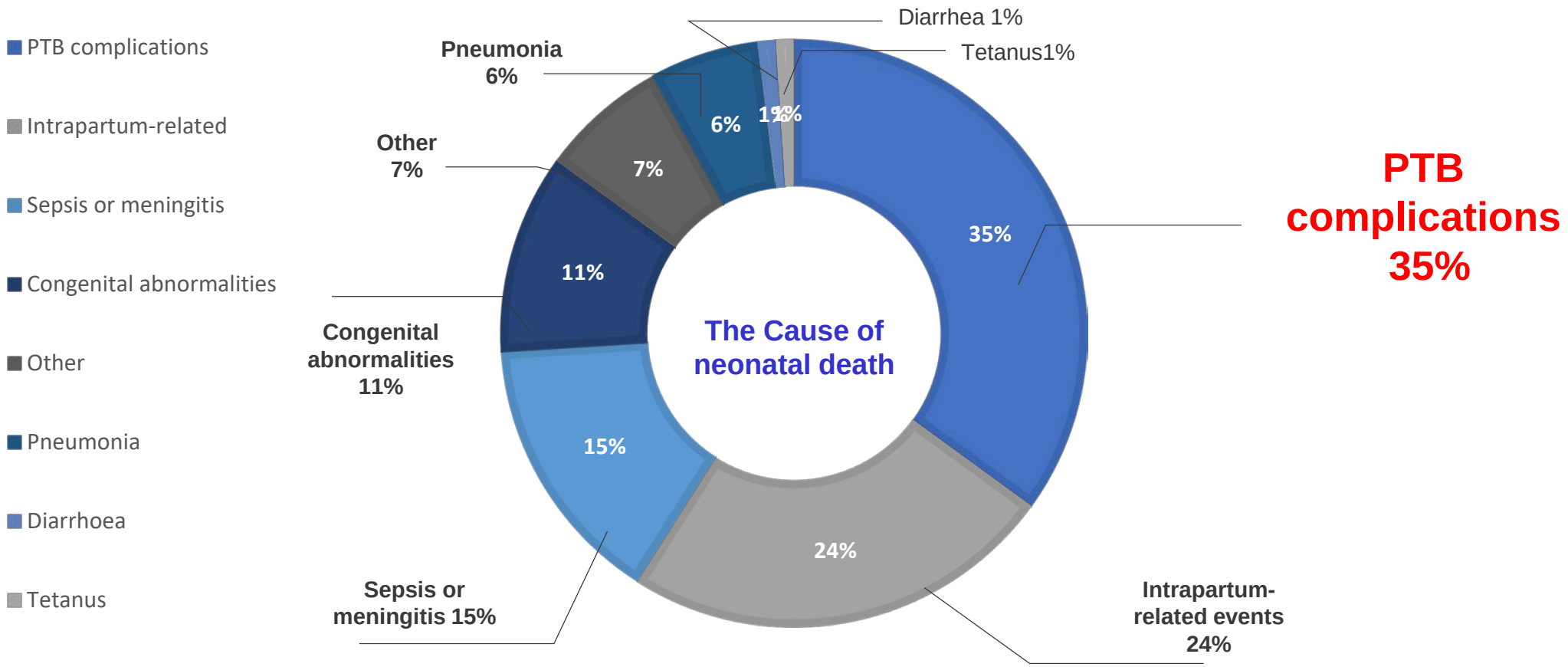


- **Cumulative incidence of spontaneous preterm first birth in 717 214 nulliparous women.**

Outcome	Adjusted odds ratios (95% CI)*					
	History of miscarriage	Number of Previous Miscarriages				*P****
		1	2	≥3	Per unit Increase**	
Preterm birth						
24–28 weeks (*n* = 689 681)	1.73 (1.57–1.90)	1.43 (1.28–1.60)	3.12 (2.59–3.57)	3.87 (2.85–5.26)	1.60 (1.50–1.70)	<0.001
29–32 weeks (*n* = 693 908)	1.36 (1.28–1.46)	1.23 (1.14–1.33)	1.86 (1.60–2.15)	2.68 (2.14–3.36)	1.32 (1.26–1.39)	<0.001
33–36 weeks (*n* = 722 634)	1.18 (1.14–1.22)	1.12 (1.08–1.16)	1.36 (1.25–1.47)	1.81 (1.59–2.06)	1.16 (1.13–1.19)	<0.001

Oliver-Williams et al. (2013): bjog "Previous miscarriage and the subsequent risk of preterm birth in Scotland, 1980–2008"

