Threatened Abortion

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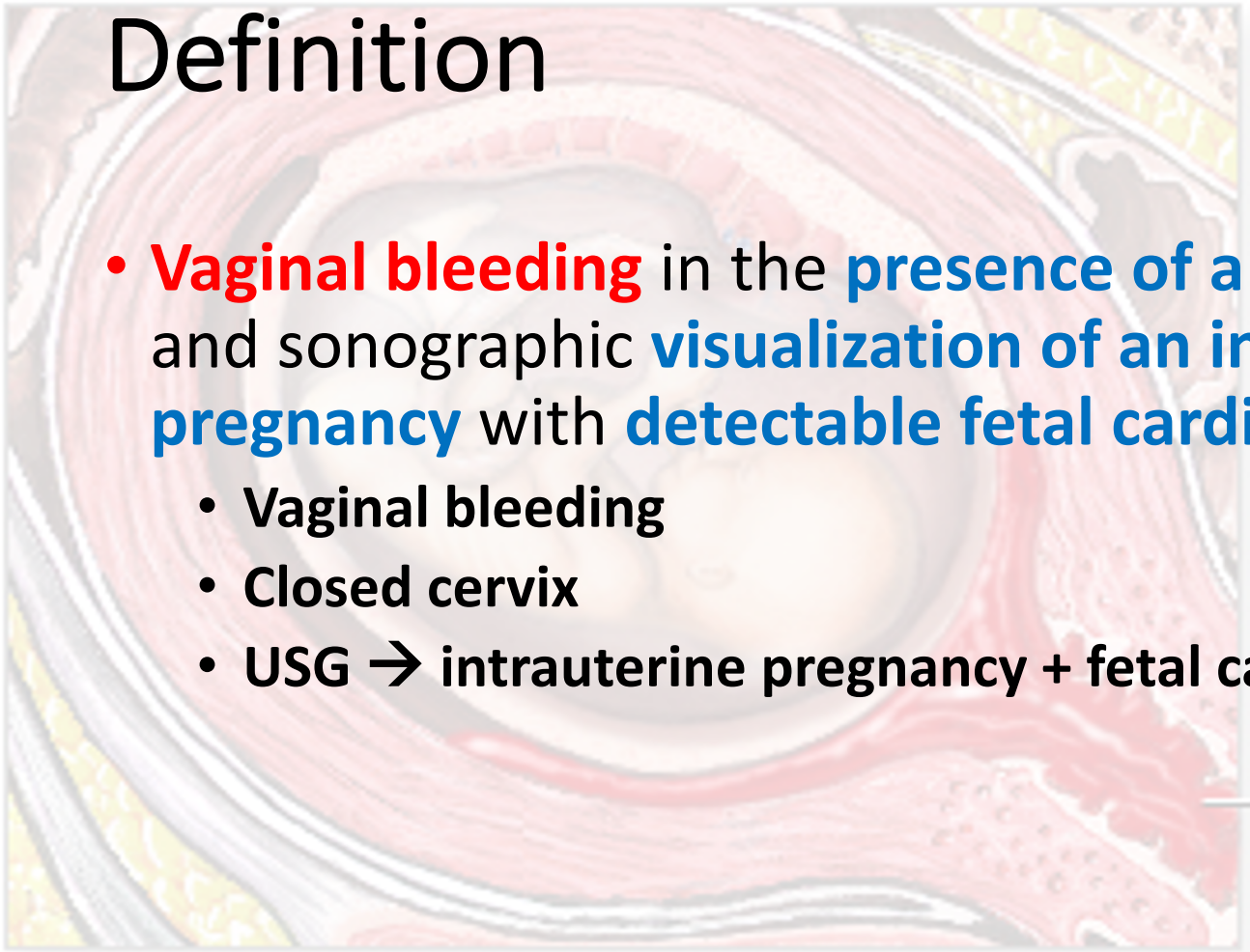
Outlines

1. Definition
2. Etiology
3. Pathophysiology
4. Evaluation
5. adverse pregnancy outcomes
6. management of threatened abortion

Vaginal bleeding

Definition

- **Vaginal bleeding** in the **presence of a closed cervix** and sonographic **visualization of an intrauterine pregnancy** with **detectable fetal cardiac activity**
  - **Vaginal bleeding**
  - **Closed cervix**
  - **USG → intrauterine pregnancy + fetal cardiac activity**



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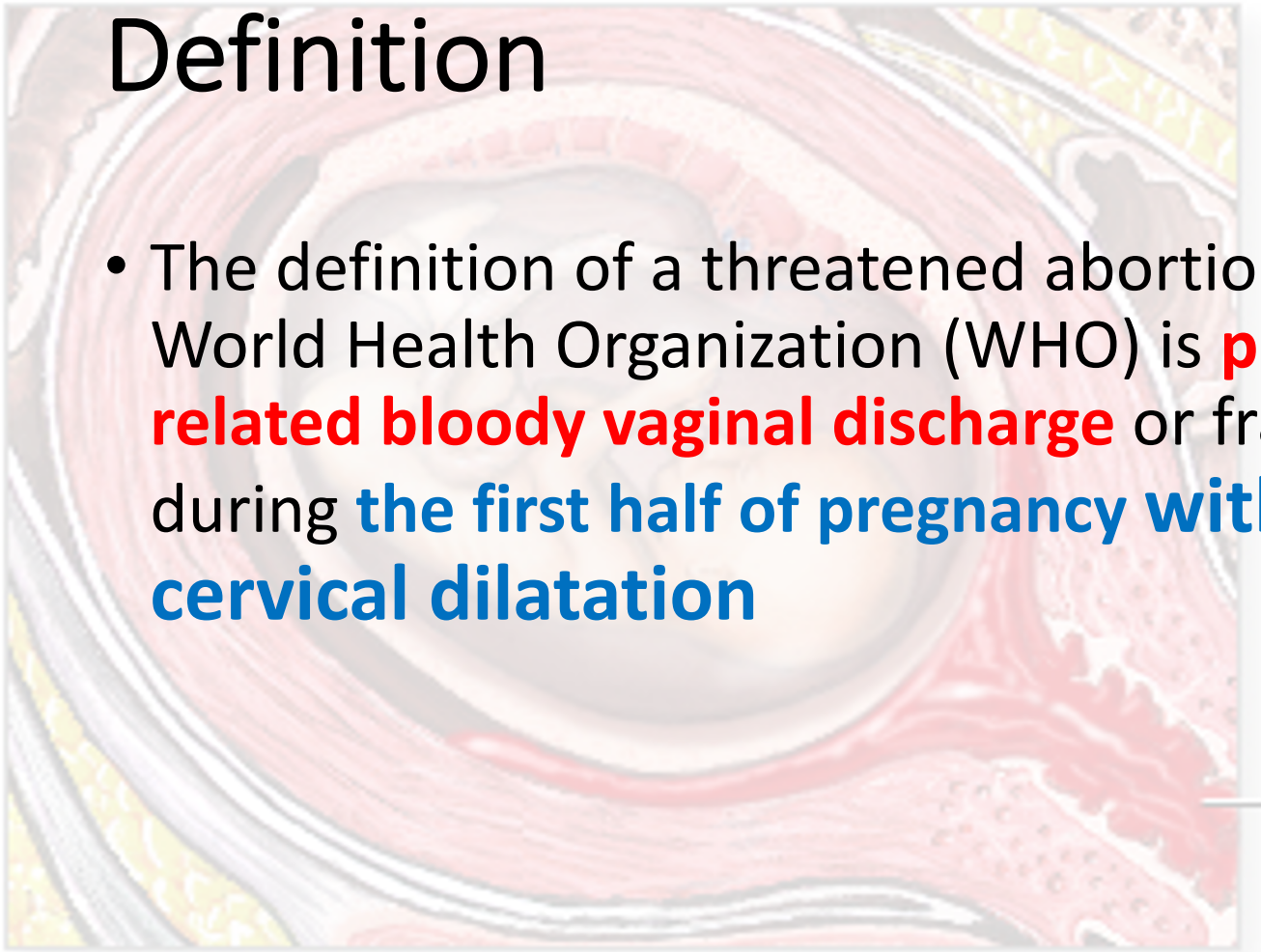
Threatened spontaneous abortion

