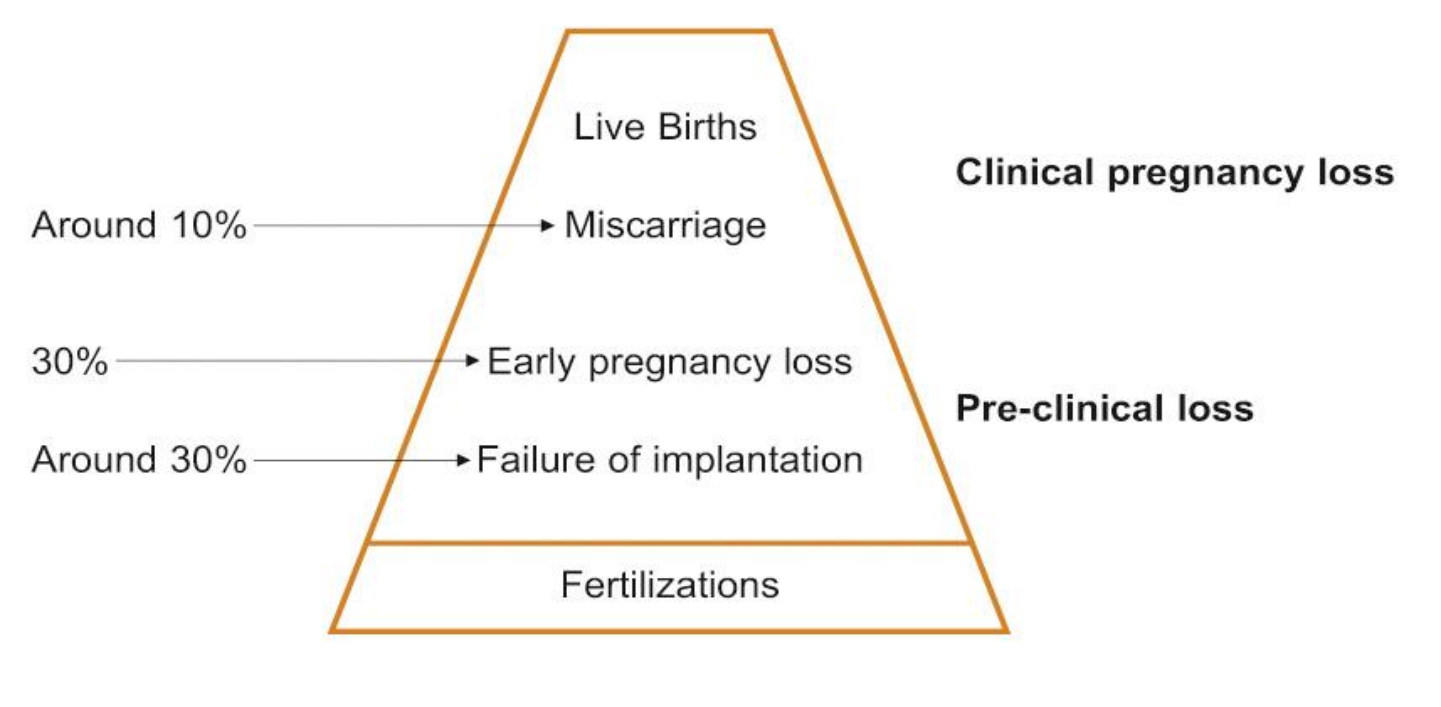
Treatment of threatened and recurrent miscarriage

Incidence of pregnancy loss

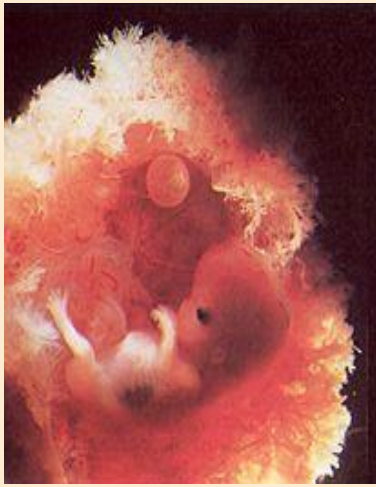


Around 70% of conceptions are lost prior to live birth

Once a woman has had a positive pregnancy test, there is around a 10% risk of having a miscarriage

Macklon và cộng sự 2002; Regan và cộng sự 1989. Everett 1997

Causes of pregnancy loss and recurrent abortion



- **Explainable (50-60%)**
- - endocrine
  - anatomical
  - genetic
  - infections
  - autoimmune antibodies
  (Anticardiolipin, Lupus , APLA)

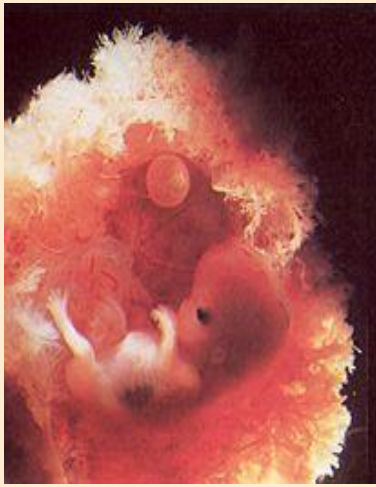
Raghupathy R. *Seminars in Immunology* 2001; 13: 219-227.

Causes of recurrent abortion

– **Unexplained (40-50%)**

– deficient immuno-suppression

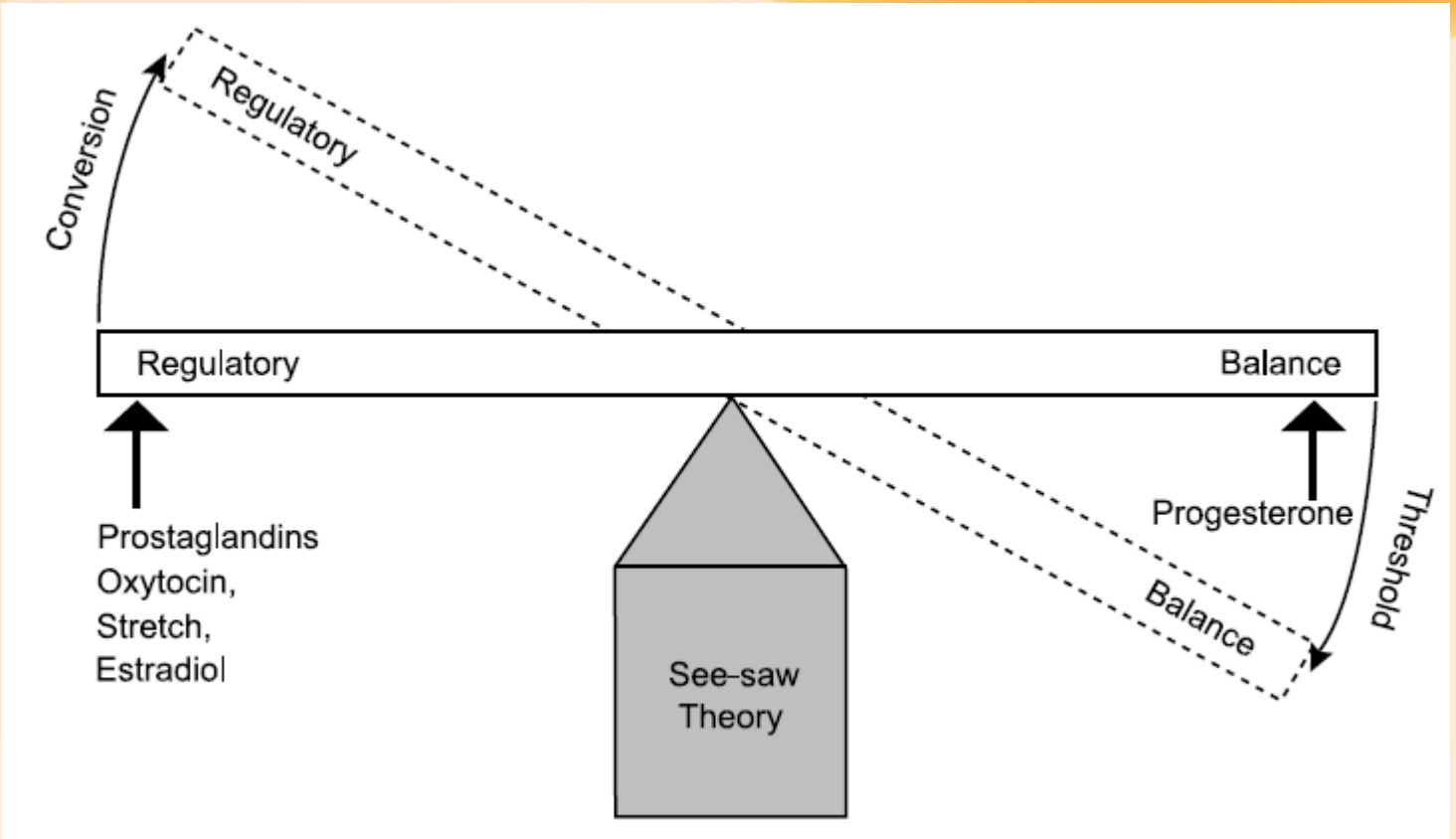
- ↑ maternal Th1 cytokines
- ↓ maternal Th2 cytokines



Raghupathy R. *Seminars in Immunology* 2001; 13: 219-227.