PTB, the most common cause of neonatal mortality



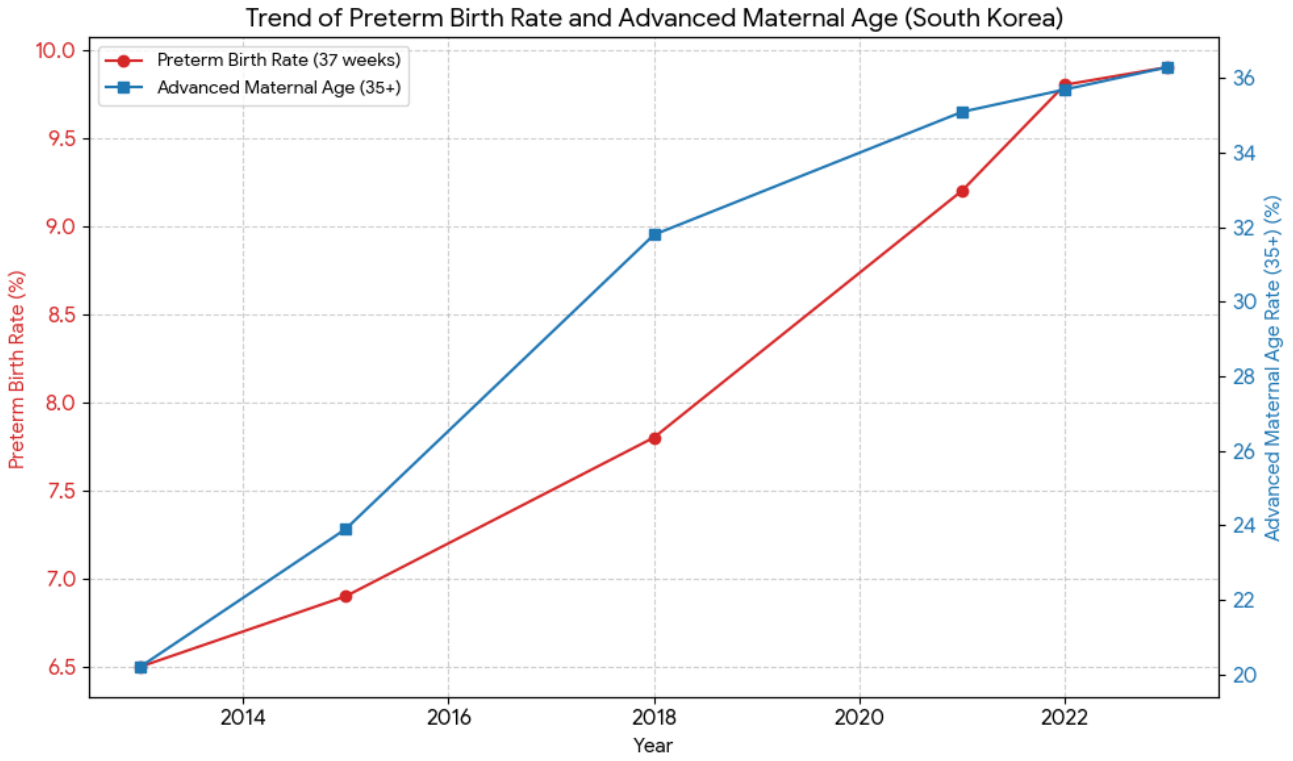
UN Inter-Agency Group for Child Mortality Estimation. Levels and trends in child mortality: Report 2017.