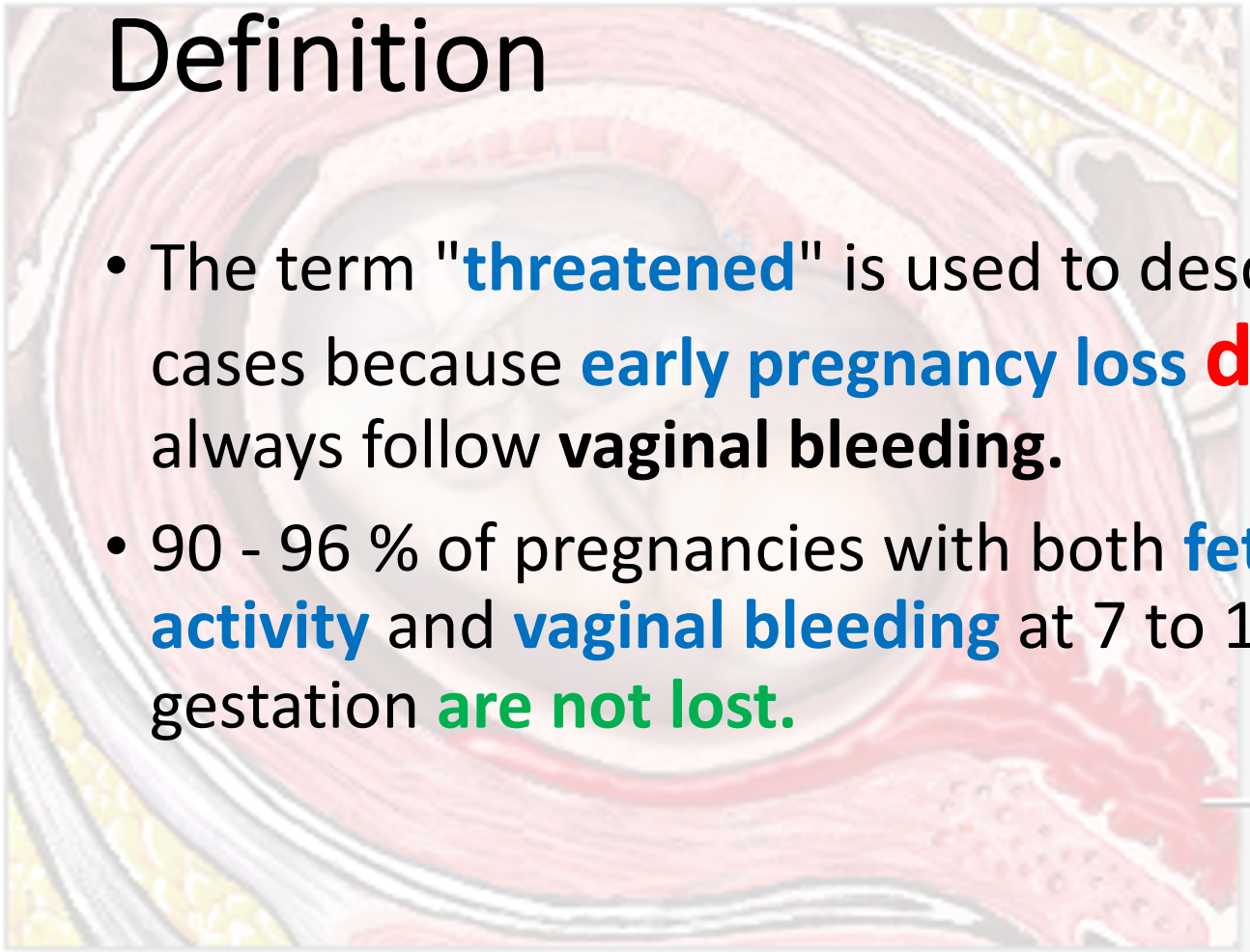
Definition

- The definition of a threatened abortion by the World Health Organization (WHO) is **pregnancy-related bloody vaginal discharge** or frank bleeding during **the first half of pregnancy without cervical dilatation**



Definition

- The term "**threatened**" is used to describe these cases because **early pregnancy loss** **does not** always follow **vaginal bleeding.**
- 90 - 96 % of pregnancies with both **fetal cardiac activity** and **vaginal bleeding** at 7 to 11 weeks of gestation **are not lost.**



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Etiology

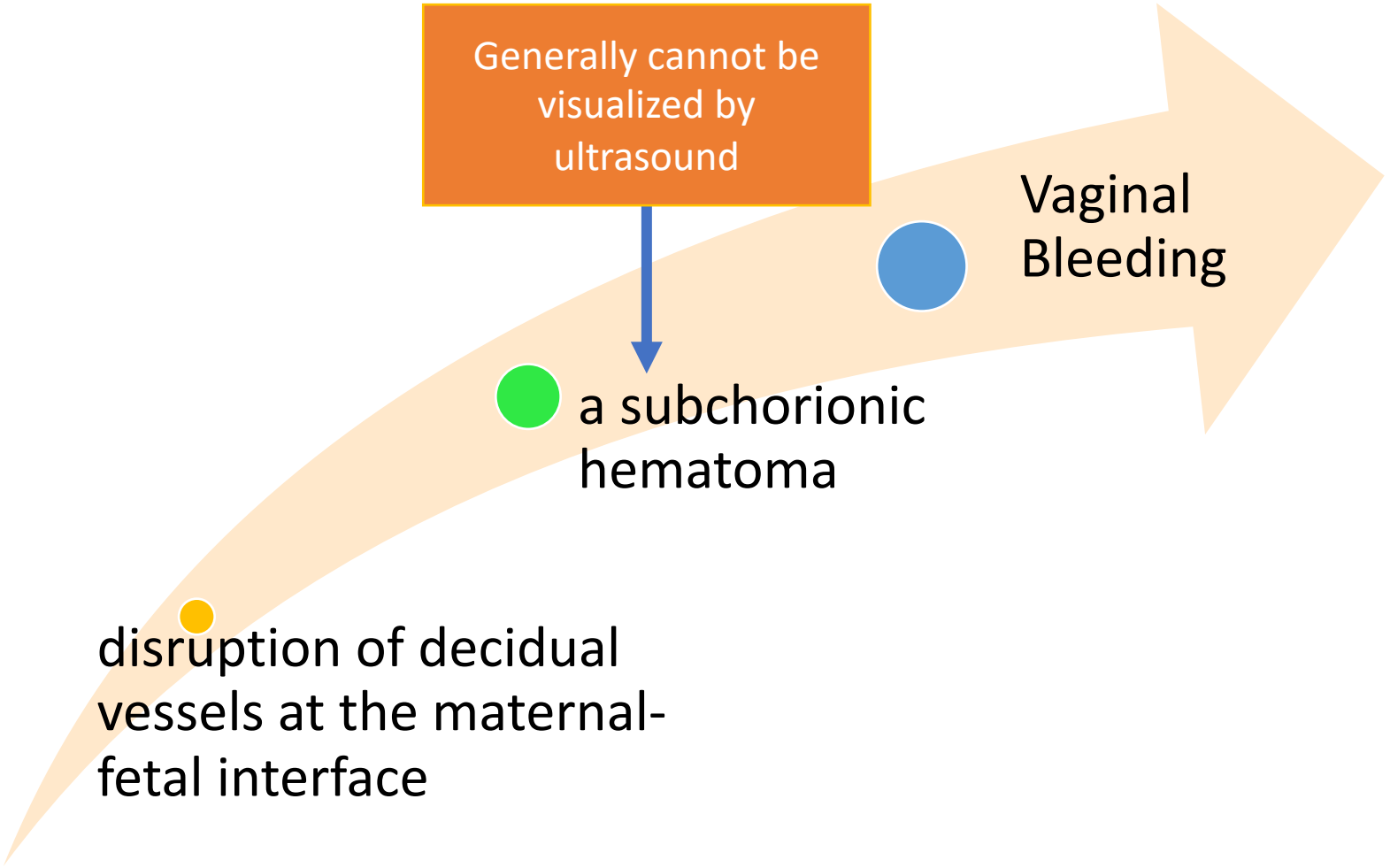
- The exact etiology of a threatened or spontaneous abortion is **not always known.**
- Some factors such as
  - Fetal chromosome abnormalities
  - Maternal diseases Ex: DM, HT ,chronic kidney disease
  - Advanced maternal age
  - Uterine anomalies
  - **Hormonal deficit**
  - Infection
  - Etc.