Caused by Progesterone hormone deficiency

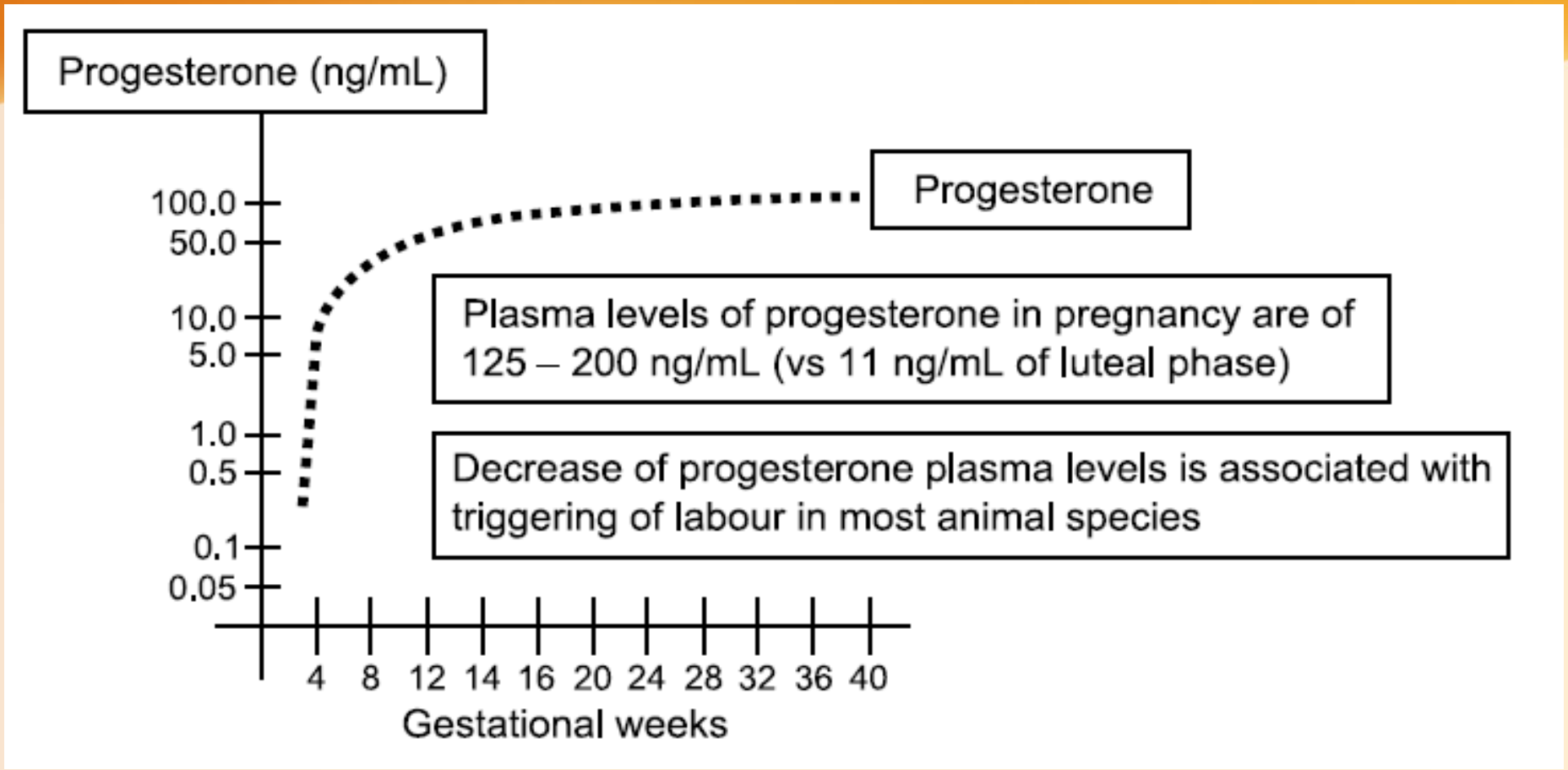
Progesterone decline is a sign of delivery process



Csapo's 'see-saw theory'. Progesterone deficiency is a prerequisite to terminate pregnancy.

G.C. DI RENZO ET AL. RCOG 2005 BJOG

Progesterone levels needed during pregnancy



- ***Plasma levels of progesterone in pregnancy are of 125-200 ng/ml (vs 11 ng/ml of luteal phase)***
- ***Decrease of progesterone plasma levels is associated with triggering of labor in most animal species***

G.C. DI RENZO ET AL. RCOG 2005 BJOG

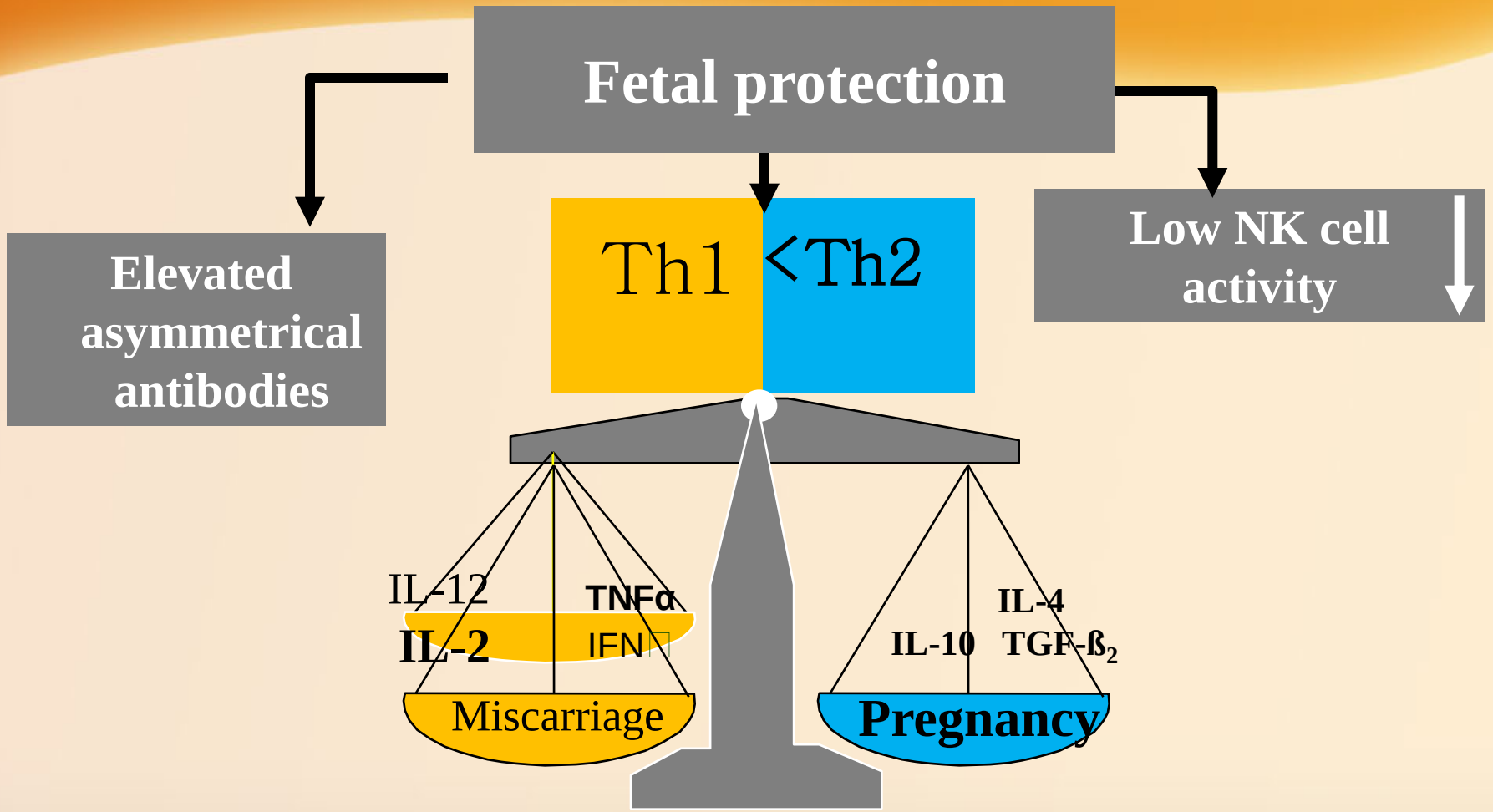
Caused by immune system

Phenomenon of fetal elimination and destruction on immuno-endocrine aspect

- Through antibodies
- Through Th1 cells
- Through NK cells

Th1 : T helper cells type 1
NK : Natural Killer cells

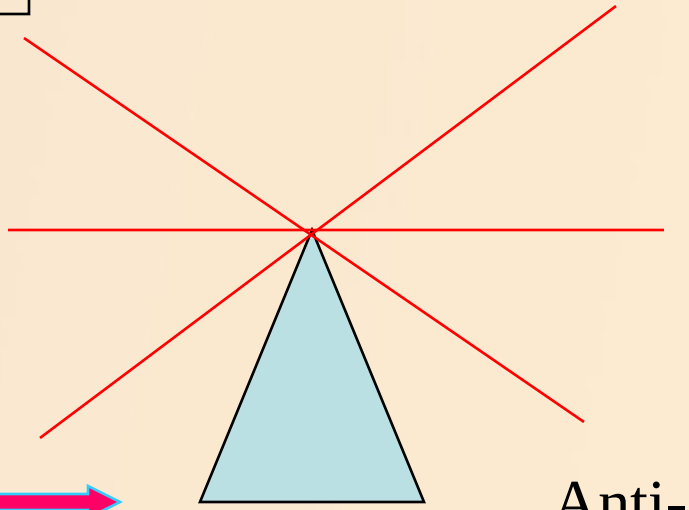
Fetal protection through immunity process



Th1 cytokines versus Th2 cytokines

Th1 & natural killing cells (IL 2, IFNy, TNF)

