Updates on use of oral progestogens in pregnancy

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Progesterone: The vital role

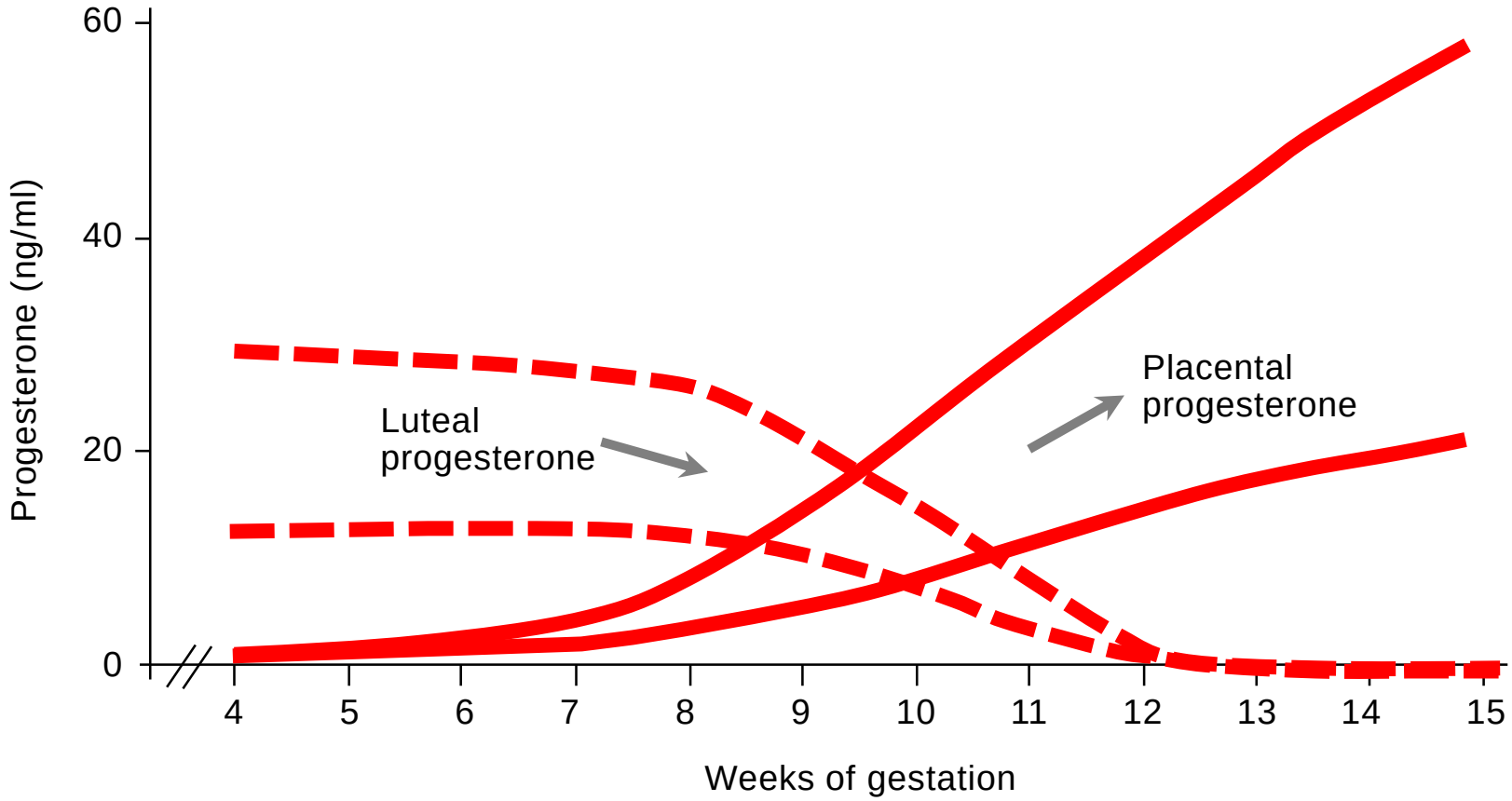
- Creating suitable endometrial environment for implantation.
- Maintenance of pregnancy

  Corpus luteum in early first trimester

  Placental source from late first trimester

- Inadequate production lead to infertility and pregnancy loss
- Lutectomy prior to 7 weeks or disruption of binding progesterone receptors by Mifepristone result in pregnancy loss

Progesterone Production: Luteal Placental Shift



Adapted from: Schindler AE. Gynecol Endocrinol 2004; 18(1): 51-57.

Progestogens that mimic activity of progesterone used extensively to overcome progesterone deficiency associated with infertility & miscarriage

But, are all progestogens the same ?

- Progestogenic potency
- Receptor-binding selectivity
- Bioavailability
- Route of administration

Micronized progesterone

- High doses required when used orally due to its low and variable bioavailability
- Lead to side effects such as drowsiness, nausea, and headaches.
- Vaginal micronized progesterone may not be fully absorbed, may be washed out with vaginal bleeding, and may cause local irritation

Dydrogesterone or 6-dehydro-retroprogesterone

- Bent shape and retro-structure
- 5.6 times higher bioavailability than progesterone
- Can be administered orally
- Highly selective for progesterone receptor
- Not bind to androgenic receptors
- High bioavailability and receptor selectivity translate into a significantly lower therapeutic dose
- Requires a 10–20 times lower oral dose compared with micronized progesterone

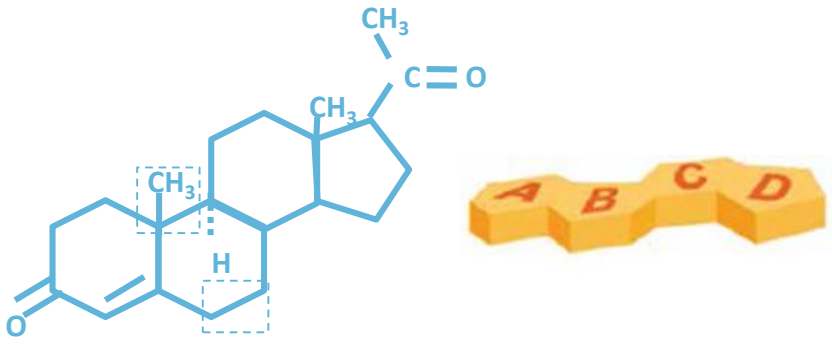
Dydrogesterone and Micronized Progesterone Are Synthesized from a Natural Source

Dydrogesterone is a retroprogesterone, a stereoisomer of progesterone, with an additional double-bond between carbon 6 and 7[1]

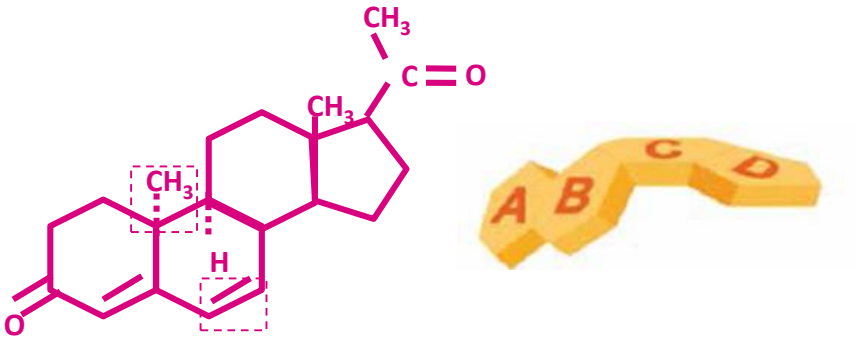
Dydrogesterone, shaped by light,[2] enhances the progestogenic effects[3]

- No estrogenic, androgenic, or glucocorticoid effects[3]
- Does not inhibit ovulation, at normal dosage[3]
- Anti-androgenic potential of dydrogesterone is less pronounced in comparison to progesterone[4]