May associated with Threaten abortion

Vaginal bleeding

Mouri M, Hall H, Rupp TJ. Threatened Abortion. 2021 May 19. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 28613498.

Pathophysiology



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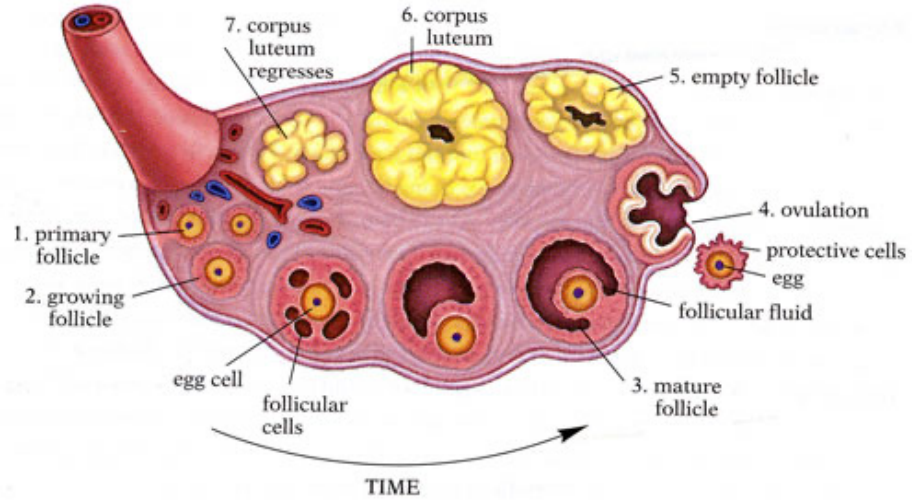
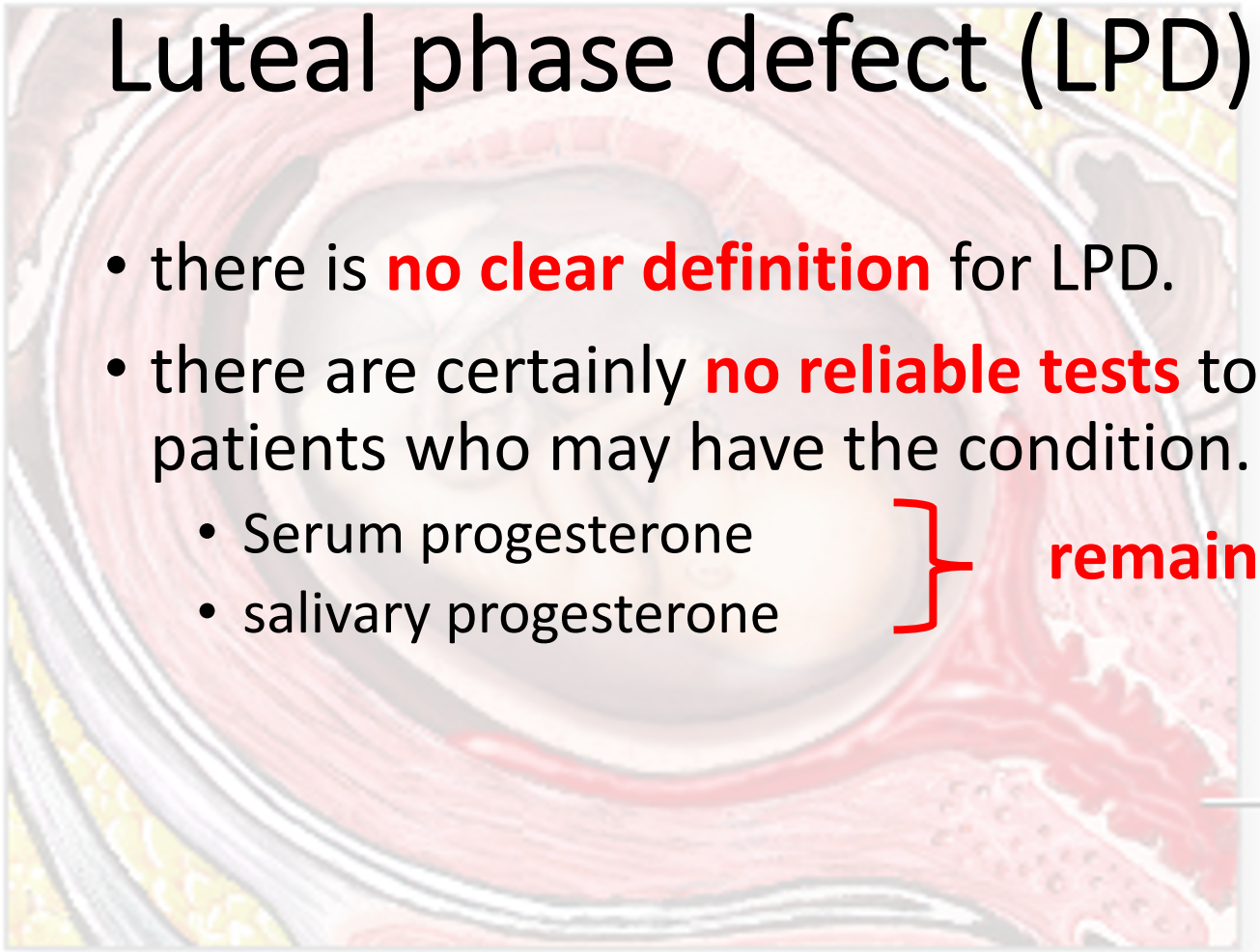
Luteal phase defect (LPD)