Preterm birth (PTB) rate : Korea

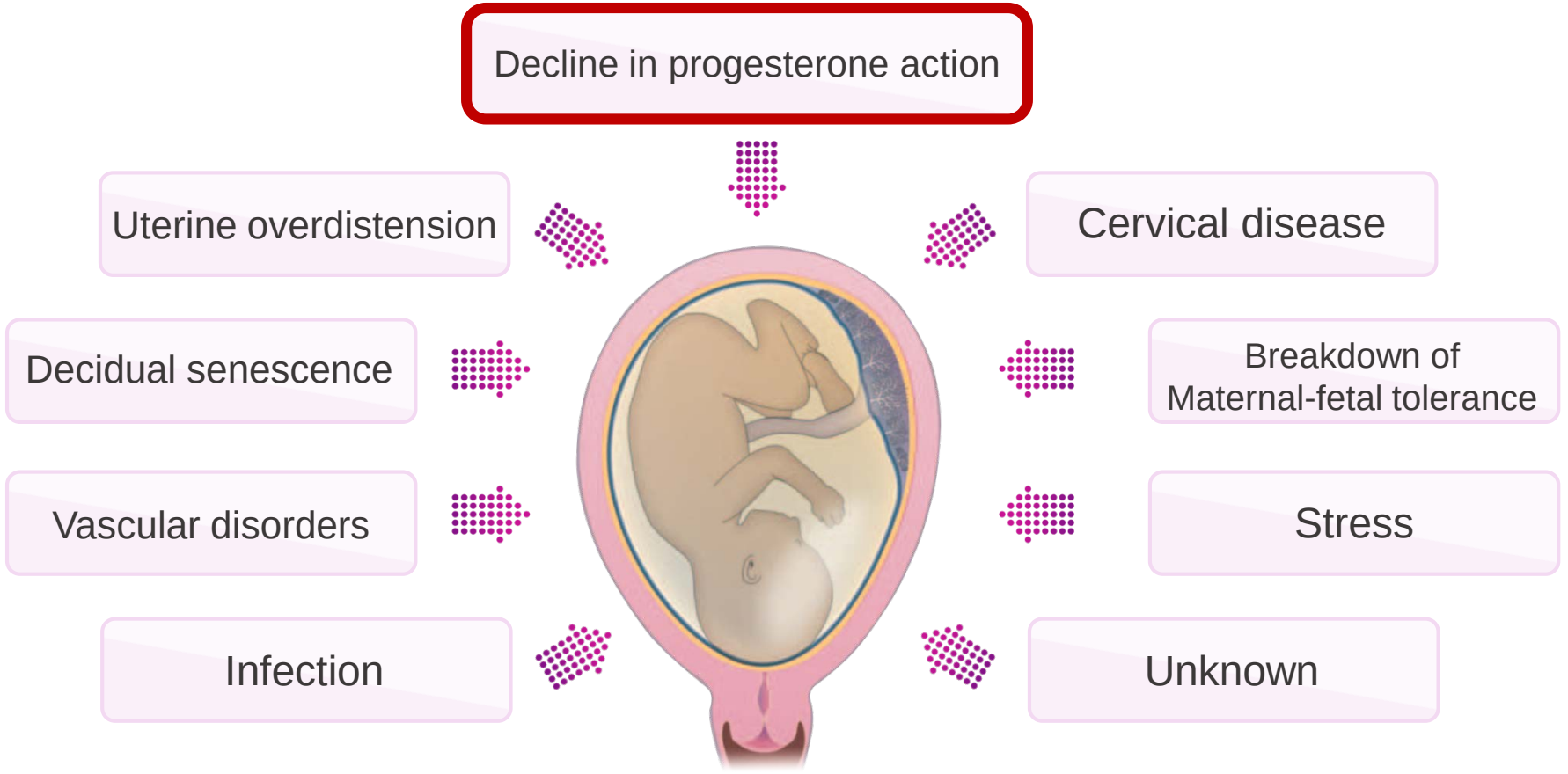
국내 조산율 및 고령산모 비중 추이 (2013-2023)

- **조산율: 1.5 배 증가,**
  6.5에서 9.9% 로 증가
- **고령산모 비중: 약 1.8배 증가**
  20%에서 36.3% 로 증가
- **고령 임신으로 인한 여러 합병증으로 인해 조기분만 불가피**