IL 3, IL 4, IL 5
IL 6, IL 10, IL 13

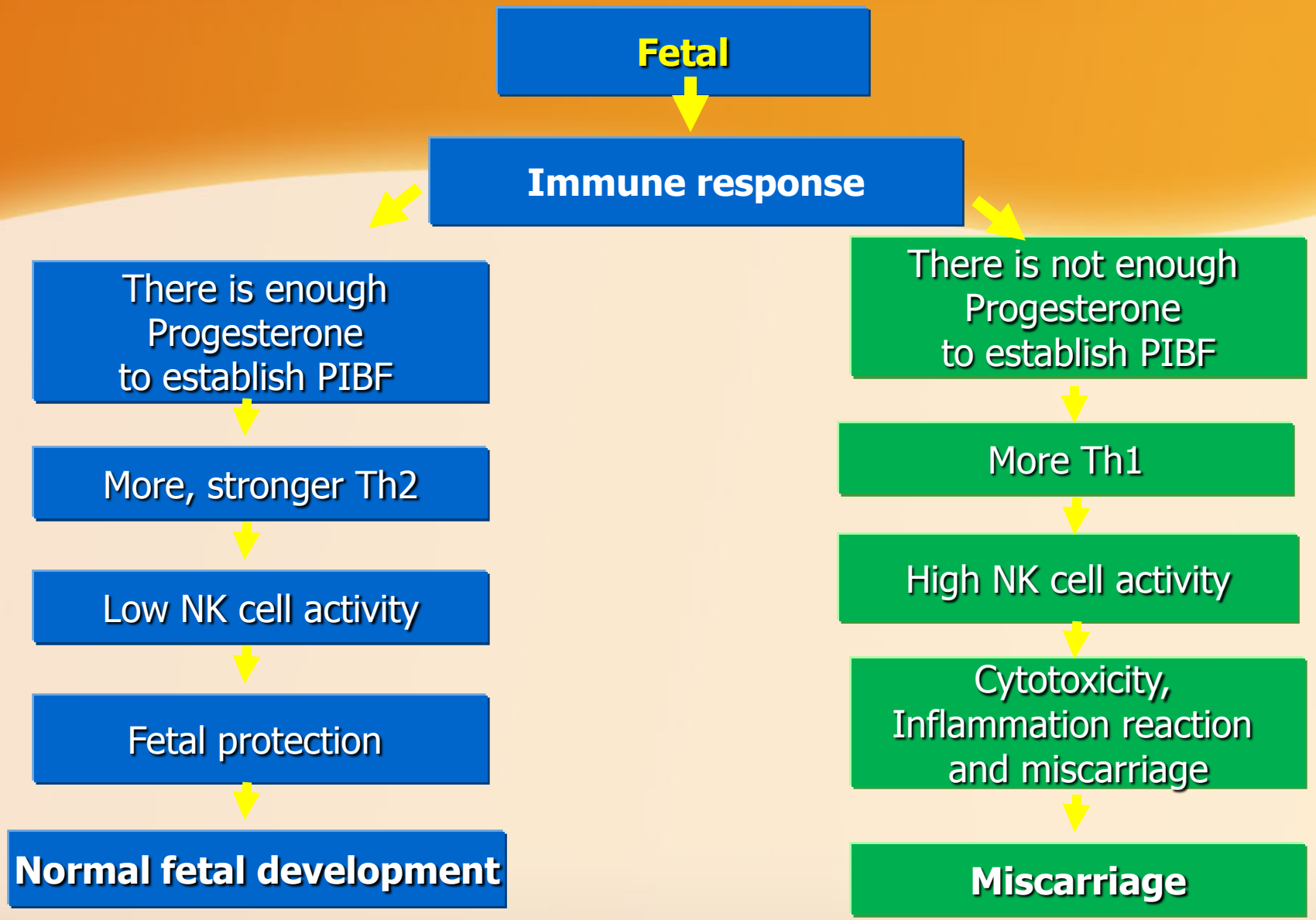


Th1 cytokines

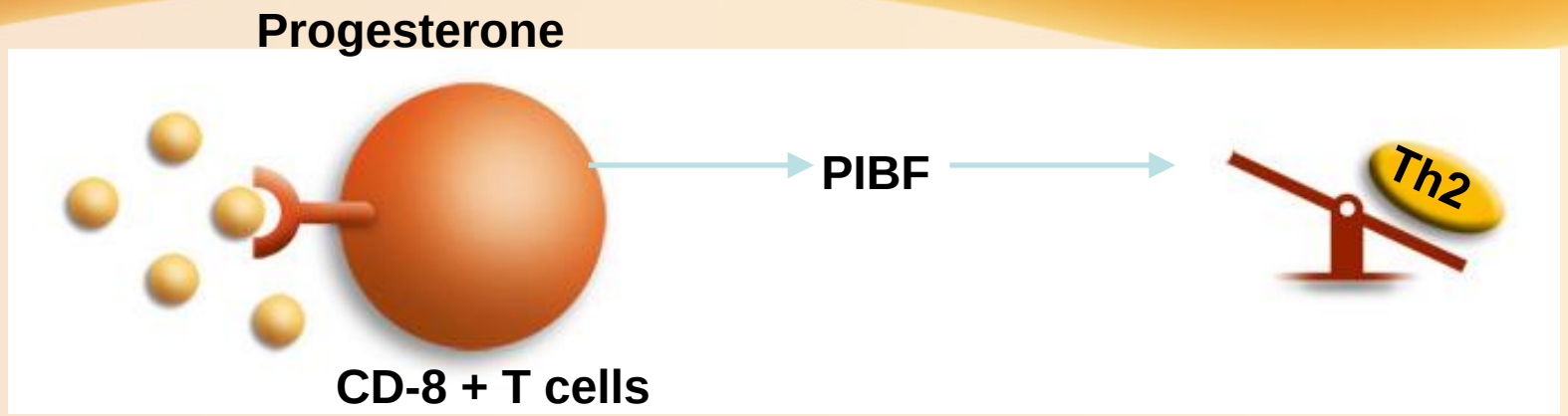
Th2 cytokines

Inflammatory support (Miscarriage)

Anti-inflammatory (Success)


Fetal
Immune response
There is enough Progesterone to establish PIBF
More, stronger Th2
Low NK cell activity
Fetal protection
Normal fetal development
There is not enough Progesterone to establish PIBF
More Th1
High NK cell activity
Cytotoxicity, Inflammation reaction and miscarriage
Miscarriage

Potential relationship between the endocrine and immune system



Progesterone plays an essential role to maintain pregnancy. It is produced by the corpus luteum until weeks 7-9, then placenta takes over this function.[1]

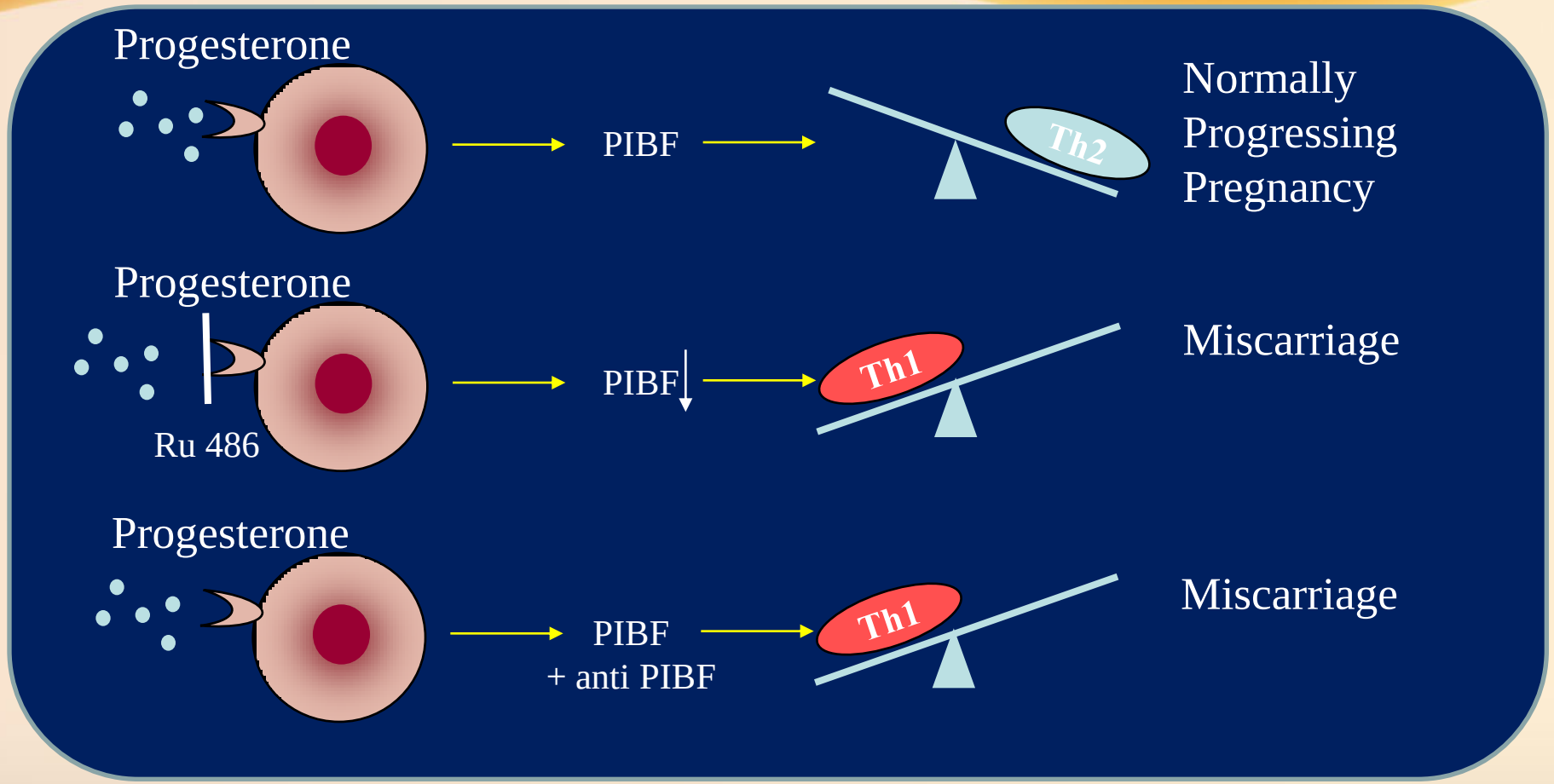
Progesterone stimulates the production of progesterone-induced blocking factor (PIBF) and generate T helper cell responses (Th)2.[2,3]

1. Norwitz 2001; 2. Szekeres-Bartho & Wegmann 1996; 3. Szekeres-Bartho 2002

PIBF *(Progesterone-induced Blocking Factor)*

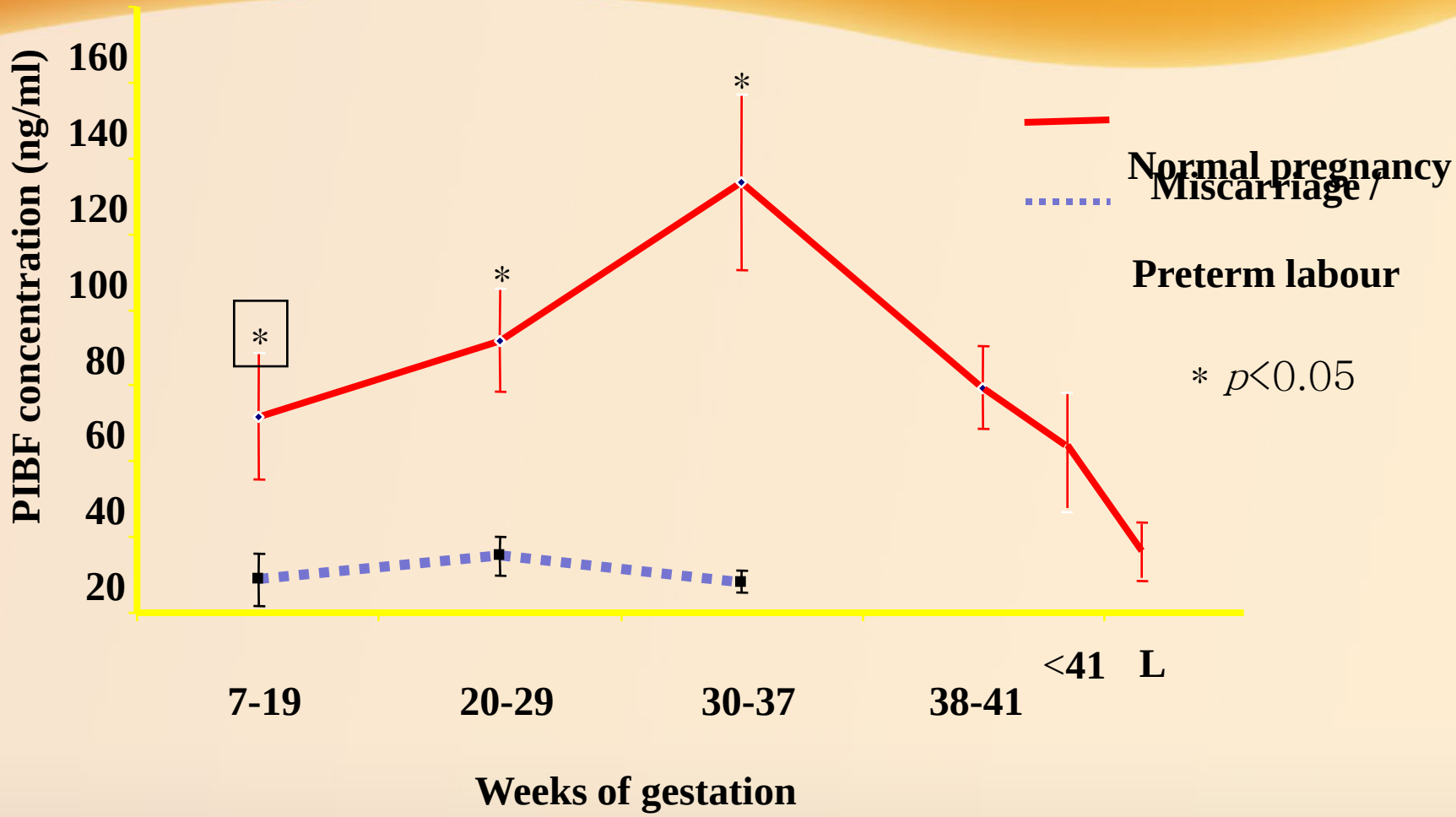
- Produced after activation of P-receptors
- Produced by CD56 cells and PBMC*
- Induces asymmetric antibodies (non-cytotoxic)
- Supports Th2 (pregnancy-protective) dominance
- Reduces activity of NK cells
- PIBF is key to embryo survival
- * - PBMC = Peripheral Blood Mononuclear Cell