- **LPD** is considered to be one of the **causes of a euploid miscarriage.**
- **The corpus luteum** in the ovary produces **progesterone** during early pregnancy.
- **Progesterone** is essential for **maintaining the decidua.**



Luteal phase defect (LPD)



Luteal phase defect (LPD)

- there is **no clear definition** for LPD.
- there are certainly **no reliable tests** to identify patients who may have the condition.
  - Serum progesterone
  - salivary progesterone

} **remained unclear.**

Evaluation

- **History** → Preg Hx, Medical Hx, present illness
- **Physical exam** → vaginal and pelvic examination
- **measurement of beta-human chorionic gonadotropin (beta-hCG)**
  - A beta-hCG level of **1500 IU/mL to 2000 IU/mL** → Gestational sac on ultrasound
- **TVS** → locate the pregnancy + **fetal cardiac activity**
- **Hb and Hct** → monitor blood loss
- **Rh blood group** -- > **Rhogram in Rh negative mother**

Vaginal bleeding

Mouri M, Hall H, Rupp TJ. Threatened Abortion. 2021 May 19. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 28613498.

Adverse pregnancy outcomes
(increased in threaten abortion)

Maternal outcomes	Perinatal outcomes
Placenta previa	Preterm ruptured membranes
Placental abruption	Preterm birth
Manual removal of placenta	Low-birthweight infant
Cesarean delivery	Fetal-growth restriction
	Fetal and neonatal death

William Obstetrics 25th edition 2018

Management of threatened abortion

- **Expectantly** without any medical or surgical interventions.
- Patients should be **educated** on the importance of **follow-up** if
  - excessive vaginal bleeding
  - Abdominal pain
  - Fever
- Analgesia can be provided **(NSAIDs should be avoided)**

Mouri M, Hall H, Rupp TJ. Threatened Abortion. 2021 May 19. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 28613498.

Management of threatened abortion

- **Follow-up** is recommended with **serial transvaginal ultrasounds**
- Clinicians can consider **serial quantitative beta hCG testing** as recommended for **a pregnancy of unknown origin.**
- **Bedrest** and **other activity restrictions**
  - → **not** been found to be **efficacious** in the **prevention**
  - → **increase** the risk of **deep vein thrombosis** and/or **pulmonary embolism**

Mouri M, Hall H, Rupp TJ. Threatened Abortion. 2021 May 19. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 28613498.

Management of threatened abortion

- Clinicians should recommend patients that start or continue to take **prenatal vitamins** with **folic acid supplementation**.

Mouri M, Hall H, Rupp TJ. Threatened Abortion. 2021 May 19. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 28613498.

Management of threatened abortion

- **How about Progesterone ?????**

Mouri M, Hall H, Rupp TJ. Threatened Abortion. 2021 May 19. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 28613498.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Progesterone in Women with Bleeding in Early Pregnancy

A. Coomarasamy, A.J. Devall, V. Cheed, H. Harb, L.J. Middleton, I.D. Gallos, H. Williams, A.K. Eapen, T. Roberts, C.C. Ogwulu, I. Goranitis, J.P. Daniels, A. Ahmed, R. Bender-Atik, K. Bhatia, C. Bottomley, J. Brewin, M. Choudhary, F. Crosfill, S. Deb, W.C. Duncan, A. Ewer, K. Hinshaw, T. Holland, F. Izzat, J. Johns, K. Kriedt, M.-A. Lumsden, P. Manda, J.E. Norman, N. Nunes, C.E. Overton, S. Quenby, S. Rao, J. Ross, A. Shahid, M. Underwood, N. Vaithilingam, L. Watkins, C. Wykes, A. Horne, and D. Jurkovic

PRISM trial (PRogesterone In Spontaneous Miscarriage trial)

n engl j med 380;19 nejm.org May 9, 2019

400 mg of micronized progesterone (**Utrogestan**, Besins Healthcare) or matching **placebo** **twice daily**, from the time of randomization through **16 completed weeks of gestation**