➡ **조산율 상승**

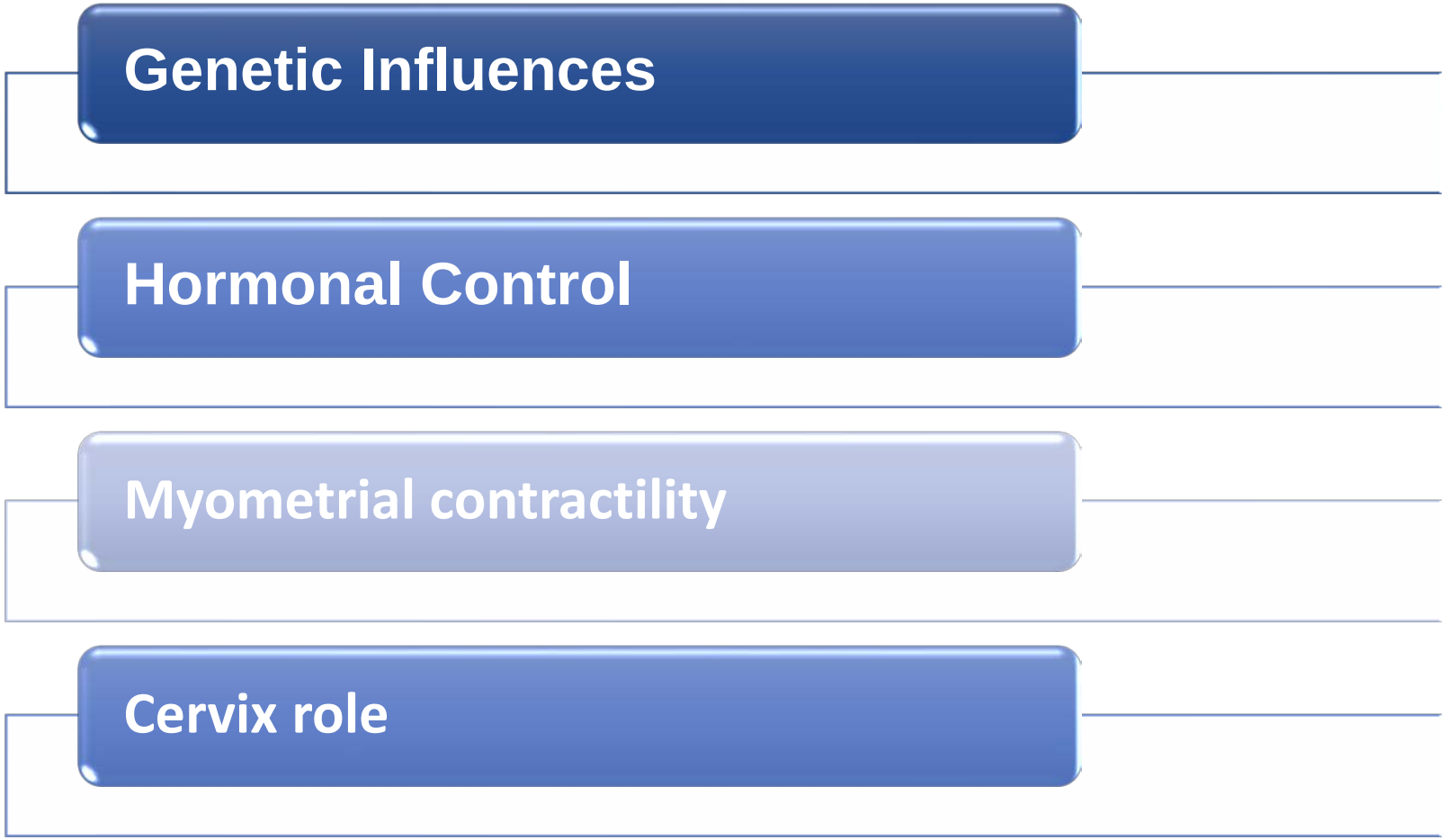


Preterm labor: one syndrome, many causes



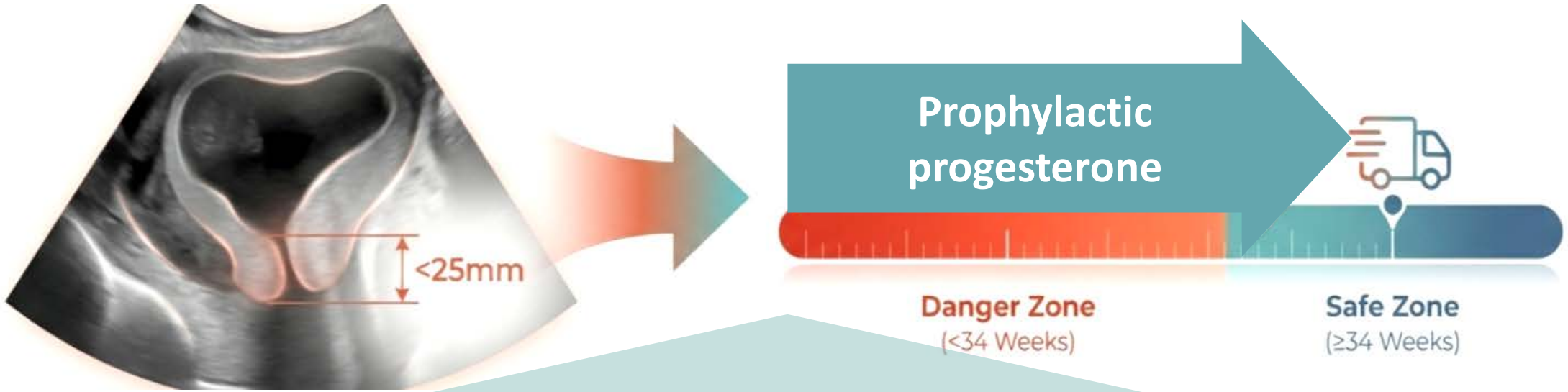
Romero R, et al. Science 2014;345:760–765.