Progesterone-induced Blocking Factor (PIBF)
Link between the endocrine and immune system



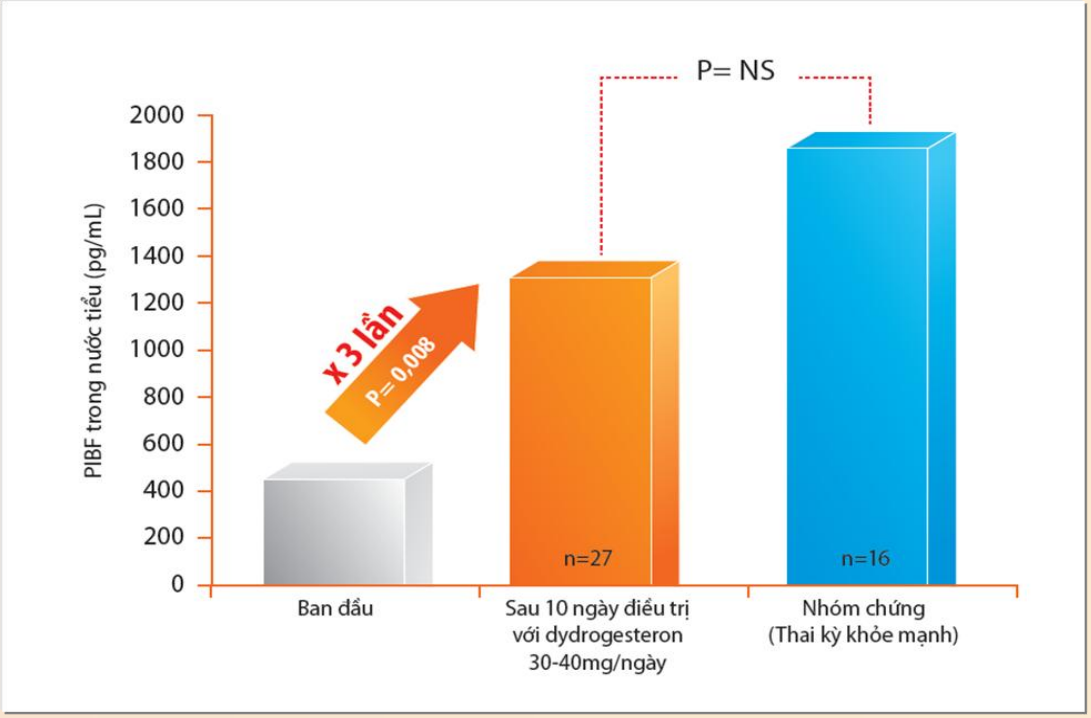
Szekeres-Bartho J và cộng sự. Int Immunopharm 2001; 1:1037-1048.

PIBF concentrations in normal and high risk pregnancies



Polgar B et al. Biol Reprod 2004; 71:1699-1705.

Dydrogesterone improves PIBF concentration in patients with threatened miscarriage



Kalinka J, American Journal of reproductive Immunology 2005

Open label study in normal pregnant or threatened miscarriage women (6-12 weeks)
-27 pregnant women with threatened miscarriage used dydrogesterone at the dose of 30-40 mg/day x 10
- 16 normal pregnant

PIBF concentration in the group of pregnant women with threatened miscarriage is equivalent to the group of healthy women after 10 days of treatment with dydrogesterone

Dydrogesterone improves effectively the Th1/Th2 ratio

Table 2. Cytokine ratios before and after addition of progestogen to stimulated cultures.

Cytokine ratio	PHA	PHA + dydrogesterone	PHA + progesterone	P^*	P^{**}
IFN/IL-4	2855	140	1255	0.0001	0.006
IFN/IL-6	4.2	0.3	2.7	0.0001	0.002
IFN/IL-10	43	5	33	0.0001	0.33
TNF/IL-4	327	110	127	0.02	0.006
TNF/IL-6	0.5	0.3	0.3	0.0001	0.009
TNF/IL-10	5	4	3	0.52	0.4

* Values for PHA compared with PHA + dydrogesterone.

** Values for PHA compared with PHA + progesterone.

The study was carried out in 32 pregnant women with unexplained recurrent miscarriage to evaluate effectiveness of dydrogesteron in the generation of Th1 cytokines.

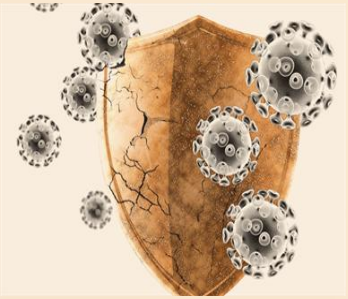
. Raj Raghupathy, Modulation of cytokine production by dydrogesteron in lymphocytes from women with recurrent miscarriage, BJOG 2005

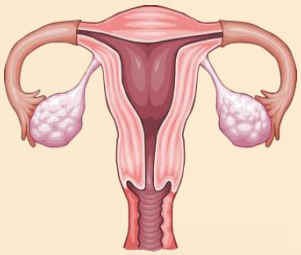
Efficacy of Progesterone in protection of pregnancy

Efficacy of Progesterone supplementation in pregnancy

Progesterone –
helps to maintain pregnancy

- **Regulates immune response**
- **Prevents inflammation response**
- **Reduces uterine contractions**
- **Improves uterine-placental circulation**





Prevents miscarriage for patients with threatened miscarriage, recurrent miscarriage

ORIGINAL ARTICLE

The Impact of Dydrogesterone Supplementation on Serum Cytokine Profile in Women with Threatened Abortion

Jarosław Kalinka[1], Michał Radwan[2]

[1]Department of Perinatology, I Division of Gynecology and Obstetrics, Medical University of Lodz;
[2]Department of Operative and Endoscopic Gynecology, Polish Mother's Memorial Hospital – Research Institute, Lodz, Poland

American Journal of Reproductive Immunology **55** (2006) 115–121 © 2006 Blackwell Munksgaard

AJRI 2005; 53: 166–171

American Journal of Reproductive Immunology

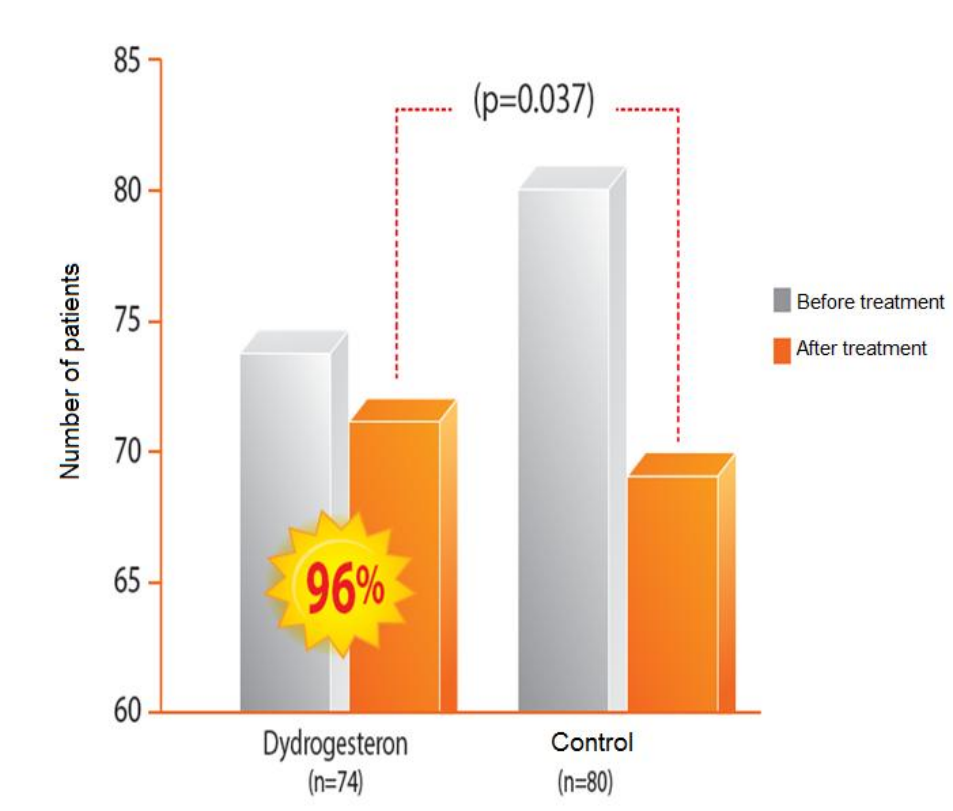
The Impact of Dydrogesterone Supplementation on Hormonal Profile and Progesterone-induced Blocking Factor Concentrations in Women with Threatened Abortion

Kalinka J, Szekeres-Bartho J. The impact of dydrogesterone supplementation on hormonal profile and progesterone-induced blocking factor concentrations in women with threatened abortion. AJRI 2005; 53:166–171 © Blackwell Munksgaard, 2005

Jarosław Kalinka[1], Julia Szekeres-Bartho[2,3]

[1]Department of Perinatology, I Division of Gynecology and Obstetrics, Medical University of Lodz, Poland;

Efficacy of Dydrogesterone in patients with signs of clinical threatened abortion



RCT (Malaysia): Gestational age < 13 weeks, unexplained threatened miscarriage

❖Group 1: 74 pregnant women.