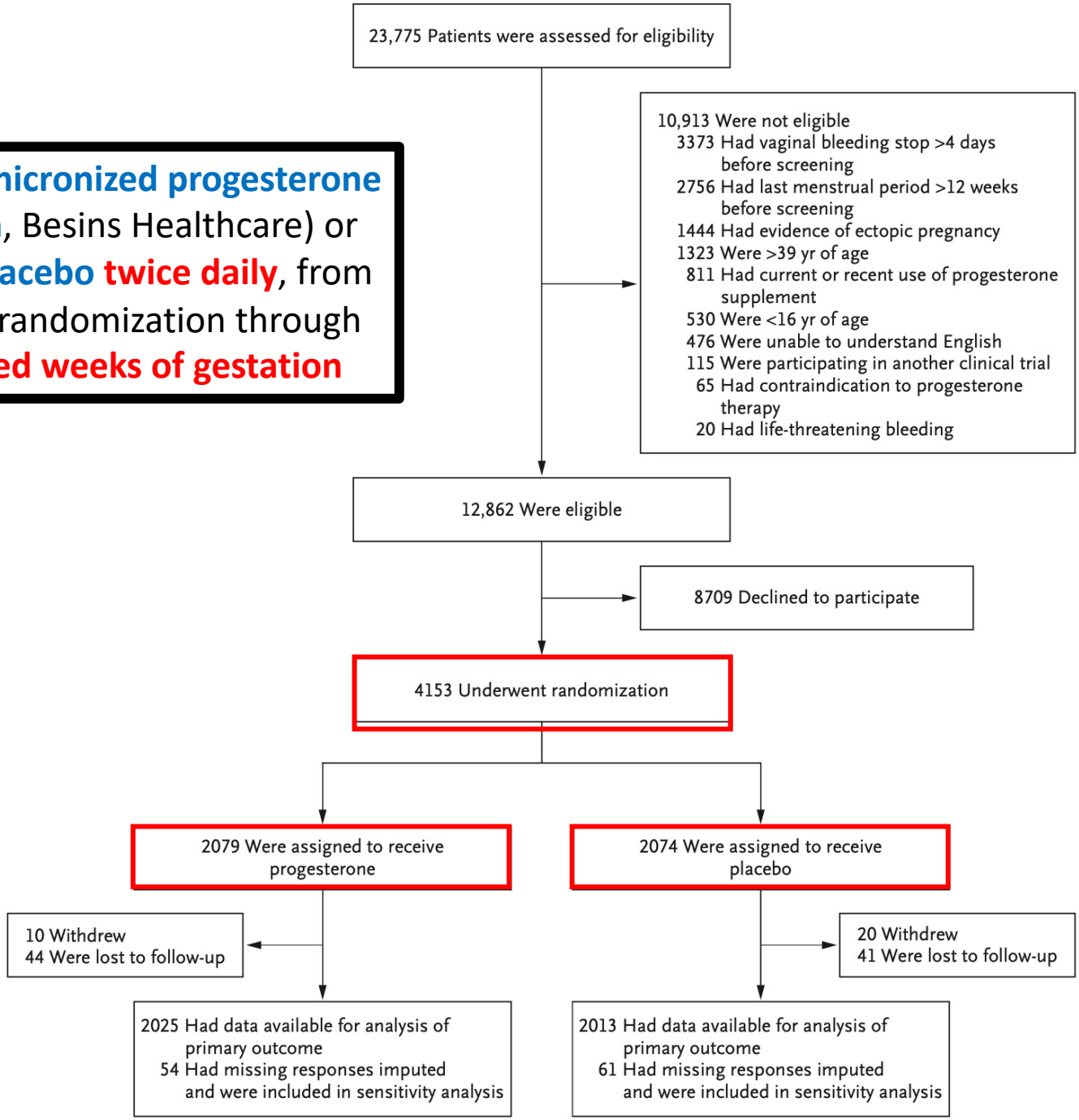


Table 2. Primary Outcome and Secondary Outcomes.*

Outcome	Progesterone (N=2025)	Placebo (N=2013)	Relative Rate or Mean Difference (95% CI)†
Primary outcome — no. (%)			
Live birth at ≥34 wk	1513 (75)	1459 (72)	1.03 (1.00 to 1.07)‡
Secondary maternal outcomes — no. (%)§			
Ongoing pregnancy at 12 wk	1672 (83)	1602 (80)	1.04 (1.01 to 1.07)
Miscarriage, defined as loss of pregnancy at <24 wk¶	410 (20)	451 (22)	0.91 (0.81 to 1.01)
Live birth at <34 wk	68 (3)	64 (3)	1.06 (0.76 to 1.49)
Ectopic pregnancy	0	2 (<1)	—
Stillbirth, defined as intrauterine death at ≥24 wk	5 (<1)	6 (<1)	0.82 (0.25 to 2.66)
Termination of pregnancy‖	34 (2)	36 (2)	0.94 (0.59 to 1.50)
Secondary neonatal outcomes among women with live births at ≥24 wk§			
Gestational age at delivery**			
Wk of gestation	38 wk 4 days±2 wk 4 days	38 wk 4 days±2 wk 3 days	0.11 days (–0 wk 1 day to 0 wk 2 days)†
No. of women	1581	1521	
Birth weight††			
Mean weight — g	3242±656	3261±659	–21 (–67 to 25)†
No. of infants	1604	1539	
Death at 28 days of neonatal life — no./total no. (%)‡‡	8/1605 (<1)	2/1533 (<1)	3.84 (0.80 to 18.40)†

Expert Reviews ajog.org

Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence

Arri Coomarasamy, MD, MRCOG; Adam J. Devall, PhD; Jan J. Brosens, PhD; Siobhan Quenby, MD, FRCOG; Mary D. Stephenson, MD; Sony Sierra, MD; Ole B. Christiansen, MD; Rachel Small, BSc; Jane Brewin, BSc; Tracy E. Roberts, PhD; Rima Dhillon-Smith, PhD, MRCOG; Hoda Harb, PhD; Hannah Noordali, PhD; Argyro Papadopoulou, BSc; Abey Eapen, PhD, MBBS; Matt Prior, MRCOG; Gian Carlo Di Renzo, MD; Kim Hinshaw, MBBS, FRCOG; Ben W. Mol, MD, PhD; Mary Ann Lumsden, MD, FRCOG; Yacoub Khalaf, MD, FRCOG; Andrew Shennan, MD, FRCOG; Mariette Goddijn, MD, PhD; Madelon van Wely, PhD; Maya Al-Memar, PhD, MRCOG; Phil Bennett, PhD, FRCOG; Tom Bourne, PhD, FRCOG; Raj Rai, MD, MRCOG; Lesley Regan, MD, FRCOG; Ioannis D. Gallos, MD, MRCOG

Coomarasamy et al. Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence. Am J Obstet Gynecol 2020.

TABLE 2

PRISM trial: vaginal micronized progesterone in women with threatened miscarriages

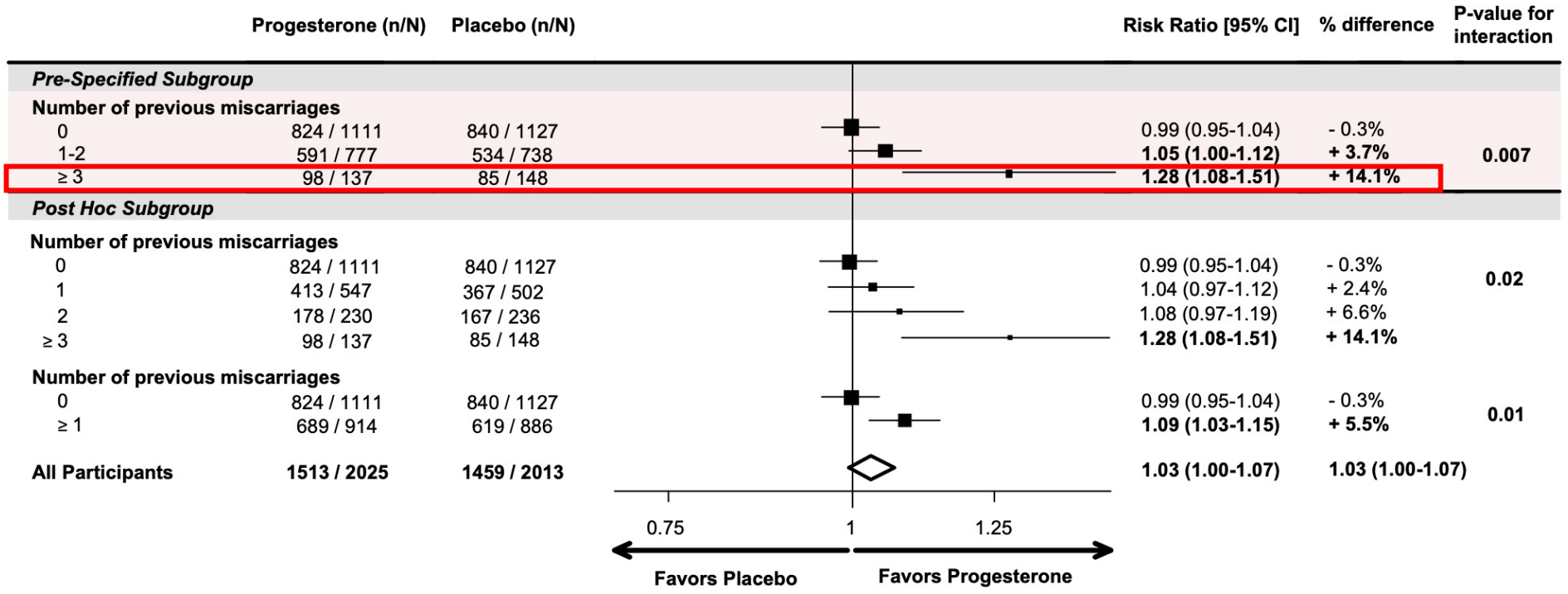
Population	Women with vaginal bleeding during the first 12 weeks of pregnancy
Intervention	400 mg of micronized progesterone taken vaginally or rectally twice daily from randomization until 16 weeks of gestation
Comparison	Placebo
Primary outcome	Live birth $\geq$34 weeks
Sample size and power	4153 patients 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 et al. Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence. Am J Obstet Gynecol 2020.

FIGURE 2

PRISM trial data on live birth >34 weeks by the number of previous miscarriages



CI, confidence interval; *PRISM*, PRogesterone In Spontaneous Miscarriage.