Progesterone



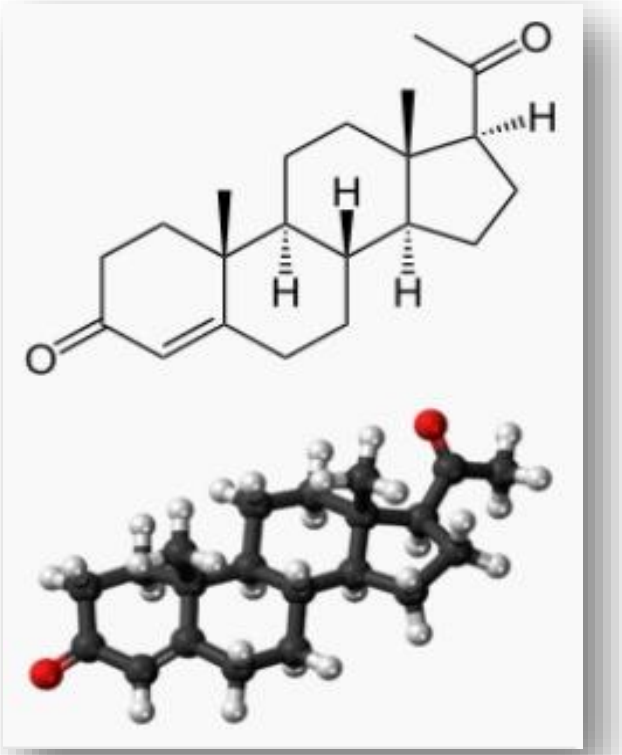
Dydrogesterone



1. Kuhl H. Climacteric 2005; 8 (Suppl 1): 3–63. 2. Fischer M. Agnew Chem Int Ed Engl 1978; 17: 16-26
3. Schindler AE. Maturitas 2009; 65S: S3–S11. 4. Rižner TL et al. Steroids. 2011;76(6):607–15

PROGESTERONE: NOMENCLATURE

Progestational steroid ketone



Progesterone and Threatened Miscarriage

Threatened miscarriage

- Vaginal bleeding with or without abdominal pain
- No cervical dilatation
- First 20 weeks
- Occur in 15-20% of pregnancies , a half proceed to miscarriage
- May relate to premature birth, abruption, PIH , FGR

Threatened miscarriage : Treatment Option

- Confirmation of intrauterine, viable
- Bed rest and hCG (for luteal support) are not supported by 2 Cochrane reviews
- Progesterone plays a pivotal role

- 1 Aleman A, Althabe F, Beliza´n J, Bergel E. Bed rest during pregnancy for preventing miscarriage. Cochrane Database Syst Rev 2005;2:
- 2. Devaseelan P, Fogarty PP, Regan L. Human chorionic gonado- trophin for threatened miscarriage. Cochrane Database Syst Rev 2010;5:CD007422

Progestogen for treating threatened miscarriage (Review)

Wahabi HA, Abed Althagafi NF, Elawad M, Al Zeidan RA

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 3

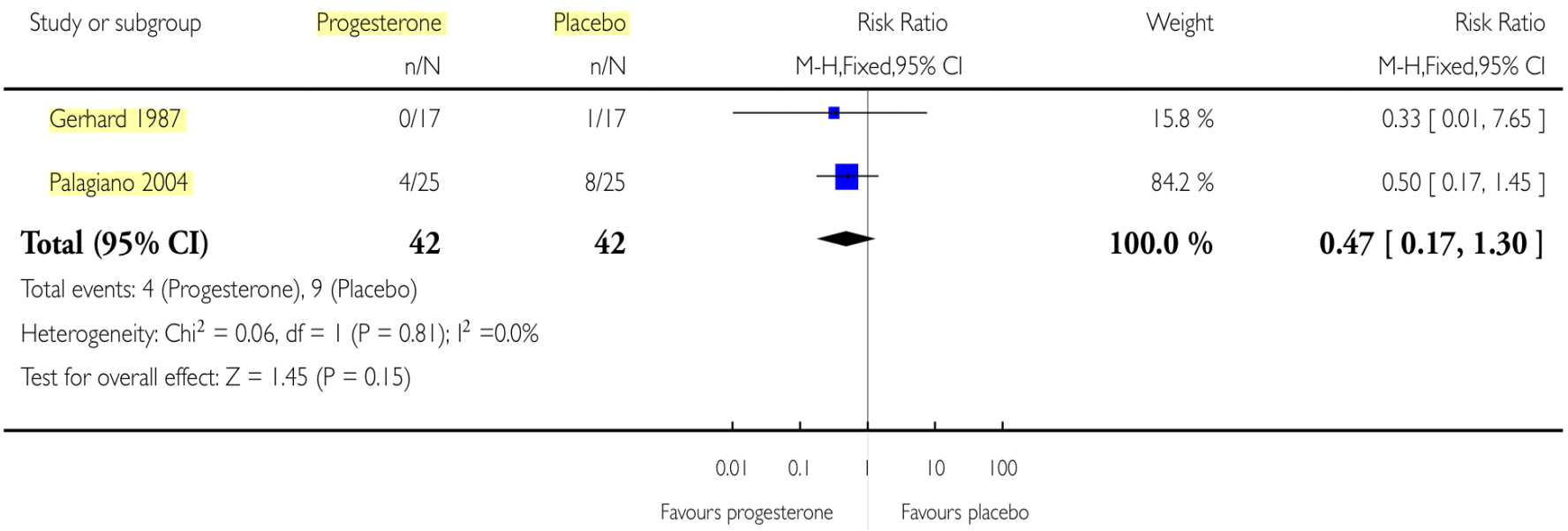
- Vaginal progesterone in Threatened Miscarriage
- 2 studies recruited
- 84 patients enrolled
- Vag progesterone : 4/42 (9.5%) Miscarriage
- Placebo : 9/42 (21.4%) Miscarriage
- RR 0.47; 95% CI 0.17 to 1.30

Analysis 1.1. Comparison 1 Progesterone versus placebo, Outcome 1 Miscarriage.

Review: Progestogen for treating threatened miscarriage

Comparison: 1 Progesterone versus placebo

Outcome: 1 Miscarriage



- No evidence to support routine use of progestogens for treatment of threatened miscarriage.
- Recommend investigation of the use of progestogens in this important & common health problem through multicentre methodologically-sound, randomized studies.

Dydrogesterone in Threatened Miscarriage

Omar 2005

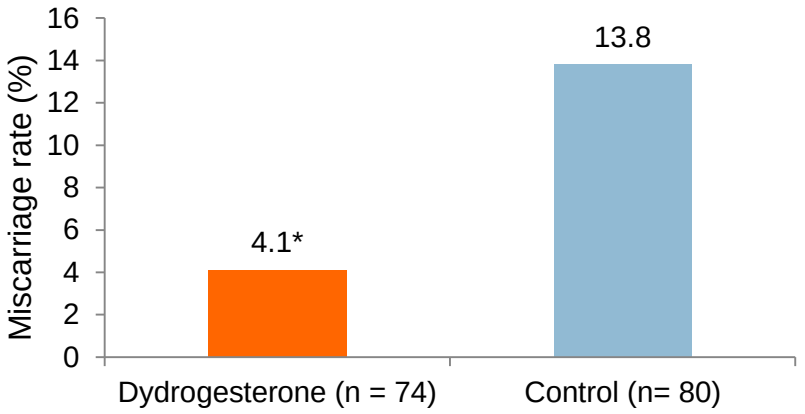
Design

- Registration records of 154

(GA <13 weeks) presenting with vaginal bleeding

- Dydrogesterone 40 mg followed by 10 mg b.i.d. until bleeding stopped, bed rest and received folic acid
- Control group: bed rest and folic acid only
- Women followed up until 20 weeks gestation
- Malaysia

Results



*p = 0.037

Odds ratio: 3.773, 95% CI: 1.009 – 14.108

Dydrogesterone treated women had a significantly lower miscarriage rate compared to the control group (4.1% vs. 13.8%, p =0.037)

Adapted from: Omar MH, et al. J Steroid Biochem Mol Biol 2005; 97(5): 421-425.