진통 발생 시기를 결정하는 요인들



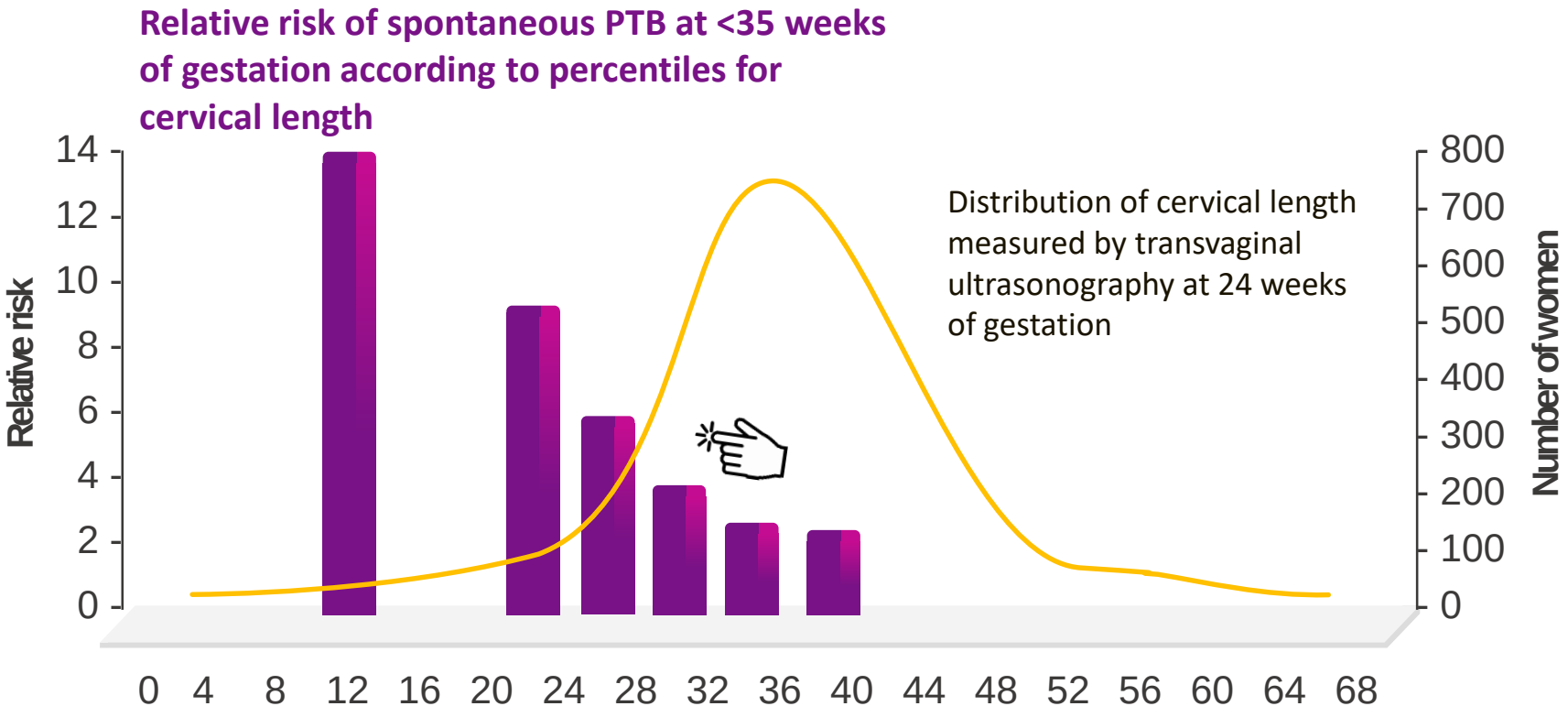
1. Eur J Obstet Gynecol Reprod Biol 2007; 134: pp. 188-191.