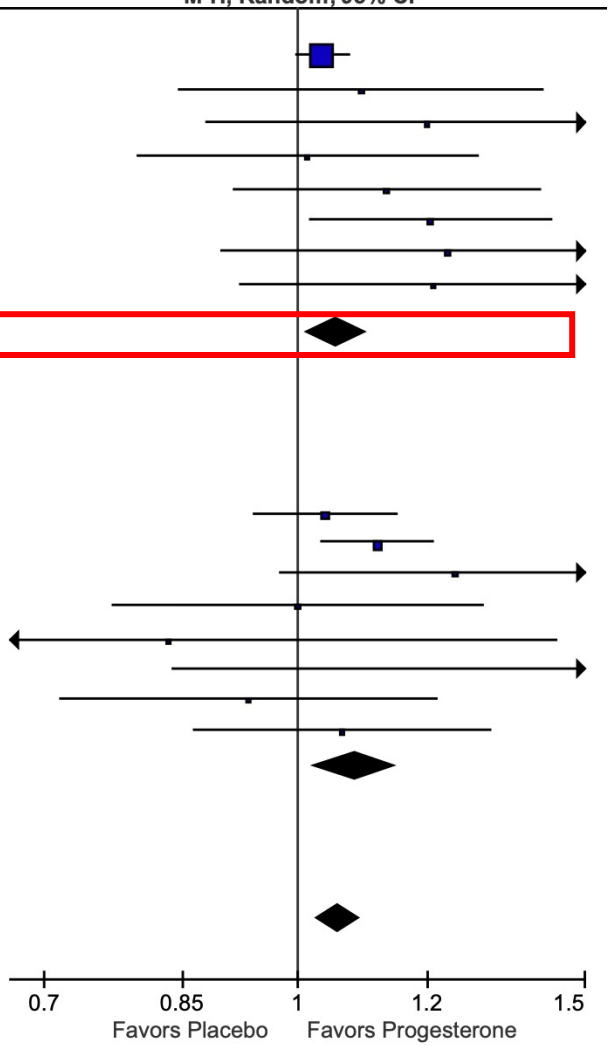
Coomarasamy et al. Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence. Am J Obstet Gynecol 2020.

Number of previous miscarriage >= 3 Risk ratio 1.28 (1.08-1.51)

FIGURE 7

Live birth or ongoing pregnancy outcome for all progesterone and progestogen studies

PRISM trial



	ogesterone		Placebo or no treatment			Risk Ratio
	ents	Total	Events	Total	Weight	M-H, Random, 95% CI
Threatened miscarriage						
Coomarasamy 2019 (a)	1513	2025	1459	2013	61.5%	1.03 [1.00, 1.07]
Turgal 2017 (b)	26	32	26	35	1.5%	1.09 [0.85, 1.41]
Yassaee 2014 (c)	24	30	20	30	0.9%	1.20 [0.88, 1.64]
Alimohamadi 2013 (c)	47	72	47	73	1.5%	1.01 [0.80, 1.29]
El-Zibdeh 2009 (d)	65	86	40	60	1.8%	1.13 [0.91, 1.41]
Pandian 2009 (c)	78	96	64	95	2.9%	1.21 [1.02, 1.43]
Palagiano 2004 (e)	21	25	17	25	0.8%	1.24 [0.90, 1.70]
Gerhard 1987 (c)	23	26	19	26	1.1%	1.21 [0.92, 1.59]
Subtotal (95% CI)		**2392**		**2357**	**71.8%**	**1.05 [1.01, 1.08]**
Total events	1797		1692			
Heterogeneity: Tau² = 0.00; Chi² = 6.92, df = 7 (P = 0.44); I² = 0%						
Test for overall effect: Z = 2.66 (P = 0.008)						
Recurrent miscarriage						
Coomarasamy 2015 (f)	262	398	271	428	8.2%	1.04 [0.94, 1.15]
Kumar 2014 (e)	163	175	144	173	13.8%	1.12 [1.04, 1.21]
El-Zibdeh 2005 (d)	64	82	30	48	1.4%	1.25 [0.98, 1.60]
MacDonald 1972 (e)	17	20	17	20	1.2%	1.00 [0.77, 1.30]
Klopper 1965 (g)	10	18	10	15	0.3%	0.83 [0.48, 1.44]
Le Vine 1964 (f)	11	15	7	15	0.2%	1.57 [0.84, 2.92]
Goldzieher 1964 (h)	18	23	26	31	1.2%	0.93 [0.72, 1.22]
Swyer 1953 (c)	47	60	39	53	1.9%	1.06 [0.86, 1.31]
Subtotal (95% CI)		**791**		**783**	**28.2%**	**1.08 [1.03, 1.14]**
Total events	592		544			
Heterogeneity: Tau² = 0.00; Chi² = 6.53, df = 7 (P = 0.48); I² = 0%						
Test for overall effect: Z = 2.88 (P = 0.004)						
Total (95% CI)		**3183**		**3140**	**100.0%**	**1.06 [1.03, 1.09]**
Total events	2389		2236			
Heterogeneity: Tau² = 0.00; Chi² = 14.48, df = 15 (P = 0.49); I² = 0%						
Test for overall effect: Z = 3.78 (P = 0.0002)						
Test for subgroup differences: Chi² = 0.55, df = 1 (P = 0.46), I² = 0%						

Footnotes

(a) Live birth after 34 weeks of gestation; adjusted for minimization variables. (b) Term live births. Re-included 11 miscarriages that were excluded after randomisation. (c) Term live births. (d) Quasi-randomised trial; term live births. (e) Ongoing pregnancies not clearly defined by the authors. (f) Live birth after 24 weeks of gestation. (g) Ongoing pregnancies over 18 weeks of gestation. (h) Term births.

CI, confidence interval.

Coomarasamy et al. Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence. Am J Obstet Gynecol 2020.

BJOG An International Journal of Obstetrics and Gynaecology

DOI: 10.1111/1471-0528.16261
www.bjog.org

Systematic review

Effect of progestogen for women with threatened miscarriage: a systematic review and meta-analysis

L Li,[a] Y Zhang,[a,b] H Tan,[a] Y Bai,[c] F Fang,[a] A Faramand,[d] W Chong,[e] Y Hai[f]