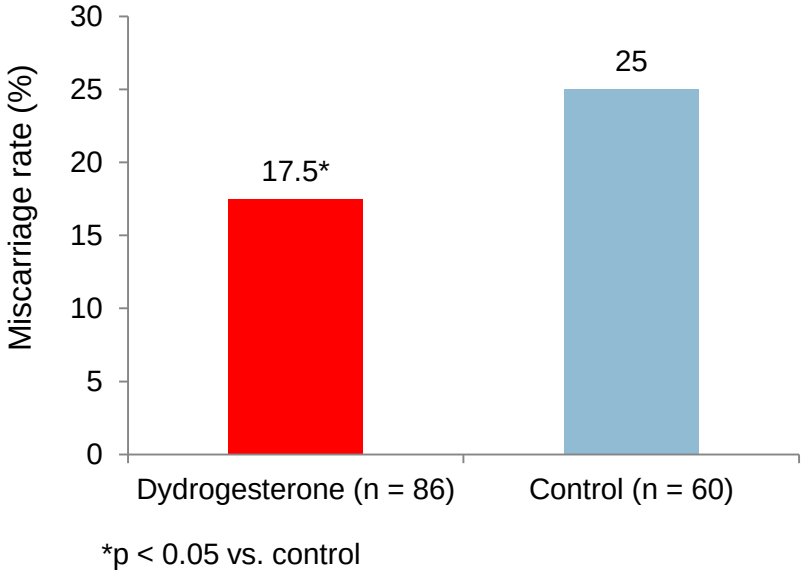
Dydrogesterone in Threatened Miscarriage

El-Zibdeh and Yousef. 2009

Design

- 146 women with vaginal bleeding during the first trimester were randomized
  - Oral dydrogesterone 10 mg b.i.d. until one week after bleeding stopped
  - Control
- All women received standard supportive care: iron, folic acid, multivitamin supplements and recommended bed rest
- Jordan

Results



*p < 0.05 vs. control

Dydrogesterone-treated women had a significantly lower miscarriage rate compared with the control group (17.5% vs. 25%, p <0.05)

No adverse events were reported during treatment
No differences were reported in obstetric complications

Adapted from: El-Zibdeh MY, Yousef LT. Maturitas 2009; 65(Suppl 1): S43-S46.

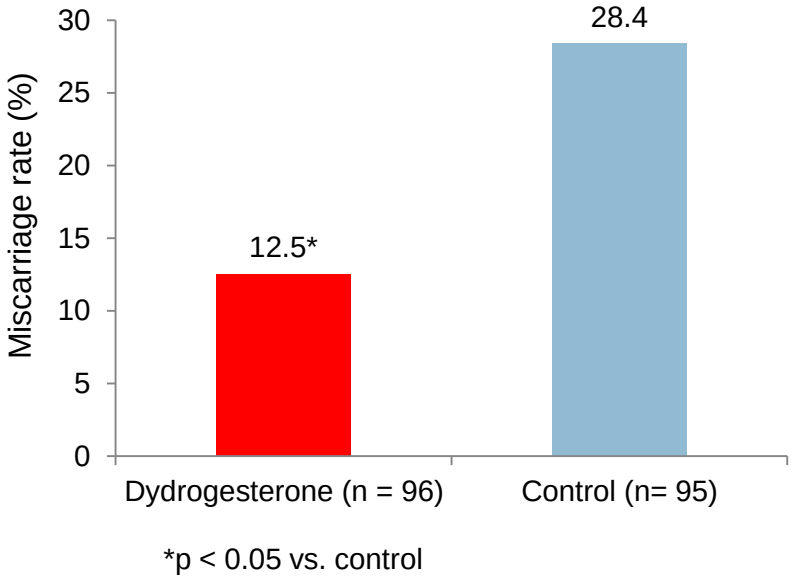
Dydrogesterone in Threatened Miscarriage

Pandian 2009

Design

- Prospective, randomized, controlled, open (blinded data analyses) study, n=191
  - Dydrogesterone 40 mg at once followed by 10 mg twice a day until week 16
  - Control group: Conservative management with bed rest only
- Study not blinded to either physician or patient
- Malaysia

Results



*p < 0.05 vs. control

Odds ratio: 0.36, 95% CI: 0.17 – 0.75

Dydrogesterone treated women had a significantly lower miscarriage rate compared to the control group (12.5 % vs. 28.4%; p<0.05)

No differences in obstetric complications

Pandian RU. Maturitas 2009; 65(Suppl 1): S47-S50.

Cochrane Library

Cochrane Database of Systematic Reviews

Progestogen for treating threatened miscarriage (Review)

Wahabi HA, Fayed AA, Esmaeil SA, Al Zeidan RA

Wahabi HA, Fayed AA, Esmaeil SA, Al Zeidan RA.
Progestogen for treating threatened miscarriage.
Cochrane Database of Systematic Reviews 2011, Issue 12. Art. No.: CD005943.
DOI: 10.1002/14651858.CD005943.pub4.

www.cochranelibrary.com

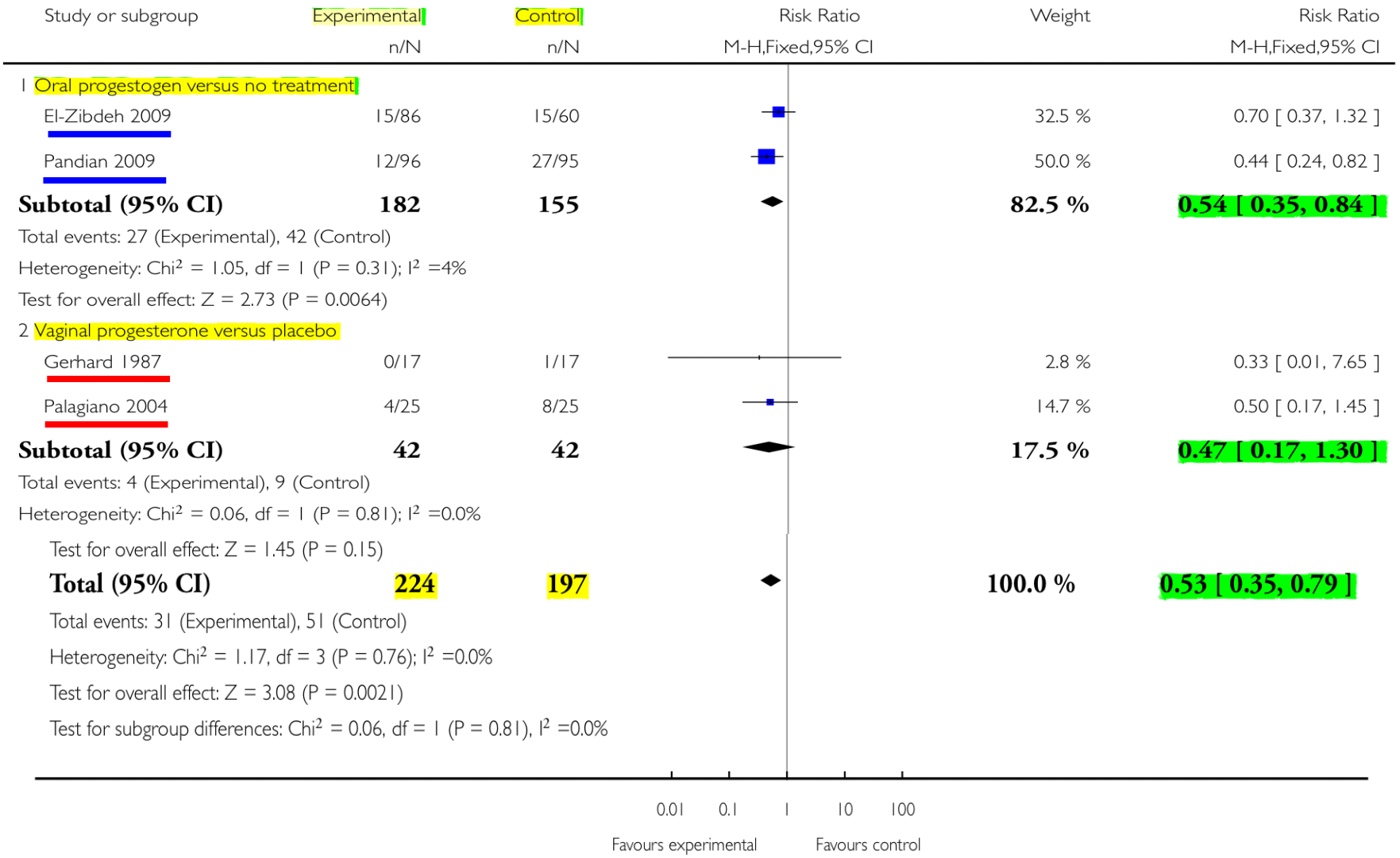
- Progestogen for threatened miscarriage 4 studies (421 participants) in the meta-analysis.
- Progestogen : 31/224 (13.8%) miscarriage vs Control : 51/197 (25.9%) miscarriage
- Reduction in spontaneous miscarriage with progestogens compared to placebo/no treatment (risk ratio (RR) 0.53; 95% CI 0.35 to 0.79).