P_4 보충과 조산 예방의 이론적 근거



프로게스테론 Functional withdrawal 교정	모태-태아 계면 국소 항염증 미세환경 조성	NF-kB 경로 억제 세포외기질(ECM) 분해 차단	기계적 팽창으로 인한 자궁 수축 관련 단백질의 발현 하향 조절(downregulation)

Shortened cervical length (CL) associated with an increased risk of PTB

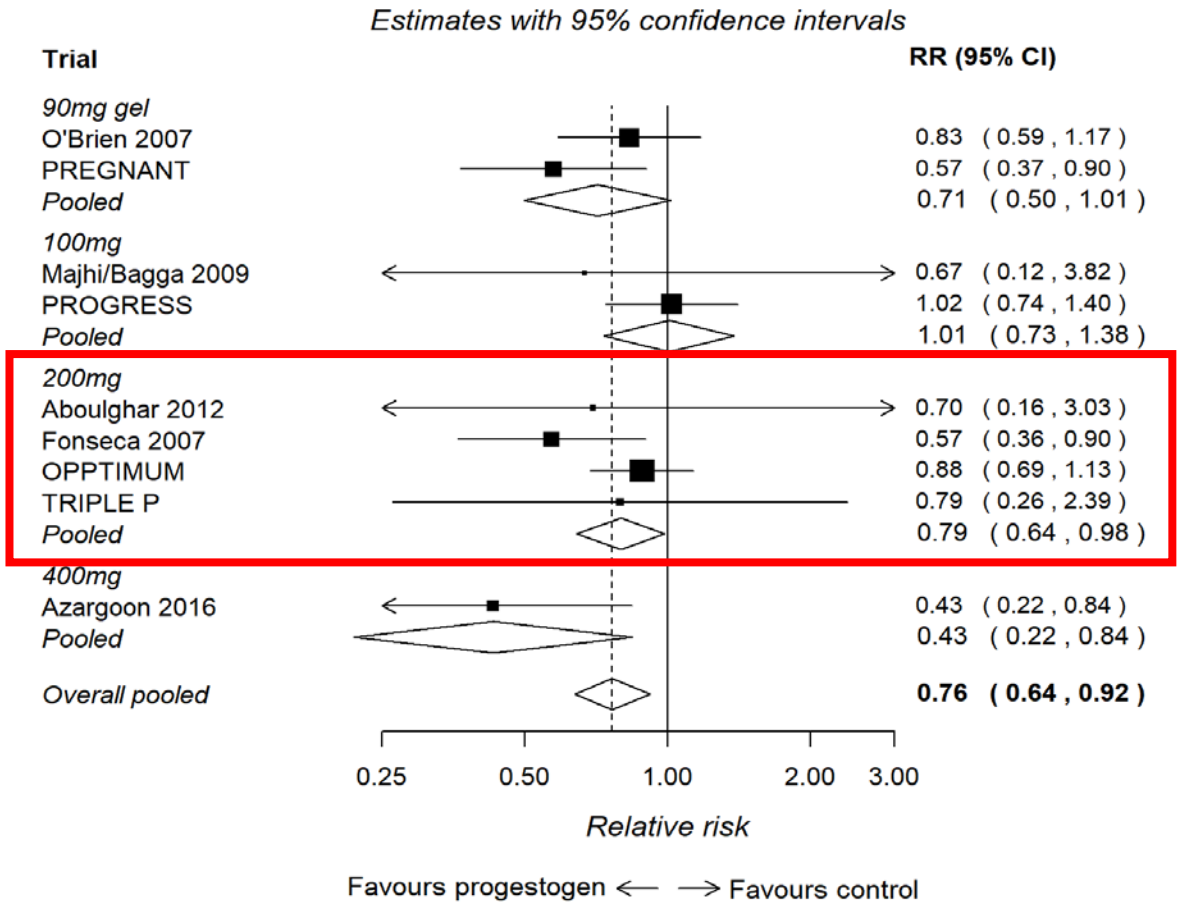


Risk of spontaneous PTB significantly increases with shortening cervix

Iams JD, et al. N Engl J Med 1996;334:567–572.