–Dydrogesteron 40 mg/day x 7, followed by 10 mg x 2 times/day
→ stopped vaginal bleeding

– Bed rest + acid folic

❖Group 2: 80 pregnant women treated bed rest + acid folic

96% of patients with threatened miscarriages have successful pregnancies after using dydrogesterone

Omar MH et al. Dydrogesterone in threatened abortion

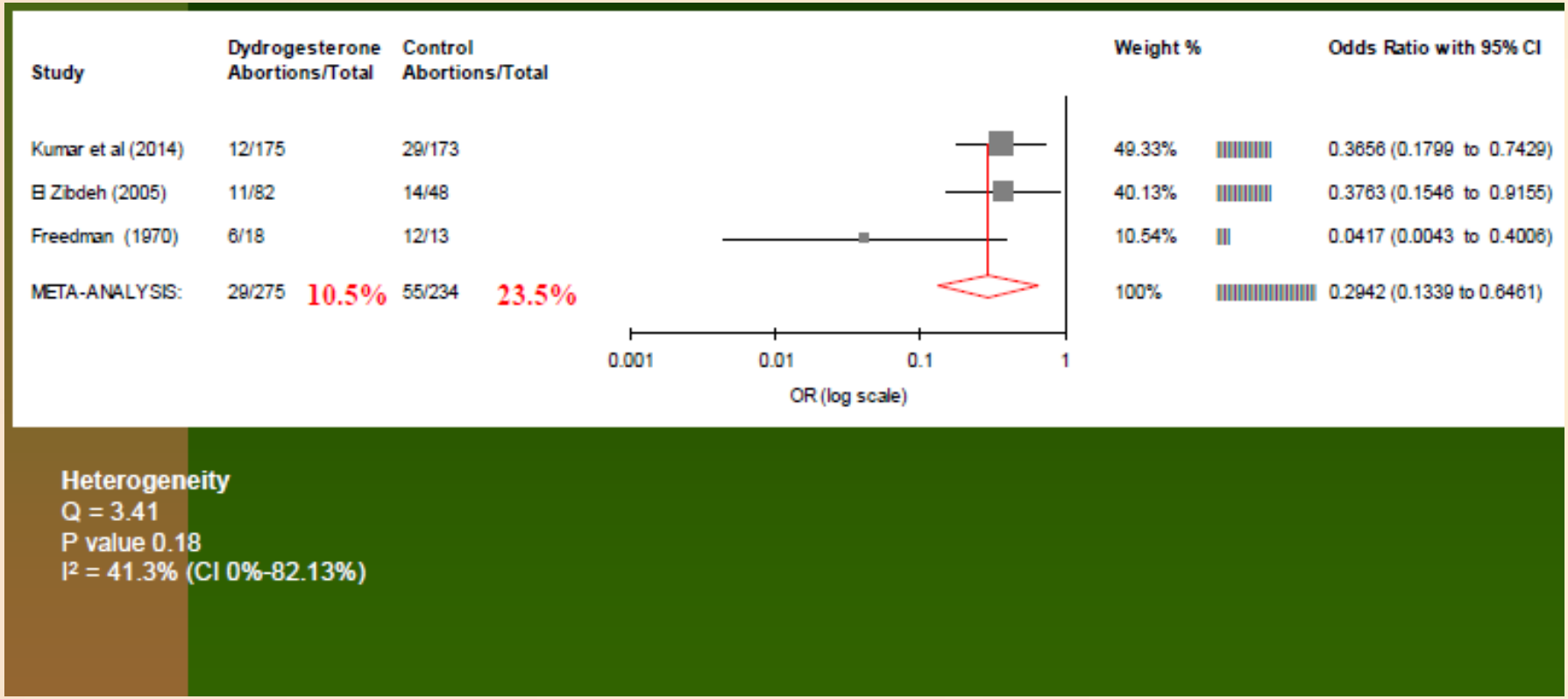
Dydrogesterone treatment increases PIBF in women with threatened miscarriage

	Day 1	Day 10	
Threatened miscarriage (n = 27)	453.3±496.3	1291.6±1132.9	p = 0.001
Control (n = 16)	1057.9±930.8	1831.6±1979.2	p = 0.26
	p = 0.008	**NS (Not Significant)**	

Mean PIBF (SD) (pg/ml)

Kalinka & Szekeres-Bartho 2005

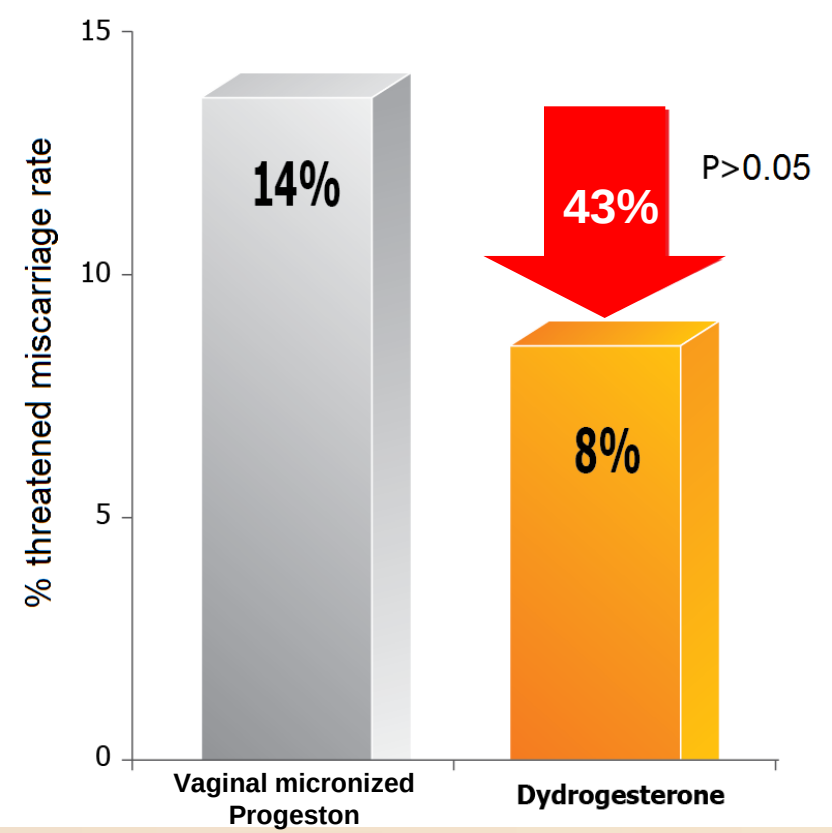
Dydrogesterone has efficacy for recurrent miscarriage



Oral Dydrogesterone reduced 55% of recurrent miscarriage rate compared to the untreated group

Carp's Metaanalysis 2012

Treatment efficacy of threatened miscarriage with dydrogesterone tends to be higher than vaginal micronized progesterone



Randomized study, double-blind, conducted in 53 patients with threatened miscarriage to compare the effects of vaginal micronized dydrogesterone and progesterone for the uterine placental circulation in early stages of pregnancy

- Group 1 (n=25): ***300 mg of vaginal micronized progestserone*** *+ oral placebo*

*- Group 2 (n=22): **30 mg of dydrogesterone** + vaginal micronized placebo.*

Follow up to the gestational week 23

K. Czajkowski et al, progesteron in threatened abortion, Fertil Steril 2007

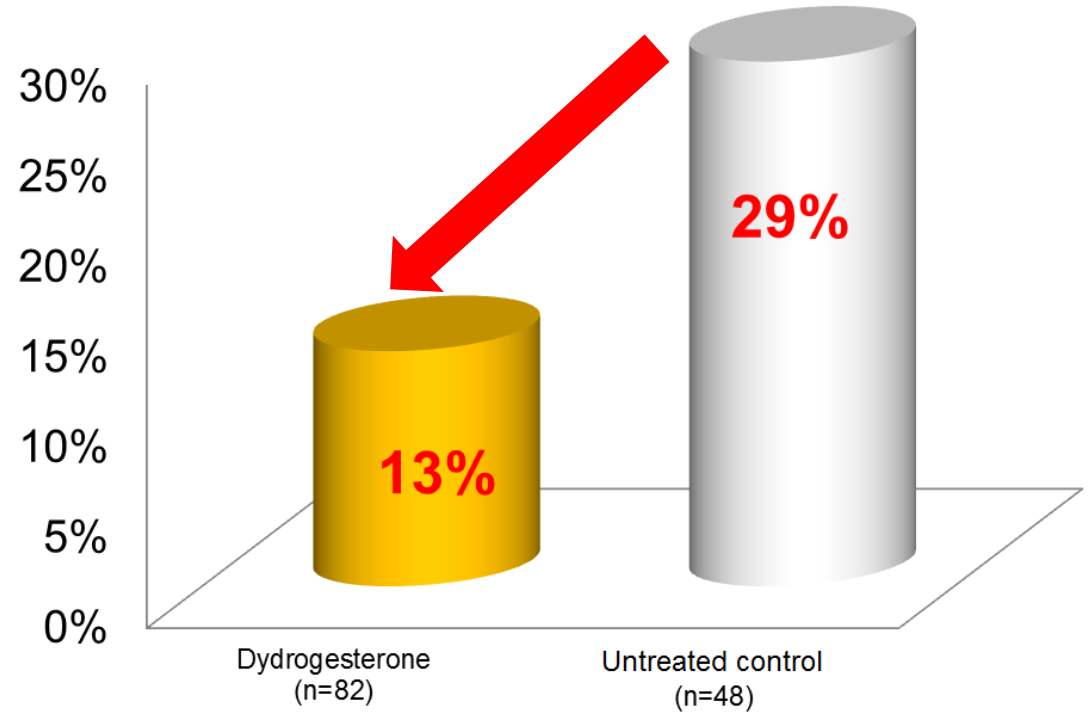
Efficacy of Dydrogesterone in recurrent miscarriage

Pregnant women (< 35 years old) with at least three unexplained consecutive miscarriages previously with the same partners were randomized into groups:

-82 patients taking oral dydrogesterone 10 mg, 2 times/day, multivitamin and bed rest