Analysis 1.1. Comparison 1 Progesterone versus placebo or no treatment, Outcome 1 Miscarriage.

Review: Progestogen for treating threatened miscarriage

Comparison: 1 Progesterone versus placebo or no treatment

Outcome: 1 Miscarriage



Gynecological Endocrinology, 2012; 28(12): 985–990

ISSN 0951-3590 print/ISSN 1473-0766 online
DOI: 10.3109/09513590.2012.702875

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PREGNANCY LOSS

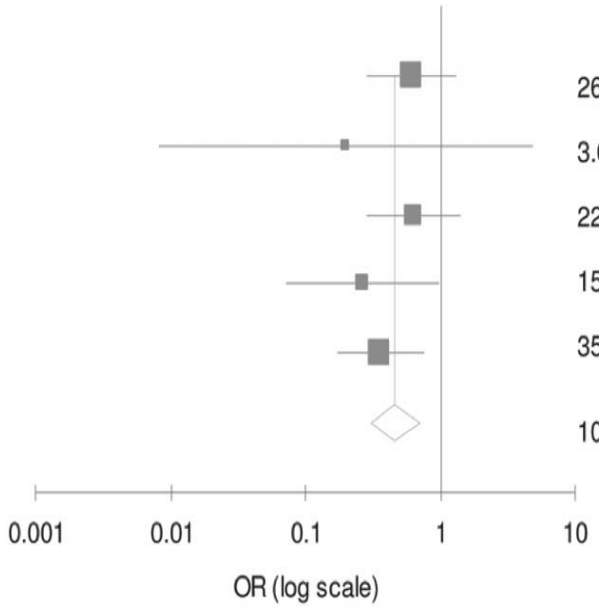
A systematic review of dydrogesterone for the treatment of threatened miscarriage

Howard Carp[1,2]

[1]Department of Obstetrics & Gynecology, Sheba Medical Center, Tel Hashomer, Israel and [2]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

- Oral dydrogesterone in threatened miscarriage
- Meta-analysis & Systematic review of 5 RCT
- 660 women fulfilled criteria
- Dydrogesterone : 44/335 (13%) miscarriage
- Control : 78/325 (24%) miscarriage
- ~ 50%% reduction in miscarriage (OR = 0.47 CI = 0.31–0.7),

Study	Dydrogesterone Abortions/Total	Control Abortions/Total	Weight %	Odds Ratio with 95%CI
Ehrenskjöld et al (11)	14/72	23/81	26.00%	0.61 (0.29 to 1.3)
Misto (12)	0/7	2/9	3.00%	0.2 (0.01 to 4.91)
El-Zibdeh & Yousef, (13))	15/86	15/60	22.00%	0.63 (0.28 to 1.42)
Omar et al (14)	3/74	11/80	15.00%	0.27 (0.07 to 0.99)
Pandianl (15)	12/96	27/95	35.00%	0.36 (0.17 to 0.76)
META-ANALYSIS:	44/335	78/325	100%	0.47 (0.31 to 0.7)



Heterogeneity
Q = 2.46
P value 0.6514
I^2 = 0% (CI 0%-79.2%)

- Five RCTs demonstrated that Dydrogesterone was associated with a lower trend to miscarriage than standard care

  - This trend reached statistical significance in two of the studies.

  In Mistò's trial, the numbers were too small to reach statistical significance.

Comparing 3 Systematic Reviews of Progestogens in Threatened Miscarriage

Progesterone alone Wahabi 2008[1]	Progesterone and Dydrogesterone Wahabi 2011[2]	Dydrogesterone alone Carp 2012[7]
Data set: **Intravaginal progesterone**: 2 studies[3,4] (**n=84**) Dydrogesterone: no studies	**Data set:** **Intravaginal progesterone**: 2 studies (**n=84**) **Dydrogesterone**: 2 studies[5,6] (**n=337**)	**Data set:** **Dydrogesterone**: 5 studies[5,6,8,9,10] (**n=660**)
Main results: **No effectiveness** for vaginal progesterone compared to placebo in reducing risk of miscarriage	Main results: Evidence of reduction of spontaneous miscarriage by progestogens compared to placebo 0.53 (CI = 0.35–0.79)	**Main results:** **Statistically significant reduction** in the odds ratio for miscarriage after dydrogesterone compared to standard care of 0.47 (CI = 0.31–0.7)

1 Wahabi HA, Abed Althagafi NF, Elawad M, Progestogen for treating threatened miscarriage (Review), 2008; The Cochrane Library, Issue 4

2 Wahabi HA, Fayed AA, Esmaeil SA, et al. Progestogen for treating threatened miscarriage (Review). 2011; The Cochrane Library, Issue 12

3 Palagiano A, Bulletti C, Pace MC, et al. Effects of vaginal progesterone on pain and uterine contractility in patients with threatened abortion before twelve weeks of pregnancy. Annals of the New York Academy of Sciences 2004;1034: 200 – 10

4 Gerhard I, Gwinner B, Eggert-Kruse W, Runnebaum B. Double-blind controlled trial of progesterone substitution in threatened abortion. Biological Research in Pregnancy and Perinatology 1987; 8, 26–34

5 El-Zibdeh MY, Yousef LT. Dydrogesterone support in threatened miscarriage. Maturitas 2009; 65 (1), 43–46

6 Pandian RU. Dydrogesterone in threatened miscarriage: a Malaysian experience. Maturitas 2009; 65 Suppl 1: S 47 – 50

7 Carp H, A systematic review of dydrogesterone for the treatment of threatened miscarriage. Gynecological Endocrinology 2012, 1-8

8 Mistò A. [Experiences with 6-dehydro-retroprogesterone int the treatment of placental insufficiency]. Ann Ostet Ginecol Med Perinat 1967;89:102–112. [Article in Italian]

9 Ehrenskjöld ML, Bondo B, Weile F. [Treatment of threatened abortion with dydrogesterone]. Ugeskr Laeg 1967;129:1678–1679. [Article in Danish]

10 Omar MH, Mashita MK, Lim PS, Jamil MA. Dydrogesterone in threatened abortion: pregnancy outcome. J Steroid Biochem Mol Biol 2005;97:421–425

2015 European Progestin Club Guidelines for the Treatment of Threatened Miscarriage

Recommendation 1	Grade and Reference
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 References: Wahabi 2011, Carp 2012

This guideline has been developed based on studies and clinical investigations. Therefore, it appears to be appropriate to **use all the available evidence, which are very encouraging, in a summarized form to propose guidelines by a group of European experts in order to have the gynecologists, obstetricians and reproductive medicine specialists** have direction with regard to the prevention or treatment of miscarriage for the benefit of the endangered pregnancies….