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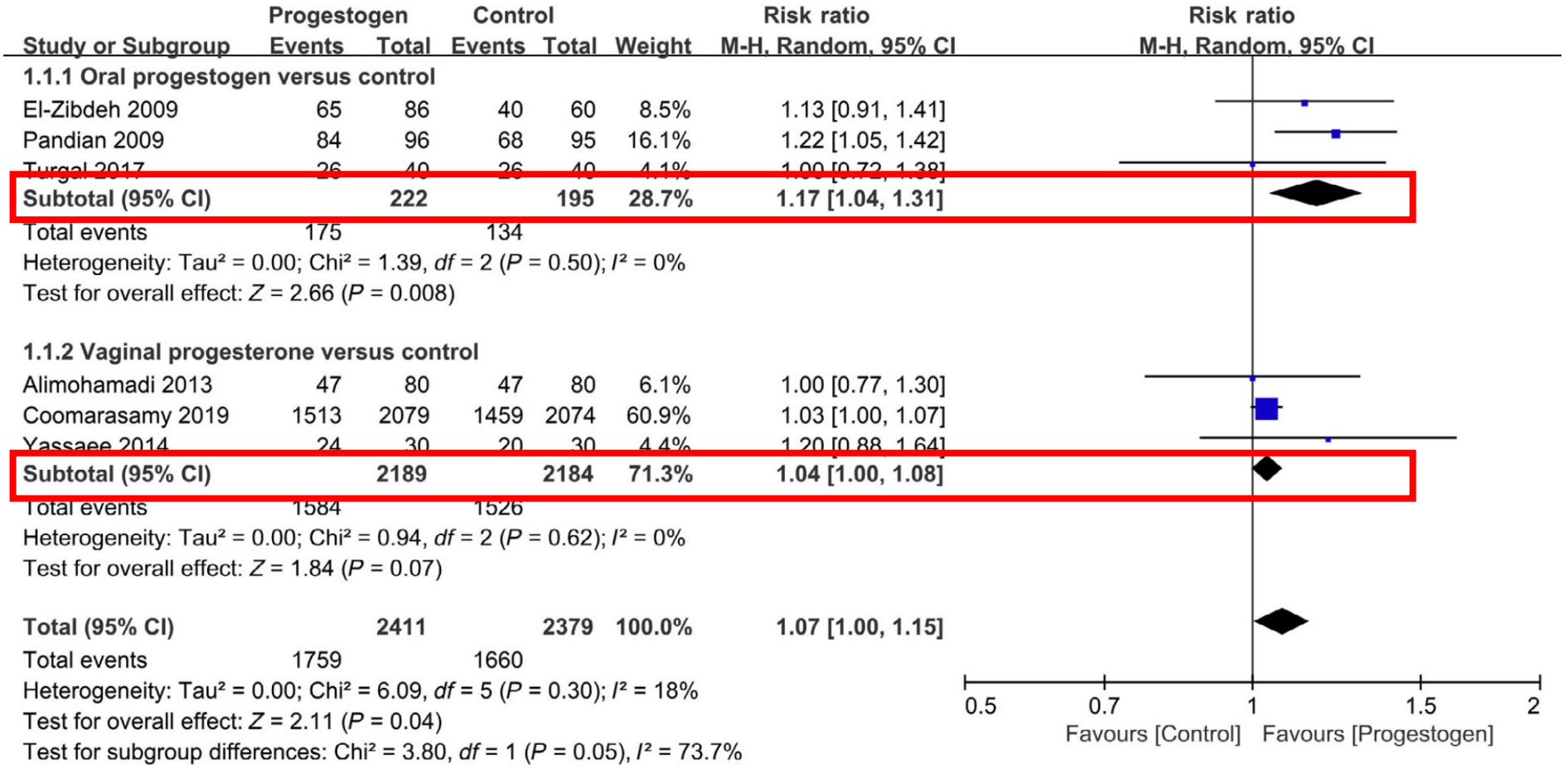
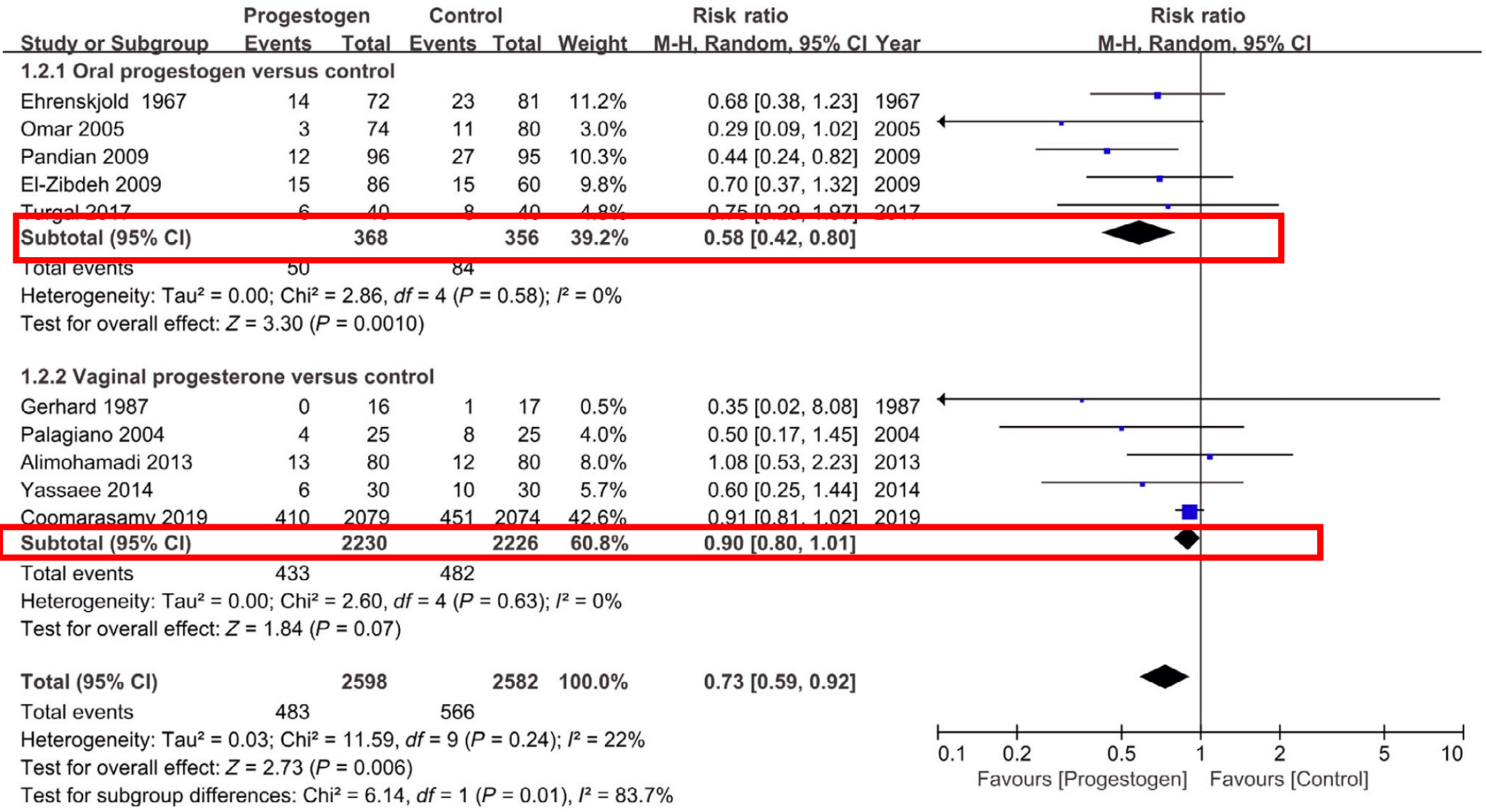
Email: fang1057@outlook.com

Accepted 25 March 2020. Published Online 20 May 2020.

Random-effects meta-analysis of progesterone **on live birth events**, stratified by oral and vaginal progesterone.



Random-effects meta-analysis of progesterone on **miscarriage events**, stratified by oral and vaginal progesterone.