-48 patients in control group: multivitamin + bed rest

Treatment to week 12 of pregnancy



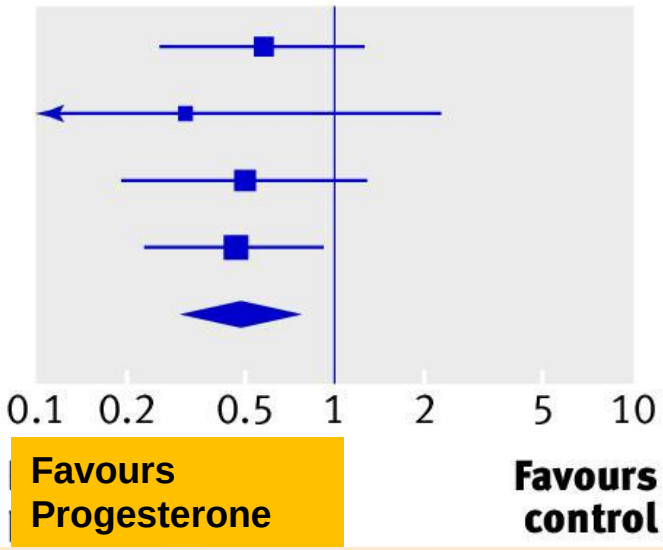
Dydrogesterone reduced more than 2 times of miscarriage risk for patients with recurrent miscarriage

Efficacy of Progesterone in preventing threatened miscarriage condition

Study	No of miscarriages: Progesterone	No of miscarriages: Control	Rate ratio (95% CI)	Weight (%)	Rate ratio (95% CI)
Swyer 1953[2]	7/27	9/20		26.14	0.58 (0.26 to 1.28)
Goldzieher 1964[3]	1/8	4/10		8.99	0.31 (0.04 to 2.27)
Le Vine 1964[4]	4/15	8/15		20.22	0.50 (0.19 to 1.31)
El-Zibdeh 2005[5]	11/82	14/48		44.65	0.46 (0.23 to 0.93)
Total (95% CI)	132	93		100.00	0.49 (0.31 to 0.76)

Test for heterogeneity: χ^2=0.39, df=3, P=0.94, I^2=0%

Test for overall effect: z=3.13, P=0.002



Progesterone achieved efficacy of preventing miscarriage and recurrent miscarriage **up to 51%** compared to group of patients who used/did not use placebo

Coomarasamy BMJ 2011

Efficacy of using vaginal micronized progesterone in the treatment of patients with threatened miscarriage

Review: Progestogen for treating threatened miscarriage

Comparison: 1 Progesterone versus placebo

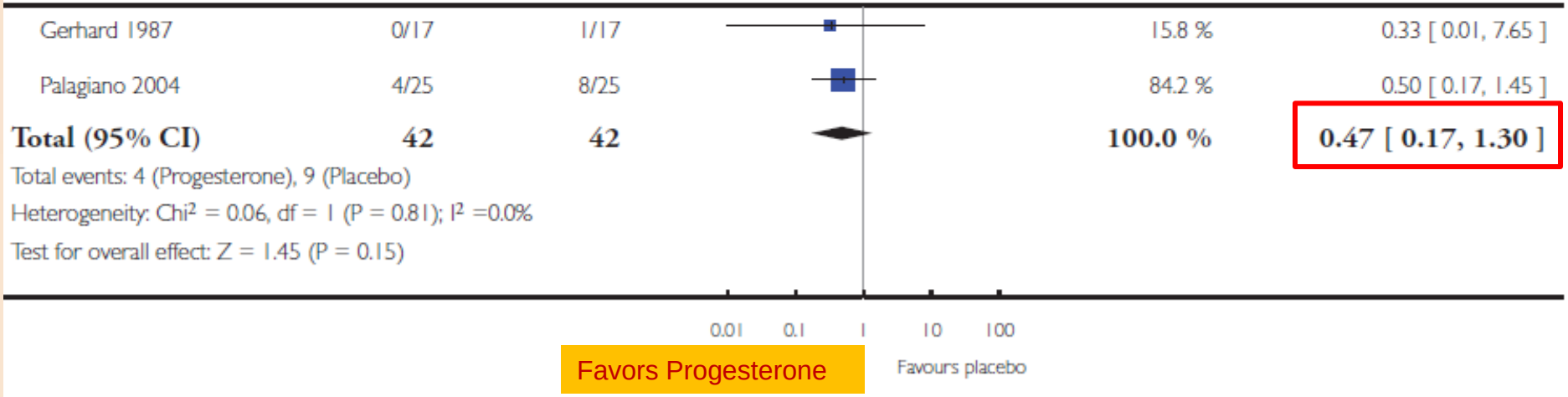
Outcome: 1 Miscarriage

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gerhard 1987	0/17	1/17		15.8 %	0.33 [0.01, 7.65]
Palagiano 2004	4/25	8/25		84.2 %	0.50 [0.17, 1.45]
Total (95% CI)	**42**	**42**		**100.0 %**	**0.47 [0.17, 1.30]**

Total events: 4 (Progesterone), 9 (Placebo)

Heterogeneity: $Chi^2 = 0.06$, df = 1 (P = 0.81); $I^2 = 0.0\%$

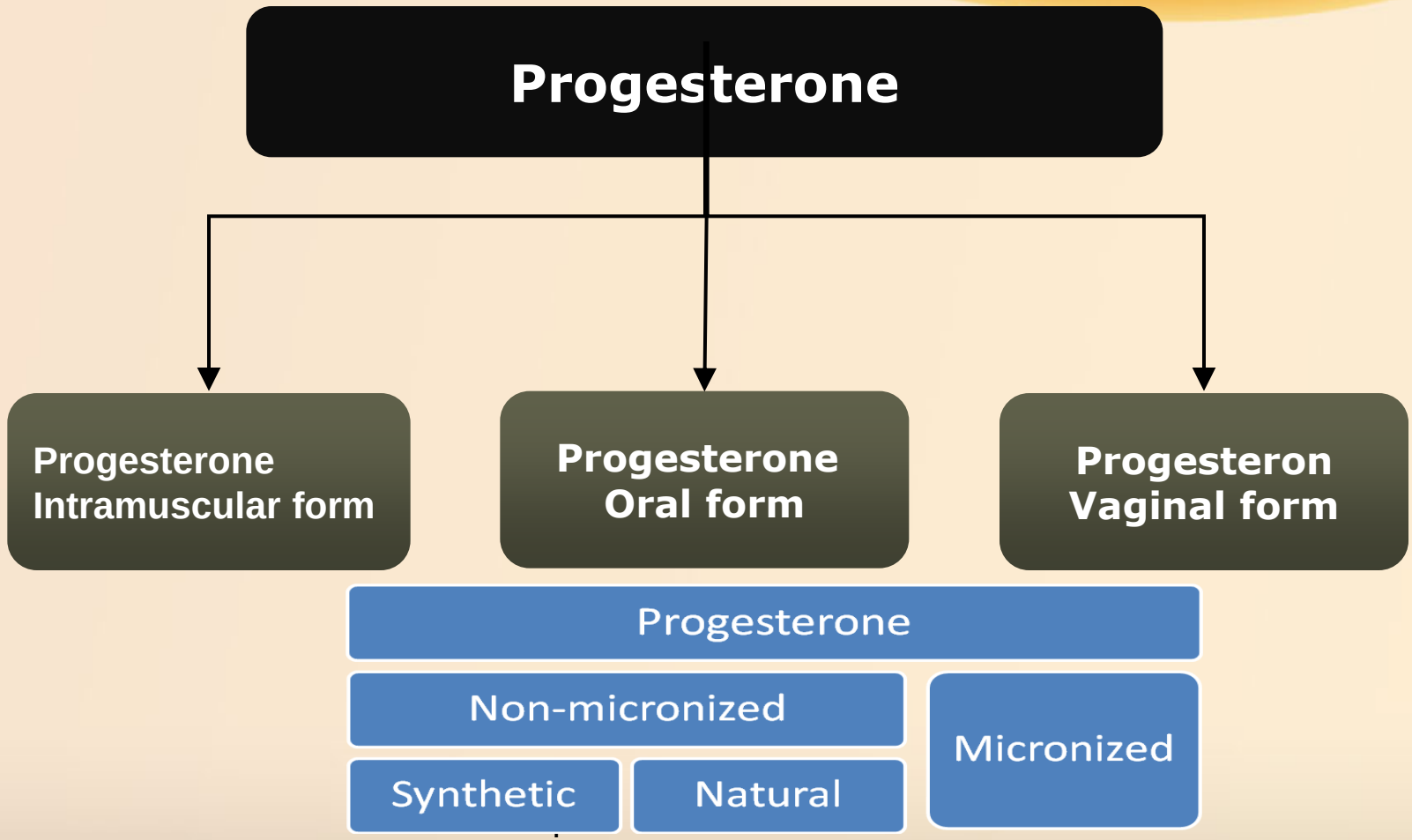
Test for overall effect: Z = 1.45 (P = 0.15)



Patients who used vaginal micronized Progesterone in the treatment of threatened miscarriage **reduced 47%** of rate of patients with miscarriage.

Cochrane Database of Systematic Reviews 2007, Issue 3.

Routes of administration of Progesterone



Synthetic Progestins

- Progesterone analogues were synthesized in order these hormones can be used orally
- Used first for contraception
- Many of these compounds are associated with glucocorticoid, androgen and mineralocorticoid receptors, side effects (acne, weight gain, depression, mood changes, irritability

Micronized Progesterone
Oral metabolism

Oral progesterone undergoes many consecutive steps of metabolism:

- in intestine (bacteria with 5β-reductase activity)
- in intestinal wall (5α-reductase)
- in liver (5β-reductase, 3ααnd 20α-hydroxylase)

- ✓ **5α -pregnanolone and 5β -pregnanolone (GABA *A*)**
- ✓ **5α -pregnanedione and 5β -pregnanedione (anti-mitotic, tocolytic)**