For women presenting with a **clinical diagnosis of threatened miscarriage, there is now data from meta-analyses of several small studies which suggest that the progestogen, namely dydrogesterone, is better than placebo or no therapy in reducing the rate of spontaneous miscarriage.**

Schindler AE et al. Gynecol Endocrinol 2015. 31(6):447-9.

2013 Australian and New Zealand Guidelines

Recommendation	Grade and Reference
For women presenting with a clinical diagnosis of threatened miscarriage, there is now preliminary evidence of a reduction in the rate of spontaneous miscarriage with the use of progestins.	Consensus-based recommendation Reference: Wahabi 2011

For women presenting with a clinical diagnosis of threatened miscarriage, there is now preliminary evidence of a reduction in the rate of spontaneous miscarriage with the use of progestins. This conclusion is based on data from four RCTs including 411 women. **Miscarriage was significantly less likely to occur on progestins than placebo or no treatment (risk ratio 0.53; 95% CI 0.35 to 0.79)**, with no evidence of increase in the rate of antepartum hemorrhage, pregnancy-induced hypertension, or congenital abnormalities. Again, there was clinical heterogeneity in these trials, with two reporting on the use of oral **dydrogesterone** and two reporting on vaginal progesterone.

The evidence suggesting **benefit of progestins for women with recurrent miscarriage and now, particularly, for women with threatened miscarriage**, remains preliminary and additional well designed studies are required to confirm these findings.

Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) 2013. http://www.ranzcog.edu.au/doc/progesterone-support-of-the-luteal-phase-and-early-pregnancy.html (Last accessed March 2014).

Progesterone in Recurrent Miscarriage

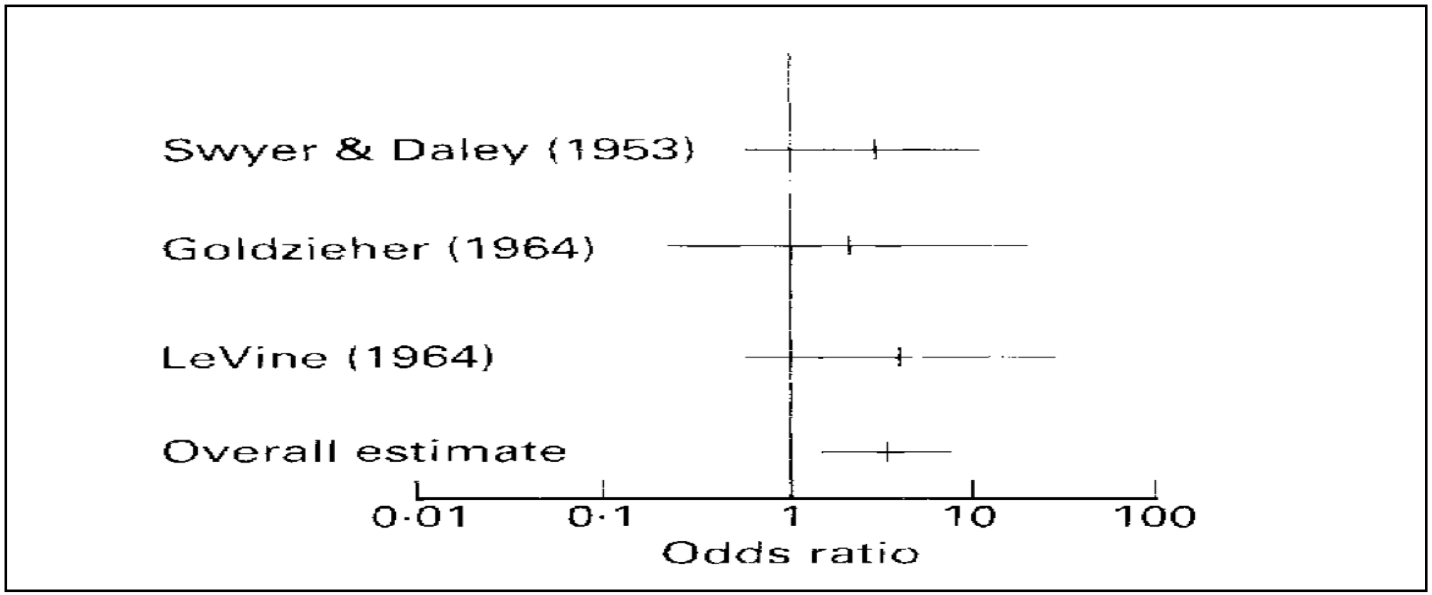
Recurrent miscarriage

- Loss of 3 or more consecutive pregnancies (RCOG, ESHRE)
- Loss of 2 or more consecutive pregnancies (ASRM)
- Effect 1 % of couples trying to conceive
- Pose clinical and psychological consequences
- Established causes are APS, Chromosomal, uterine anomaly
- Half of the cases show No clear cause " Unexplained RPL"
- Role of progestogen in Unexplained RPL is challenging

British Journal of Obstetrics and Gynaecology
March 1989, Vol. 96, pp. 275–280

Efficacy of progesterone support for pregnancy in women with recurrent miscarriage. A meta-analysis of controlled trials

SALIM DAYA



OR 3.09, 95% CI 1.28-7.42

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Journal of Steroid Biochemistry & Molecular Biology 97 (2005) 431–434
The Journal of Steroid Biochemistry & Molecular Biology
www.elsevier.com/locate/jsbmb

Dydrogesterone in the reduction of recurrent spontaneous abortion☆

M.Y. El-Zibdeh*

Department of Obstetrics and Gynaecology, Islamic Hospital, Amman, P.O. Box 910201, Jordan

- 180 women with unexplained RM recruited to DD (n=82), hCG im (n=50) , no Rx (n=48)
- Start from pregnancy confirmation until 12 weeks
- Abortion rates were lower in DD (13.4%) compared to control (29%)

Table 3
Pregnancy outcome in the dydrogesterone, hCG and control groups ($n = 180$)

	Dydrogesterone ($n = 82$)	hCG ($n = 50$)	Control ($n = 48$)
Abortion (n; %)	11 (13%)*	9 (18%)	14 (29%)
Viable pregnancy (n; %)	71 (87%)	41 (82%)	34 (71%)

* $p = 0.028$ vs. control.

Progestogen for preventing miscarriage

David M Haas[1], Patrick S Ramsey[2]

[1]Department of Obstetrics and Gynecology, Indiana University School of Medicine, India
Fetal Medicine, Department of Obstetrics and Gynecology, Uniformed Services Univers

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Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 10, 2013.

- Subgroup analysis of 4 trials with 225 women ≥ 3 RM, progestogen showed significant decrease in miscarriage compared to placebo or no treatment

- Treatment for these women may be warranted given the reduced rates of miscarriage in the treatment group

Analysis 1.3. Comparison 1 Progestogen versus placebo/no treatment, Outcome 3 Miscarriage (women with previous recurrent miscarriage only).