Cochrane Library

Cochrane Database of Systematic Reviews

Progestogens for preventing miscarriage: a network meta-analysis (Review)

Devall AJ, Papadopoulou A, Podesek M, Haas DM, Price MJ, Coomarasamy A, Gallos ID

Devall AJ, Papadopoulou A, Podesek M, Haas DM, Price MJ, Coomarasamy A, Gallos ID. Progestogens for preventing miscarriage: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2021

Summary of findings 1. Live birth

Patient or population: women with threatened miscarriage or a history of recurrent miscarriage

Interventions: multiple progestogens (vaginal micronized progesterone, oral micronized progesterone, dydrogesterone and 17-α-hydroxyprogesterone)

Comparison: placebo and dydrogesterone

Outcome: live birth

Settings: hospitals

Treatment	Direct evidence		Indirect evidence		Anticipated absolute effects for direct estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with intervention	Risk with comparator	Risk difference with intervention
Threatened miscarriage							
Vaginal micronized progesterone versus placebo	1.03 [1.00, 1.07]	⊕⊕⊕⊕ HIGH	Unavailable	-	761 per 1000 (vaginal micronized progesterone)	725 per 1000 (placebo)	**36 more per 1000** (from 36 fewer to 123 more)
Subgroup analysis: number of previous miscarriages							
No previous miscarriages and early pregnancy bleeding	0.99 [0.95, 1.04]	⊕⊕⊕⊕ HIGH	Unavailable	-	739 per 1000 (vaginal micronized progesterone)	747 per 1000 (placebo)	**7 fewer per 1000** (from 37 fewer to 30 more)
One or more previous miscarriages and early pregnancy bleeding	1.08 [1.02, 1.14]	⊕⊕⊕⊕ HIGH	Unavailable	-	755 per 1000 (vaginal micronized progesterone)	699 per 1000 (placebo)	**56 more per 1000** (from 14 more to 105 more)
Dydrogesterone versus placebo	0.98 [0.89, 1.07]	⊕⊕⊕⊖ MODERATE[a]	Unavailable	-	816 per 1000 (dydrogesterone)	833 per 1000 (placebo)	**17 fewer per 1000** (from 92 fewer to 58 more)

Summary of findings 2. Miscarriage (defined as delivery before 24 weeks of gestation)

Patient or population: women with threatened miscarriage or a history of recurrent miscarriage

Interventions: multiple progestogens (vaginal micronized progesterone, oral micronized progesterone, dydrogesterone and 17-α-hydroxyprogesterone)

Comparison: placebo and dydrogesterone

Outcome: miscarriage (defined as delivery before 24 weeks of gestation)

Settings: hospitals

Treatment	Direct evidence		Indirect evidence		Anticipated absolute effects for direct estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with intervention	Risk with comparator	Risk difference with intervention
Threatened miscarriage							
Vaginal micronized progesterone versus placebo	0.90 [0.80, 1.01]	⊕⊕⊕⊕ HIGH	Unavailable	-	201 per 1000 (vaginal micronized progesterone)	224 per 1000 (placebo)	**22 fewer per 1000** (from 45 fewer to 2 more)
Dydrogesterone versus placebo	0.90 [0.55, 1.47]	⊕⊕⊕⊖ MODERATE[a]	Unavailable	-	129 per 1000 (dydrogesterone)	143 per 1000 (placebo)	**14 fewer per 1000** (from 64 fewer to 67 more)

Authors' conclusions

- The overall available evidence suggests that **progestogens** probably make **little or no difference to live birth rate** for women with **threatened** or **recurrent miscarriage**.
- **Vaginal micronized progesterone** may **increase the live birth rate** for women with **a history of one or more previous miscarriages** and early pregnancy bleeding, with likely **no difference in adverse events.**

International guidelines: Miscarriage

GUIDELINES	RECOMMENDATIONS ON TM
European Progestin Club Guidelines 2015	For women presenting with a clinical diagnosis of **TM**, there is a **reduction in the rate of spontaneous miscarriage** with the use of **dydrogesterone.** [1]
The Royal Australian and New Zealand College of Obstetricians and Gynaecologists — Excellence in Women's Health RANZCOG 2018	Progestogen supplementation **until the second trimester** in women presenting with a clinical diagnosis of threatened miscarriage may reduce the rate of spontaneous miscarriage and may be considered. [2]
Cochrane 2018	**Treatment of miscarriage with progestogens** compared to placebo or no treatment probably reduces the risk of miscarriage. **Treatment with oral progestogen** compared to no treatment also probably **reduces the miscarriage rate**.[3]
NICE National Institute for Health and Care Excellence 2019	Data from a meta-analysis of several small studies suggest that **progestogens are better than placebo.** [4]

TM: Threatened miscarriage; RM: Recurrent miscarriage; RPL: Recurrent pregnancy loss

1. Schindler AE, Carp H, Druckmann R, *et al.* European Progestin Club Guidelines for prevention and treatment of threatened or recurrent (habitual) miscarriage with progestogens. *Gynecol Endocrinol* 2015;31(6):447–449.
2. Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG). Progesterone support of the luteal phase and in the first trimester (C-Obs 29a). March 2018. http://www.ranzcog.edu.au/component/docman/doc_details/961-c-obs-29a-progesterone-support-of-the-luteal-phase-and-early-pregnancy.html?Itemid=223l. Accessed August 2016.
3. Wahabi HA, Fayed AA, Esmaeil SA, Al Zeidan RA. Progestogen for treating threatened miscarriage. *Cochrane Database Syst Rev* 2018;(8):CD005943.
4. National Institute for Health and Care Excellence (NICE). Ectopic pregnancy and miscarriage: diagnosis and initial management. (NG126) Published April 2019. www.nice.org.uk/guidance/ng126 . Accessed Aug 2020

GUIDELINES	RECOMMENDATIONS ON TM
International Journal of Women's Health **Saudi Guidelines 2020**	**Oral progestogens**, namely **dydrogesterone**, are **well-tolerated & effectively reduce miscarriages** in women at risk of TM. [1]
Malaysia 2020	1. In patient without prior history of miscarriage, **oral dydrogesterone** can be considered, from onset of bleeding till 1 week after bleeding has stopped 2. In women with a history of ≥1 previous miscarriage, dydrogesterone 10 mg BD from the onset of bleeding up till **16 weeks of pregnancy** may be considered. 3. Dydrogesterone may be associated with fewer side effects than oral micronized progesterone. [2]
China 2021	**Oral progesterone** is preferred. **1st line treatment: Dydrogesterone** 40mg PO stat followed by 10 mg q8h until symptom remits, then U/S to confirm fetal heart beat. Thereafter, Dydrogesterone 10mg q8 h to be continued for 1~2 weeks. [3]

TM: Threatened miscarriage; BD: Twice daily; PO: per oral route; U/S: Ultra sounds; q8h: per 8 hours.

1. Arab H, Alharbi AJ, Oraif A, et al. The Role Of Progestogens In Threatened And Idiopathic Recurrent Miscarriage. *Int J Womens Health*. 2020; Apr 08;12:253]. *International Journal of Women's Health* 2019:11:589–596;
2. Eeson Sinthamoney et al., OGSM 12 May 2020 https://www.ogsm.org.my/docs/Clinical-Practice-Guidelines-on-Miscarriage-Management.pdf;
3. Qiao Jie et al., Chin J Reprod Contracep, February 2021, Vol. 41, No. 2

Conclusions

Treatment		Recommendation
Expectant management		**Recommended**
Analgesia	**Avoid NSAIDs**	**Recommended**
Follow up ultrasound		**Recommended**
serial quantitative beta hCG testing	For pregnancy of unknown location	**Recommended**
Bedrest and other activity restrictions	**Increased risk of DVT**	**Not Recommended**
prenatal vitamins with folic acid supplementation.		**Recommended**

Conclusions

Treatment	Route	Recommendation
Progesterone	Oral dydrogesterone	**Some recommended**
	Vaginal micronized progesterone	**Recommended** (a history of one or more previous miscarriages)
	17-α-hydroxyprogesterone	**Not Recommended** (no evidence)
	Oral micronized progesterone	**Not Recommended** (no evidence)