Evaluating Progestogens for Preventing Preterm birth International Collaborative

EPPPIC study: Meta-analysis of progesterone for preventing PTB (singleton pregnancy)

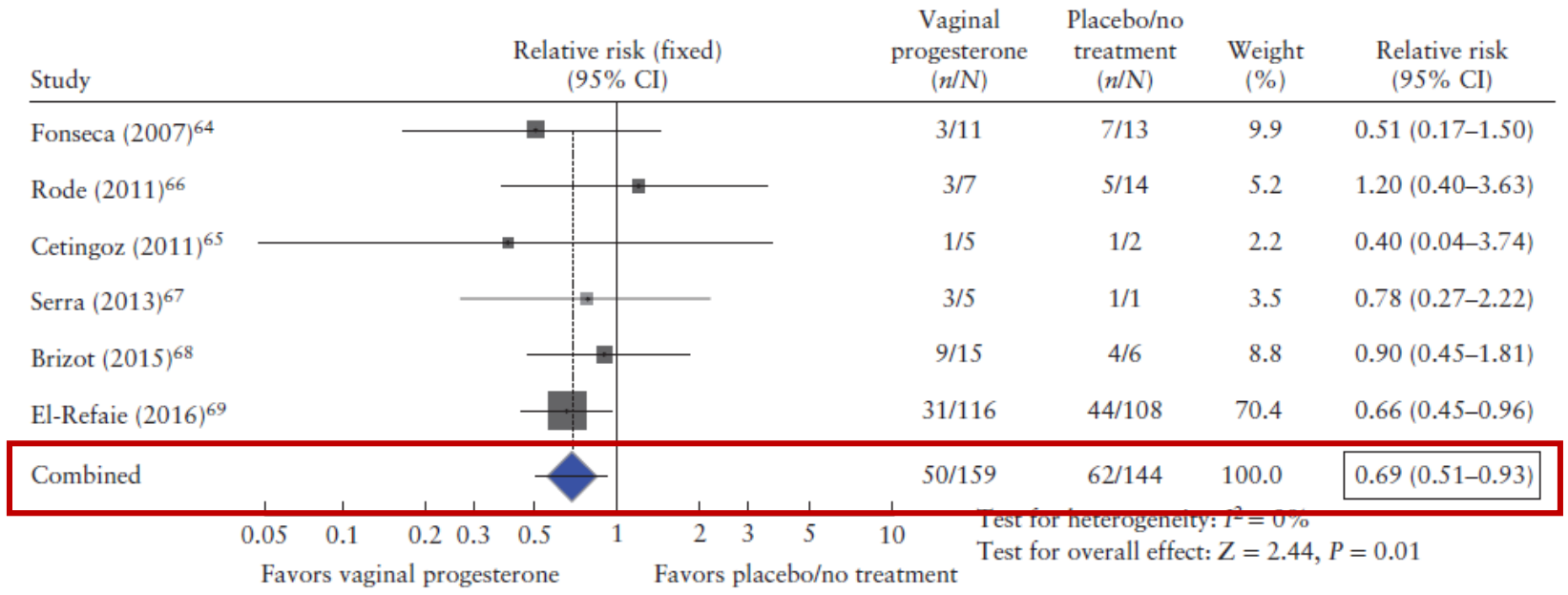


Subgroup analysis by planned **vaginal progesterone dose** in singleton pregnancies, **preterm birth before 34 weeks**

Vaginal progesterone 200mg, Significant decrease the risk of PTD

The EPPPIC Group. *Lancet*. 2021;397(10280):1183–94.

Twin gestation : vaginal progesterone on preterm deli very



0.69

Figure 3 Forest plot of the effect of vaginal progesterone on the risk of preterm birth < 33 weeks' gestation. CI, confidence interval.

Results : Reduces the risk of preterm birth occurring at < 30 to < 35 weeks of GA