Review: Progestogen for preventing miscarriage

Comparison: 1 Progestogen versus placebo/no treatment

Outcome: 3 Miscarriage (women with previous recurrent miscarriage only)

Study or subgroup	Progestogen n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Women with a history of 3 or more prior miscarriages					
El-Zibdeh 2005	11/82	14/48		7.4 %	0.37 [0.15, 0.90]
Goldzieher 1964	2/8	4/10		1.6 %	0.53 [0.08, 3.59]
Le Vine 1964	4/15	8/15		2.9 %	0.34 [0.08, 1.44]
Swyer 1953	7/27	9/20		4.1 %	0.44 [0.13, 1.46]
Subtotal (95% CI)	**132**	**93**		**16.1 %**	**0.39 [0.21, 0.72]**
Total events: 24 (Progestogen), 35 (Placebo)					
Heterogeneity: Chi^2 = 0.18, df = 3 (P = 0.98); I^2 =0.0%					
Test for overall effect: Z = 3.00 (P = 0.0027)					
2 Women with a history of 2 or more prior miscarriage					
El-Zibdeh 2005	11/82	14/48		7.4 %	0.37 [0.15, 0.90]
Goldzieher 1964	5/23	5/31		3.2 %	1.44 [0.36, 5.70]
Klopper 1965	8/18	5/15		3.1 %	1.57 [0.39, 6.25]
Le Vine 1964	4/15	8/15		2.9 %	0.34 [0.08, 1.44]
MacDonald 1972	3/20	3/20		2.0 %	1.00 [0.18, 5.55]
Shearman 1963	5/27	5/23		3.2 %	0.82 [0.21, 3.25]

Oral dydrogesterone treatment during early pregnancy to prevent recurrent pregnancy loss and its role in modulation of cytokine production: a double-blind, randomized, parallel, placebo-controlled trial

•Kumar 2014

Aim

- To study the impact of administration of dydrogesterone in early pregnancy on pregnancy outcome and its correlation with Th1 and Th2 cytokine levels.

Design

- Prospective, double-blind, randomized, placebo-controlled study.
- Women 18–35 years with ≥ 3 consecutive unexplained recurrent miscarriages
  - Oral dydrogesterone 20 mg/day (n= 175)
    - Placebo (n= 173)
- Women with no history of recurrent miscarriage:
    - Controls: no therapy (n= 174)
- Treatment was given at 4–8 weeks of gestation (enrolled after fetal heart activity confirmed) to 20 weeks

Dydrogesterone Significantly Decreased Miscarriage Rate in Recurrent Miscarriage: Kumar et al. 2014

Pregnancy outcome

Miscarriage rate decreased significantly with use of dydrogesterone *versus* placebo

6.9% *versus* 16.8% (p=0.004)

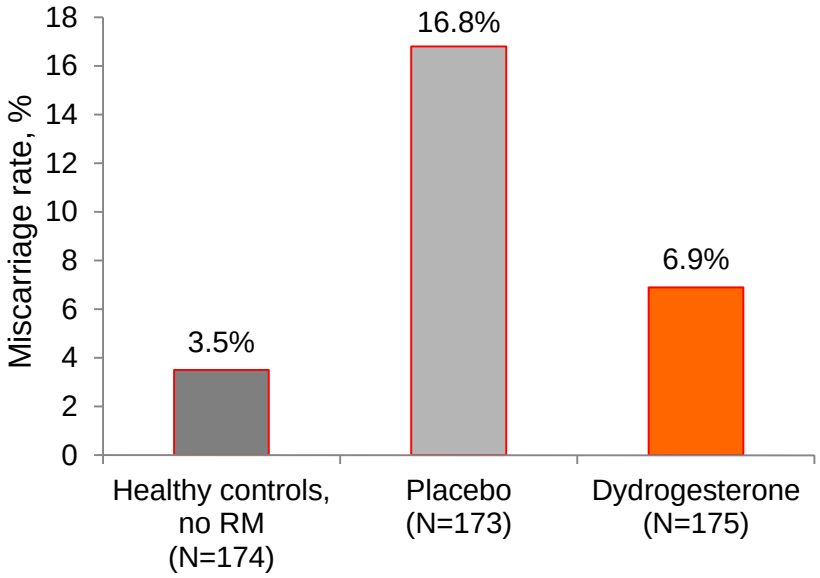
Gestational age at delivery

- Increased significantly with dydrogesterone compared with placebo (38.0 ±2.0 weeks *vs* 37.2 ±2.4 weeks; p=0.002)

Cytokine levels

- No correlation between serum Th1 and Th2 cytokine concentrations and outcome of pregnancy

Miscarriage rate



Risk of miscarriage was 2.4 times higher in the placebo *versus* dydrogesterone group

RR: 2.4 (95% CI: 1.3, 5.9); p<0.001

CI, confidence interval; Th, T helper; RM, recurrent miscarriage; RR, risk ratio

Kumar A *et al. Fertil Steril* 2014; 102(5):1357–1363.

GYNECOLOGICAL ENDOCRINOLOGY

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ISSN: 0951-3590 (print), 1473-0766 (electronic)

Gynecol Endocrinol, Early Online: 1–9
 DOI: 10.3109/09513590.2015.1006618

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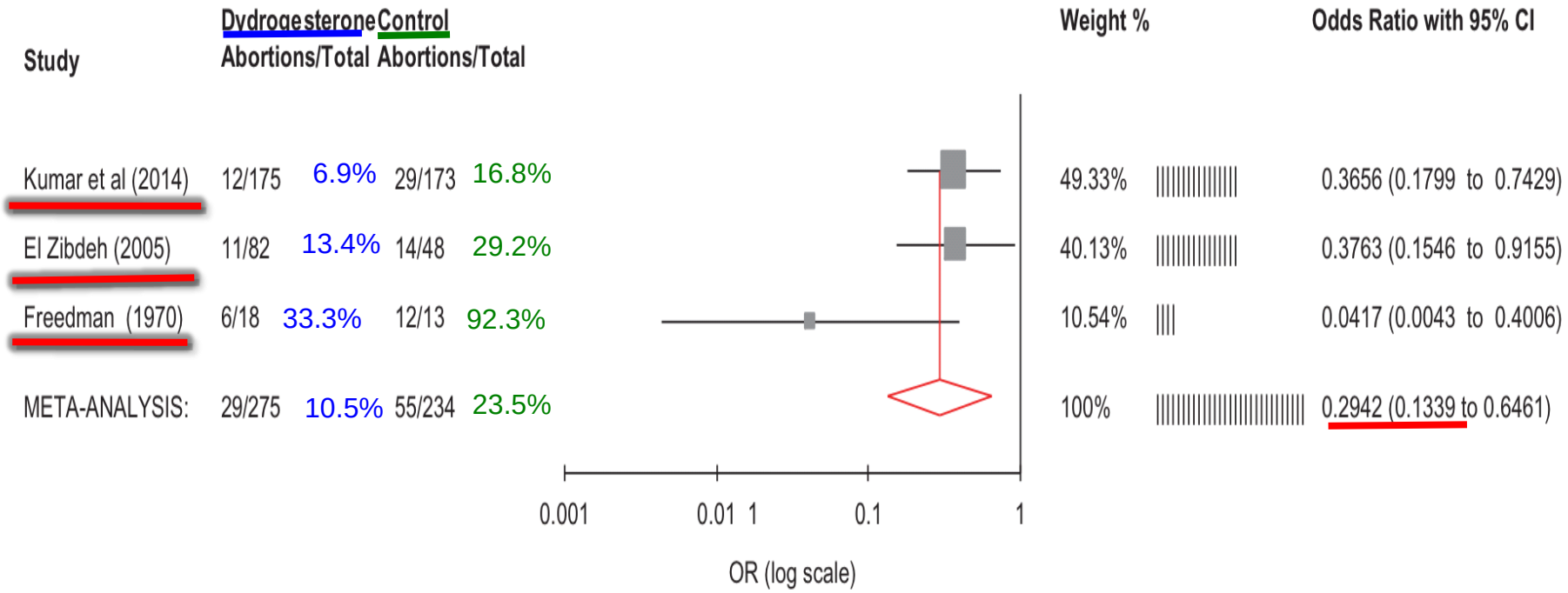
REVIEW ARTICLE