High dose use

<u>Side effects via oral route:</u>

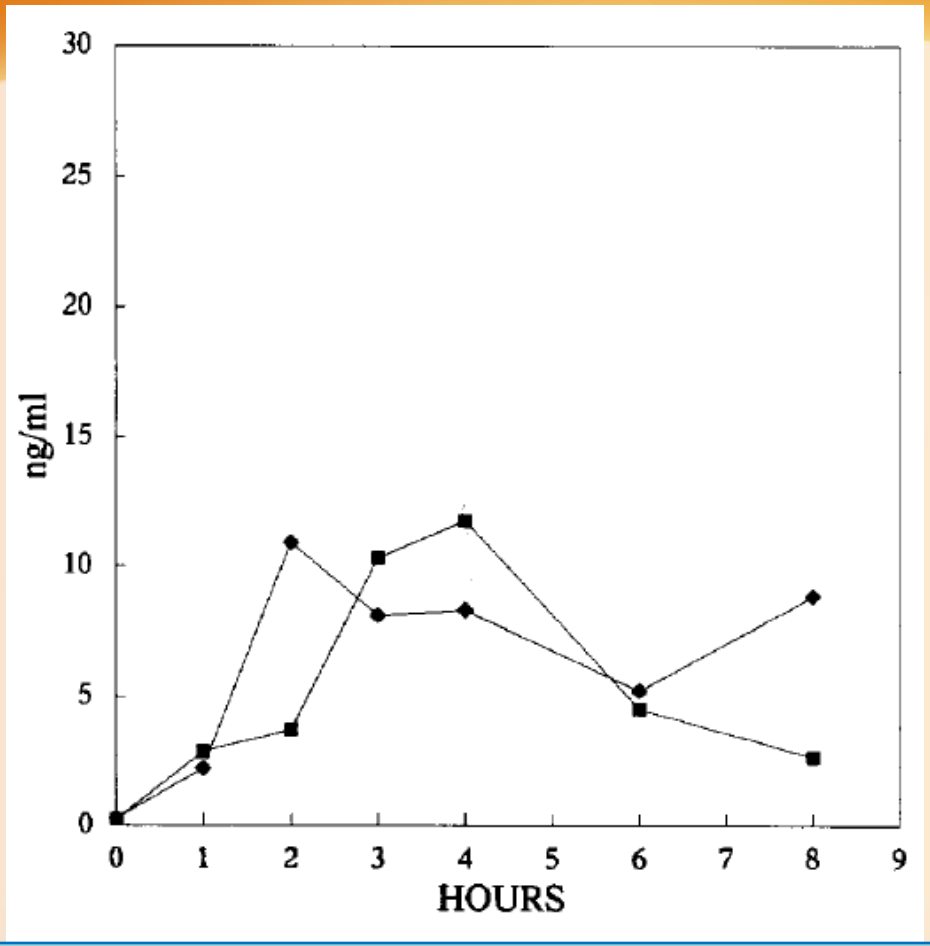
- **Increased hepatic metabolism**
- **Drowsiness, somnolence, sometimes feeling dizzy due to central nervous system effect (GABA receptor)**
- **Shorten menstruation cycles or causing breakthrough bleeding**

Micronized Progesterone
Vaginal metabolism

- Bacteria in vagina and vaginal mucosa seem **having no 5α and 5β-reductases**
- After passing through vagina, only an increase in small quantities of **5α-pregnanolone** was seen **and concentration of 5β-pregnanolone is unaffected**

The activity of progesterone on the central nervous system (CNS) can be adjusted via routes of administration

Plasma concentration of vaginal micronized versus oral Progesterone



Vaginal micronized versus oral progesterone achieved concentrations:

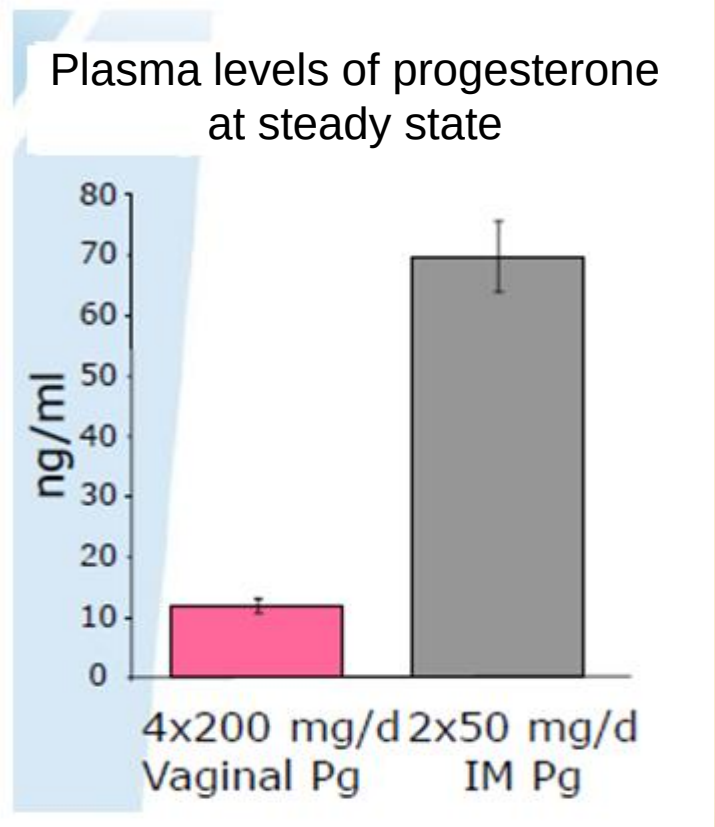
- **2 hours higher** than orally
- **Maintaining stable** during 8 hours.

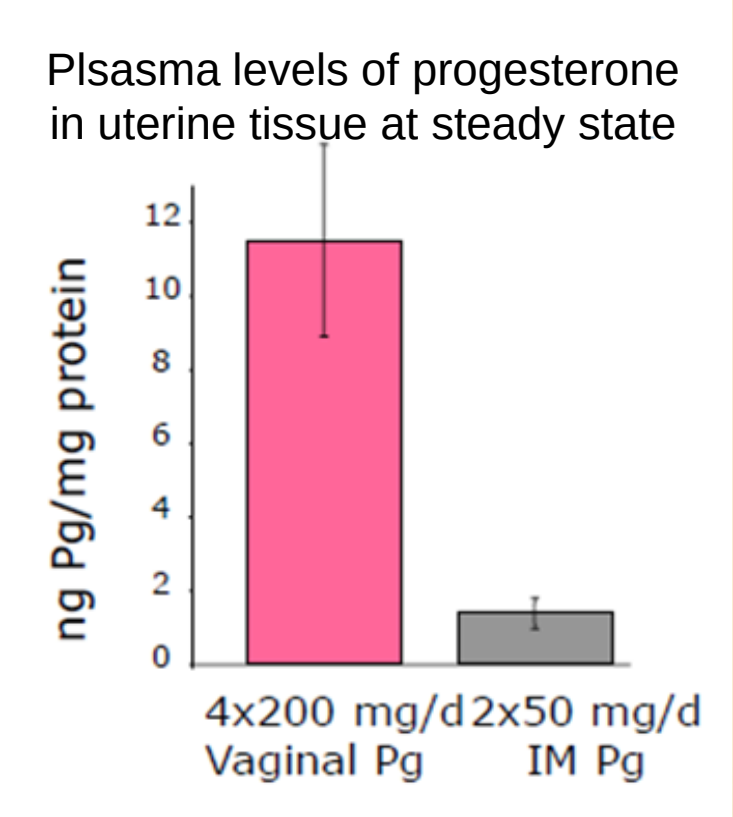
Vaginal micronized Progesterone achieved concentrations in the plasma better than oral form

B. De Lignieres et al./ Maturitas 21 (1995) 251 - 267

Pharmacokinetic data:

vaginal versus intramuscular



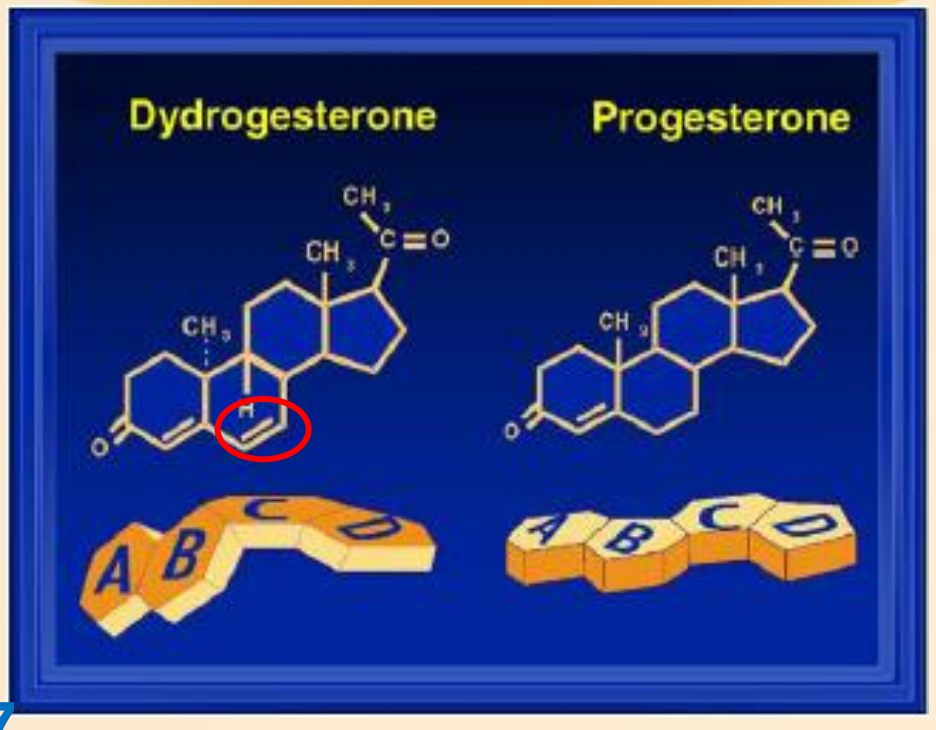


Miles A et al, *Fertil Steril 1994;* **62**: *485-90*

Dydrogesterone

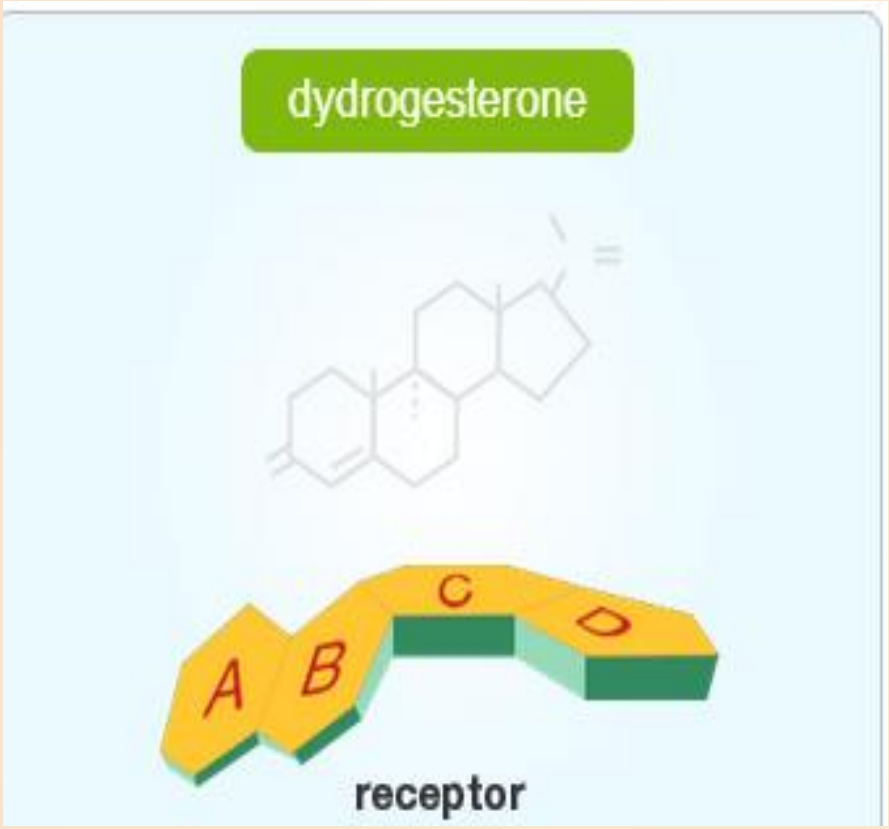
- **6-dehydro – retro progesterone**

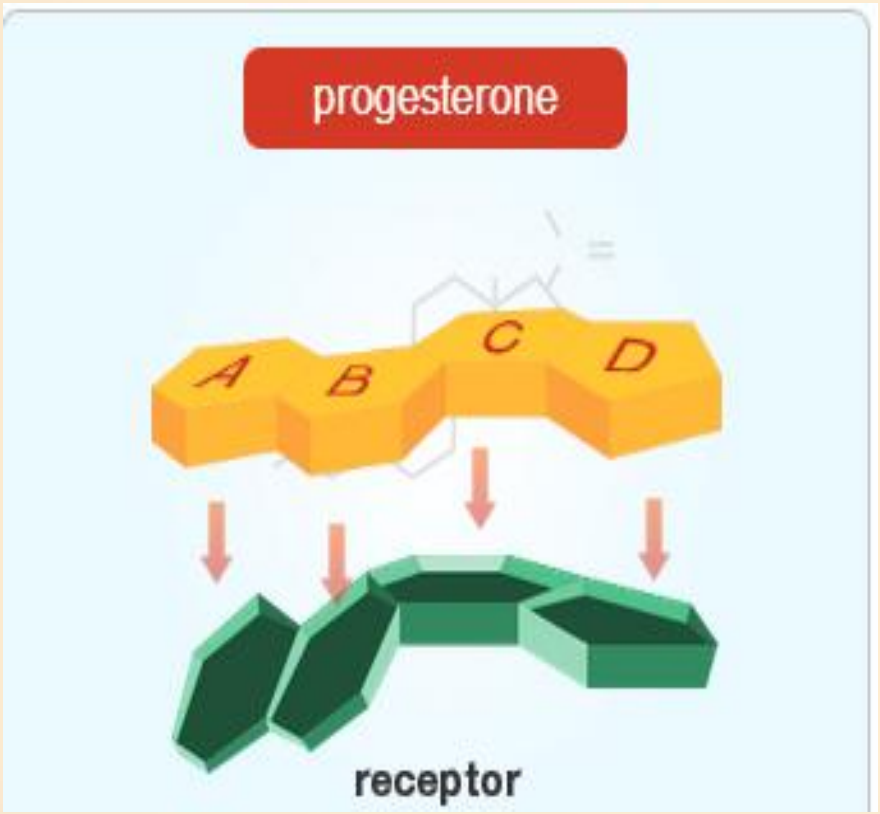
  (converted configuration)



- **Double bond at C6 = C7**
  - ✓ Dydrogesterone: fold, solid, affinity with PR
  - ✓ Progesterone: flat, tied to many other R

Dydrogesterone is highly compatible with Progesterone receptor





Comparison of biological effect between the 2 progesterone forms

Table 6
Relative binding affinities of progesterone and synthetic progestins to steroid receptors and serum binding proteins

Progestin	PR	AR	ER	GR	MR	SHBG	CBG
Progesterone	50	0	0	10	100	0	36
Dydrogesterone	75	0	–	–	–	–	–
Chlormadinone acetate	67	5	0	8	0	0	0
Cyproterone acetate	90	6	0	6	8	0	0
Medroxyprogesterone acetate	115	5	0	29	160	0	0

Dydrogesterone has strong and specific affinity with progesterone receptor

Classification and pharmacology of progestins

Adolf E. Schindler[a,*], Carlo Campa
Jorge R. Pasqualini[e], Karl

The dose is 20 times lower than micronized Progesterone

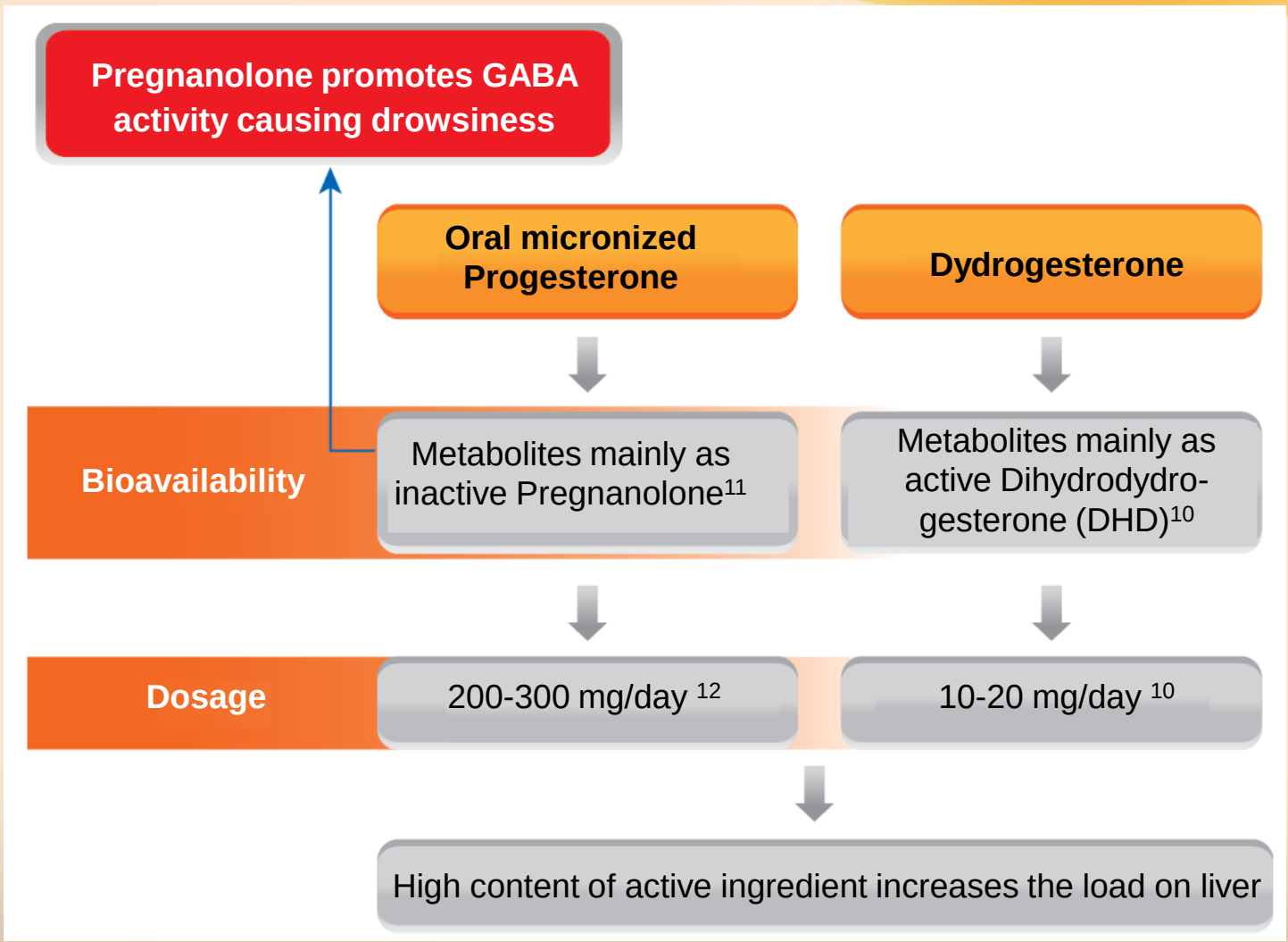
retrostructure, binds almost exclusively to the progesterone receptor. Though the binding affinity appears to be somewhat lower than that of progesterone, due to its better bioaviability and the progestogenic nature of the metabolites, the equivalence dose is 10–20 times lower, regarding endometrial proliferation. Dydrogesterone is metabolised by reduction at C20 to the 20α-hydroxy-derivative and by hydroxylation

Advantages of Dydrogesterone

Does not interfere with ovulation and does not affect fetal gender

Progestogen	Dydrogesterone	Progesterone	Testosterone and 19 nortestosterone derivative	Progesterone derivatives
Inhibition of ovulation	-	+	+	+
Estrogenic	-	±	+	-
Androgenic	-	-	+	+
Masculinisation	-	-	+	+
Dilation of uterine muscles	+	+	-	±

Rare drowsiness, less liver damage



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 DOI: 10.3109/09513590.2015.1017459

informa healthcare

ORIGINAL ARTICLE

European Progestin Club Guidelines for prevention and treatment of threatened or recurrent (habitual) miscarriage with progestogens

Adolf E. Schindler[1], Howard Carp[2], René Druckmann[3], Andrea R. Genazzani[4], Johannes Huber[5], Jorge Pasqualini[6], Karl W. Schweppe[7], and Julia Szekeres-Bartho[8]

[1]Institute for Medical Research and Education, University Clinic, Essen, Germany, [2]Department of Obstetrics & Gynecology, Sheba Medical Center, Tel Hashomer, Israel, [3]Department of Gynecology, ANEMO – Menopausecenter, Nice, France, [4]Department of Obstetrics and Gynecology, University of Pisa, Pisa, Italy, [5]Department of Obstetrics and Gynecology, Division of Gynecologic Endocrinology and Reproductive Medicine, University of Vienna, Vienna, Austria, [6]Hormones and Cancer Research Unit, Paris, France, [7]Endometriosis Center Ammerland, Westerstede, Germany, and [8]Department of Medical Microbiology and Immunology, Medical School Pecs University, Pecs, Hungary

Recommendation 1	
For women presenting with a clinical diagnosis of threatened miscarriage, there is a reduction in the rate of spontaneous miscarriage with the use of dydrogesterone.	Consensus-based recommendation [15,20].

Recommendation 2	
For women presenting with a clinical diagnosis of recurrent miscarriage, 3 or more, there is a reduction in the rate of miscarriage with the use of dydrogesterone.	Consensus-based recommendation [21,24].

Oral Dydrogesterone is recommended for pregnancies having threatened and recurrent miscarriage expression

CONCLUSION

1. **ACOG (2013):** Progesterone is used widely for recurrent miscarriage (RM), particularly unexplained recurrent miscarriage.
2. **Europe Progesterone Club guidline (2015):** recommended that dydrogesterone is used for patients with threatened and recurrent miscarriage.
3. Progesterone and PIBF concentrations are early signs to examine pregnant women with threatened miscarriage.
4. Meta-analysis showed that progesterone, dydrogesterone reduce statistically significant miscarriage rate.
5. Only Dydrogesterone has evidence in improving PIBF concentrations and reducing statistically significant recurrent miscarriage.
6. Vaginal micronized progesterone is recommended for use in the treatment of threatened miscarriage and miscarriage, it is safe and fewer side effects than oral form.

Sincere thanks