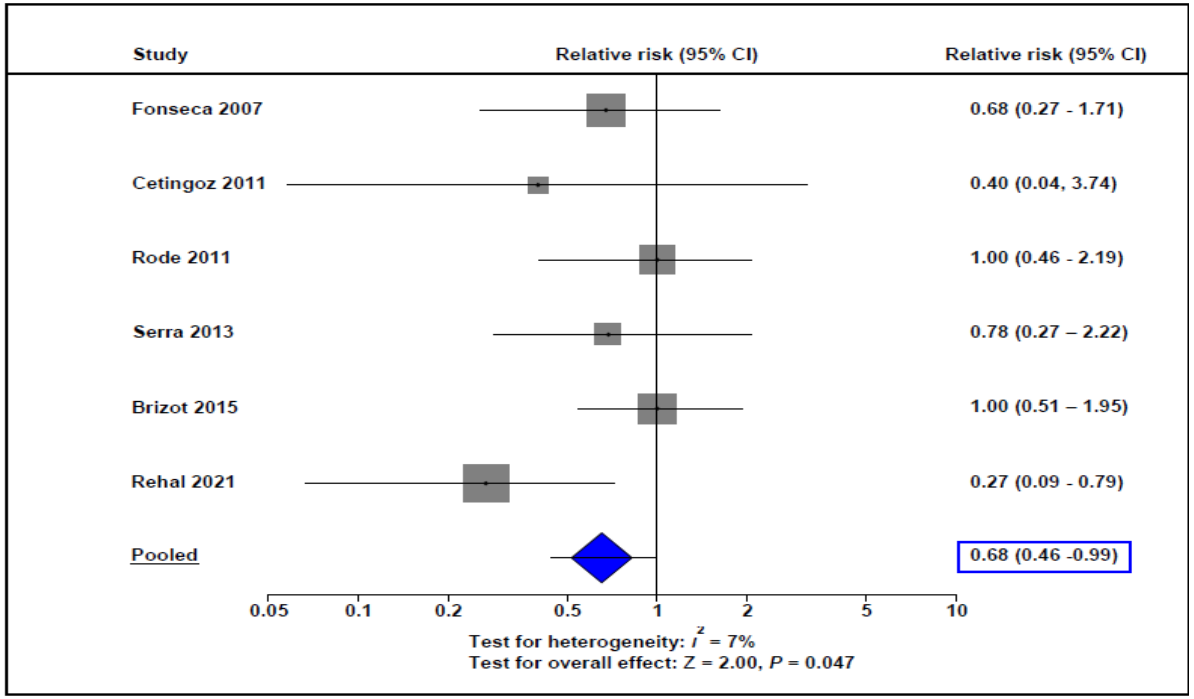
➔ ▼ neonatal mortality , ▼ some measures of neonatal morbidity

➔ Without any demonstrable deleterious effects on childhood neurodevelopment.

Romero R et al**.** *Ultrasound Obstet Gynecol 2017;* **49(3)***: 303-14*

Twin gestation: vaginal progesterone on preterm delivery

SUPPLEMENTAL FIGURE 4
Effect of vaginal progesterone on preterm birth <34 weeks of gestation in twin gestations with a transvaginal cervical length ≤25 mm



CI, confidence interval.

Conde-Agudelo. Vaginal progesterone to prevent preterm birth in twin gestations. Am J Obstet Gynecol 2023.

Vaginal Progesterone associated with a significant Reduction in the risk of preterm birth < 34 weeks GA

(46.2% vs. 65.1%
RR, 0.68;
95% CI, 0.46-0.99; *P*=0.047)

RR 0.68

Conde-Agudelo A, et al. *Am J Obstet Gynecol*. 2023;229(6);599-616.e3.

Prevention PTB and Protecting neonatal outcomes

Prophylactic vaginal progesterone in women with a short cervix (< 25mm)

Reduction in RDS (RR 0.47)

Reduction in LBW (<1,500g) (RR 0.47)

Reduction in NICU admissions (RR 0.68)

Twin pregnancies: 34- week PTB risk reduction (RR 0.71) in multiple pregnancies with a short cervix using vaginal micronized progesterone

Conde-Agudelo A, et al. *Am J Obstet Gynecol*. 2023;229(6);599-616.e3.

The Clinical Toolkit : Master synthesis

Threatened Miscarriage	Oral dydrogesterone	40 mg stat, then 10 mg BID	Continue 1-2weeks post symptom resolution
Recurrent miscarriage (with bleeding)	Vaginal micronized Progesterone	400 mg BID	Continue until 16 weeks gestation
Singleton and Short cervix ≤ 25mm / PTB history	Vaginal micronized P4 or Vaginal P4 gel	200mg/day or 90mg gel	Continue until 34 ~ 36+6 weeks GA
Twin and short cervix ≤ 25mm	Vaginal micronized P4 or Vaginal P4 gel	200mg/day or 90mg gel	Continue until 34 ~ 36+6 weeks

Progesterone integrated roles in pregnancy : master key

Endocrine Engine

- PRB activation
- Myometrial Quiescence
- Endometrial Decidualization

Immune Shield

- PIBF Cascade
- Th1 to Th2 Shift Treg Expansion
- NK cell Suppression

Progesterone as both structural builder immune guardian

-

Move from empirical prescribing To targeted mechanism driven patient care

Preterm birth prevention

Threatened/ recurrent miscarriage resolution

경청해주셔서 감사합니다

대한생식면역학회
Korean Society for Reproductive Immunology