A systematic review of dydrogesterone for the treatment of recurrent miscarriage

Howard Carp[1,2]

[1]Department of Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer, Israel and [2]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

- 3 studies involved Dydrogesterone vs control in RM
- A total of 509 patients
- 55/234 (23%) miscarriage in control
- 29/275 (10.5%) miscarriage in Dydrogesterone
- 12.5% absolute reduction



Heterogeneity

Q = 3.41

P value 0.18

I^2 = 41.3% (CI 0%-82.13%)

Comparing Two Systematic Reviews of Progestogens in Recurrent Miscarriage

Progesterone and dydrogesterone Haas and Ramsey 2013[1]	Dydrogesterone alone Carp 2015[2]
Data set for subgroup analysis in recurrent miscarriage (3+): **Four studies** (n=225) • **Dydrogesterone** • Hydroxyprogesterone caproate IM • Medroxyprogesterone • Progesterone pellets inserted within the gluteal muscle	**Data set Dydrogesterone:** **Three studies** (n=509) • Two randomized trials • One non-randomized comparative trial
Subgroup analysis: Compared to placebo or no treatment, progestogen treatment showed a **statistically significant decrease in miscarriage rate** (Peto OR 0.39, 95% CI: 0.21–0.72); however, the trials were of poor methodological quality	**Main results:** **Statistically significant reduction with dydrogesterone** in the OR for miscarriage compared to standard bed rest or placebo (OR 0.29, 95% CI: 0.13–0.65) and 13% absolute reduction in the miscarriage rate

CI, confidence interval; IM, intramuscular; OR: odds ratio

1. Haas DM, Ramsey PS. Cochrane Database Syst Rev 2013; 10: CD003511.
2. Carp H. Gynecol Endocrinol. 2015 Mar 13:1-9. [Epub ahead of print].

2015 European Progestin Club Guidelines for the Prevention of Recurrent Miscarriage

Recommendation 2	Grade and Reference
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 References: Haas 2013, Kumar 2014

This guideline has been developed based on studies and clinical investigations. Therefore, it appears to be appropriate to **use all the available evidence, which are very encouraging, in a summarized form to propose guidelines by a group of European experts in order to have the gynecologists, obstetricians and reproductive medicine specialists** have direction with regard to the prevention or treatment of miscarriage for the benefit of the endangered pregnancies….

For women presenting with a **history of three or more recurrent miscarriages, there is now data from a meta-analysis of several small studies and a large double-blind, randomized, parallel group, placebo-controlled study which suggest that the progestogen, namely dydrogesterone, is better than placebo in reducing the rate of miscarriage.**

Schindler AE et al. Gynecol Endocrinol 2015 May 2015: 1-3 [Epub ahead of print].

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Progesterone in Women with Recurrent Miscarriages

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Vaginal Micronized Progesterone vs. Placebo in Recurrent Miscarriage : Coomarasamy 2015

Aim of the PROMISE study

- Primary endpoint was live birth after 24 completed weeks of gestation

Design

- Prospective, double-blind, randomized, placebo-controlled study.
- Women 18–39 years with ≥ 3 consecutive unexplained recurrent miscarriages
  - Vaginal micronized progesterone 800 mg/day (n= 404)
  - Placebo (n= 432)
- Treatment was given after positive UPT and no later than 6 weeks of gestation

Coomarasamy A *et al. N Engl J Med* 2015; 373(22):2141–2148.

Coomarasamy 2015 – Vaginal Micronized Progesterone vs. Placebo in Recurrent Miscarriage

Live-birth rate

Live-birth rate was not significantly different between groups

65.8% (MVP) *versus* 63.3% (placebo)

RR 1.04 (95% CI: 0.94, 1.15)

Secondary endpoints

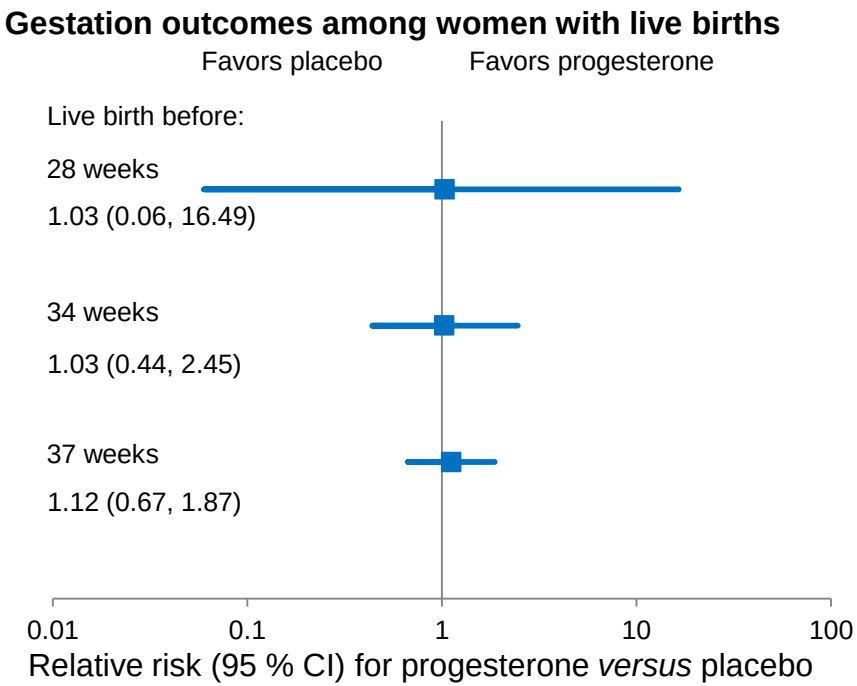
No significant differences were observed between groups in terms of:

- gestational age at delivery
- clinical pregnancy (at 6–8 weeks)
- ongoing pregnancy (at 12 weeks)
- ectopic pregnancy
- miscarriage
- stillbirth
- neonatal outcomes

CI, confidence interval; MVP, micronized vaginal progesterone; RR, relative rate

Coomarasamy A et al. N Engl J Med 2015; 373(22):2141–2148.

Distribution of gestational age



Progesterone did not significantly increase gestational age at delivery compared with placebo

Comparison
Coomarasamy *et al.* 2015 *versus* Kumar *et al.* 2014

	Coomarasamy *et al.* 2015[1]	Kumar *et al.* 2014[2]
Sponsor	UK National Institute for Health Research **Treatment by Besins Healthcare**	Indian Council of Medical Research, New Delhi, India **No pharma involvement**
Type of study	Multi-center, double-blind, randomized, placebo-controlled	Single-center, double-blind, randomized, placebo-controlled
Active drug	Utrogestan® (MVP) vaginal suppositories	**Oral dydrogesterone** tablets
Dosage	400 mg BID (800 mg daily)	10 mg BID (20 mg daily)
Treatment initiation	After a **positive urinary pregnancy** test and no later than 6 weeks of gestation	Confirmation of pregnancy, preferably at 4–8 weeks of gestation (enrolled after **fetal heart activity** confirmed)
End of treatment	Treatment ended at 12 weeks of gestation	Treatment ended at 20 weeks of gestation
Number of patients	**Total: 836 participants** • MVP: N=404 • Placebo: N=432	**Total: 522 participants** • Dydrogesterone: N=175 • Placebo: N=173 • Healthy controls: N=174

BID, twice daily; MVP, micronized vaginal progesterone

1. Coomarasamy A et al. N Engl J Med 2015; 373(22):2141–2148.
2. Kumar A et al. Fertil Steril 2014; 102(5):1357–1363.

Efficacy and Safety
Coomarasamy *et al.* 2015 *versus* Kumar *et al.* 2014

	Coomarasamy *et al.* 2015[1]	Kumar *et al.* 2014[2]
Efficacy results	**No significant difference between MVP and placebo for:** • miscarriage rate • live-births rate • median gestational age at delivery • ectopic pregnancy • stillbirth	**Significant difference between oral dydrogesterone and placebo for:** • miscarriage rate (p=0.004) • mean gestational age at delivery (p=0.002)

Safety and tolerability	• No difference in AEs between groups
	• No difference in neonatal outcomes between groups
	  • In total, 3.5% of babies
	  – MVP: 3.0% (8 / 266)
	  – Placebo: 4.0% (11 / 276)
	  – RR: 0.75 (95% CI: 0.31, 1.85)
	  • **MVP: 1 hypospadias**
	  • Placebo: 1 urachal cyst
	• No significant differences between groups in the rates of obstetrical or neonatal adverse outcomes (exploratory analysis)
		• AEs/neonatal outcomes not provided in the publication
		• Dydrogesterone showed a trend (not significant) toward reducing pregnancy complications, such as:
		  • preterm deliveries
		  • cesarean deliveries
		  • low-birth-weight babies
		  • small-for-date babies

AE, adverse event; CI, confidence interval; MVP, micronized vaginal progesterone; RR, relative risk

1. Coomarasamy A et al. N Engl J Med 2015; 373(22):2141–2148.
2. Kumar A et al. Fertil Steril 2014; 102(5):1357–1363.

Key Differences Between the Studies

- Choice of progestogen and route of administration
- Stage of pregnancy
- Higher-risk population
- Treatment duration

Important Considerations and Differences

A number of factors may explain the results observed in the PROMISE study, when comparing it with the Kumar *et al.* study[1,2]

Choice of progestogen and route of administration

- Dydrogesterone has enhanced progestogenic effects and bioavailability, and a prolonged effect, compared to micronized vaginal progesterone[3–6]

Stage of pregnancy

- Women enrolled at an earlier stage of pregnancy (<6 weeks of gestation) confirmed by urinary test, *versus* women enrolled once fetal heart had been detected[1,2]
- Women receiving dydrogesterone were more likely to be past the window of early pregnancy loss[7]

Higher-risk population

- Inclusion of older women (≤39 *vs* <35 years of age[1,2])
- Older women are at an increased risk of miscarriage due to chromosomal abnormalities that cannot be corrected with a progestogen[8]

Treatment duration

- Treatment until 12 weeks of gestation *versus* 20 weeks of gestation[1,2]

1. Coomarasamy A *et al. N Engl J Med* 2015; 373(22):2141–2148. 2. Kumar A *et al. Fertil Steril* 2014; 102(5):1357–1363. 3. Stanczyk FZ *et al. Endocr Rev* 2013; 34:171–208. 4. Schindler AE *et al. Maturitas* 2009; 65(Suppl1):S3–S11. 5. Dydrogesterone CCDS. 2016. 6. Bulletti C *et al. Hum Reprod* 1997; 12(5):1073–1079. 7. Macklon NS *et al. Hum Reprod Update* 2002; 8(4):333–343; 8. Choi TY *et al. Obstet Gynecol Sci* 2014;57(6):518–525.

Supplementation with progestogens in the first trimester of pregnancy to prevent miscarriage in women with unexplained recurrent miscarriage: a systematic review and meta-analysis of randomized, controlled trials

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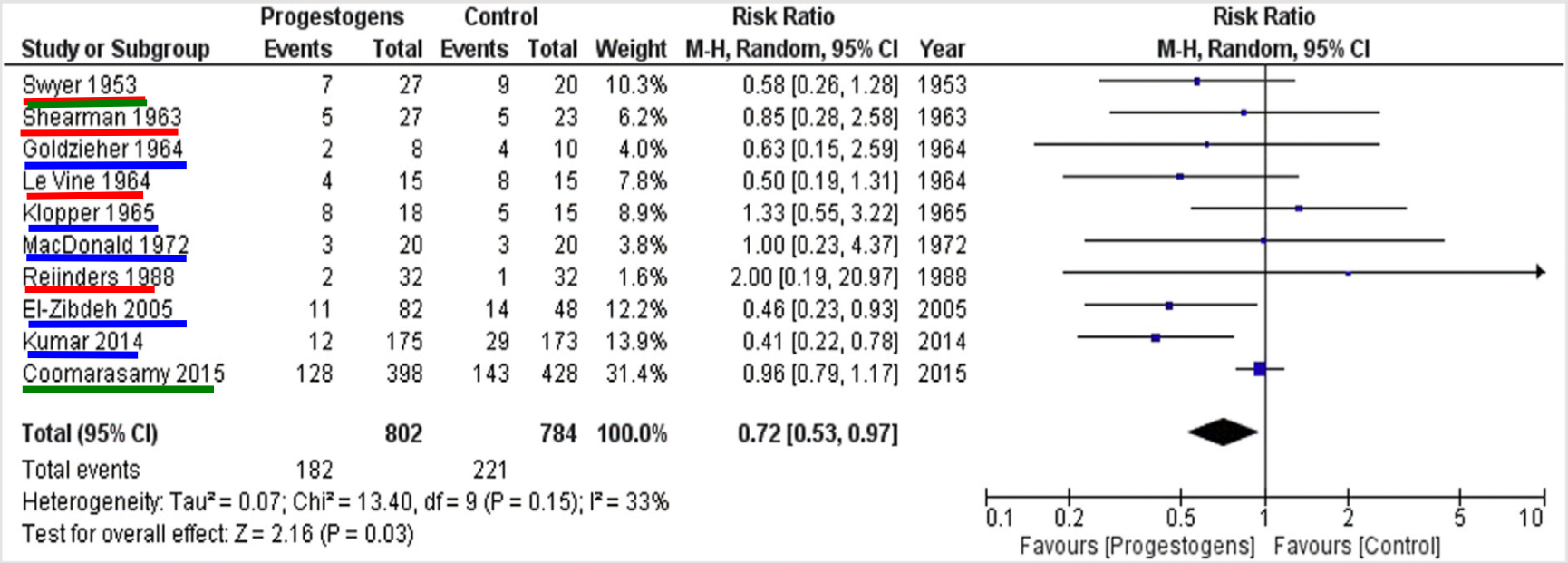
- Progesterone supplementation in unexplained recurrent miscarriage
- 10 trials , 1586 RM patients
- Interventions: Nat P, 17OHP, Dydrogesterone, Nat IM,
- Progestogen grp had lower miscarriage (RR 0.72, 95% CI 0.53-0.97)
- Progestogen grp had higher live birth rate (RR 1.07, 95% CI 1,02-1.15)

FIGURE 1



Forest plot for the risk of recurrent miscarriage in women with unexplained recurrent miscarriage. df = degrees of freedom; M-H = Mantel Haenszel.

Saccone. Progestogens for miscarriage. Fertil Steril 2016.

- Oral progestogen RR 0.61, 95% CI 0.38-0.98
- IM Progestogen RR 0.54, 95% CI 0.29-0.94
- Natural P RR 0.94, 95% CI 0.77-1.13


Thank you
For your attention