Luteal Phase Support: Optimal Vehicle and Dose

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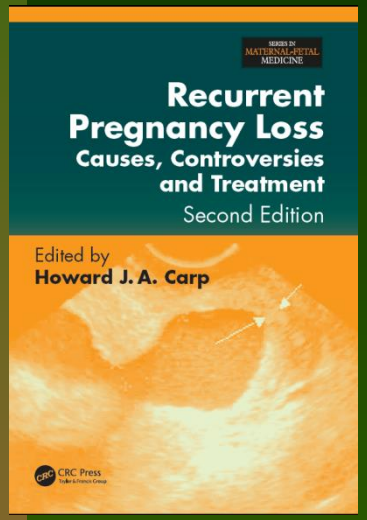
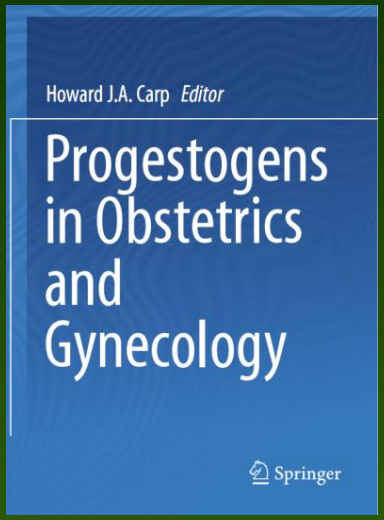
Why Am I Here?





- Concurrent infertility in 32% of RPL (Clifford et al, 1994).
- 148 RPL patients referred to ART for subsequent infertility
- 182 ART patients seen for RPL after ART (of 2316)
- Incidence of MA is 15% after ART (Schieve et al, 2003) 40% after age 40 (Turner et al, 2003)

Endpoint

- Clinical Pregnancy
- Ongoing pregnancy @ 12 weeks
- Live Births
- All are valid endpoints

Plan of Lecture

- Classification of Cycles
- Dydrogesterone
- Progesterone
- When to start
- When to stop
- IM or Vaginal
- Dose

RPL

ART

Are All Cycles Equal?

- Unstimulated Natural Cycles or fresh cyles
- Down regulated cycles with GnRH agonist or antagonist
- Creation of luteal phase e:g donor cycles after POF

Need for Luteal Support

- Theoretically, continued down-regulation by GnRHa →↓ LH
- Removal of large quantities of granulosa cells at OPU
- Supraphysiological E2 & P in early luteal phase → negative feedback. ↓LH & dysfunctional corpus luteum

What Is The Evidence That Fresh Cycles Need Luteal Support?

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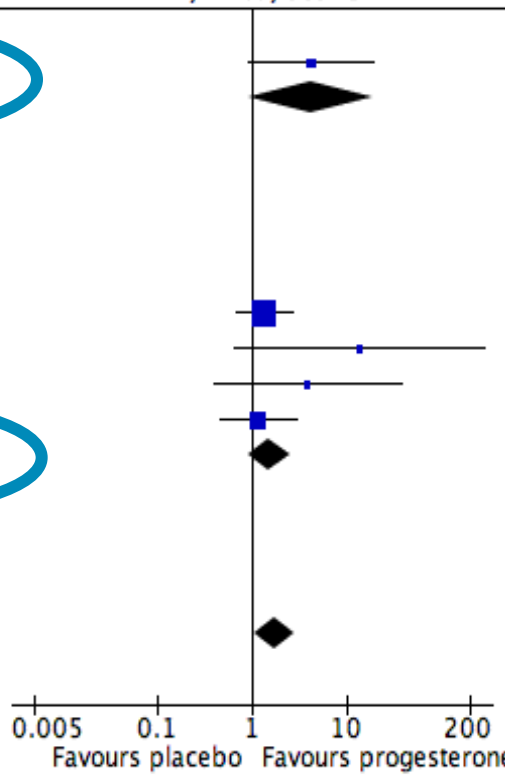
Study or Subgroup	Progesterone Events	Total	Placebo/no treatment Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.1.1 Live birth						
Abate 1999a (1)	15	104	2	52	8.9%	4.21 [0.93, 19.18]
Subtotal (95% CI)		**104**		**52**	**8.9%**	**4.21 [0.93, 19.18]**
Total events	15		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.86 (P = 0.06)						
2.1.2 Ongoing pregnancy						
Belaisch-Allart 1987 (2)	20	141	16	145	52.8%	1.33 [0.66, 2.69]
Colwell 1991 (3)	3	15	0	24	1.2%	13.72 [0.66, 286.96]
Hurd 1996 (4)	4	30	1	26	3.6%	3.85 [0.40, 36.82]
Kupferminc 1990 (5)	13	54	11	51	33.5%	1.15 [0.46, 2.87]
Subtotal (95% CI)		**240**		**246**	**91.1%**	**1.53 [0.91, 2.57]**
Total events	40		28			
Heterogeneity: $Chi^2 = 3.15$, df = 3 (P = 0.37); $I^2 = 5\%$						
Test for overall effect: Z = 1.60 (P = 0.11)						
Total (95% CI)		**344**		**298**	**100.0%**	**1.77 [1.09, 2.86]**
Total events	55		30			
Heterogeneity: $Chi^2 = 4.92$, df = 4 (P = 0.30); $I^2 = 19\%$						
Test for overall effect: Z = 2.31 (P = 0.02)						
Test for subgroup differences: $Chi^2 = 1.54$, df = 1 (P = 0.21), $I^2 = 35.1\%$						



When analysis restricted to live birth, differences between groups not significant. High heterogeneity in studies of ongoing pregnancy (Van Der Linden et al, 2015).

Current Practice

(Vaisbuch et al, 2014)

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	Current survey (June 2012)
Cycles per year	284,600
Vaginal progesterone only	77
i.m. progesterone only	5
Oral progesterone only	0.5
Combined drugs	17
HCG only	0
Duration of LPS beyond 8 weeks of gestation	72[a]

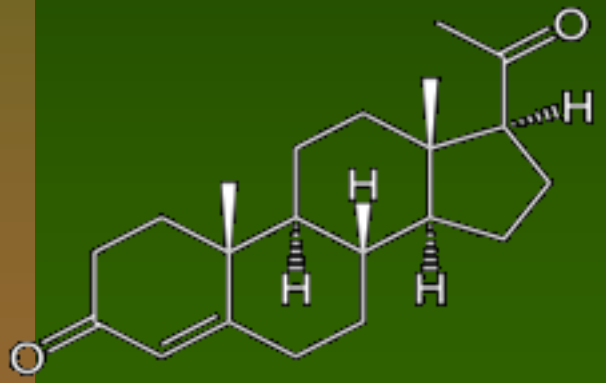
- Web based survey of real life practices reported to, "www.IVF-Worldwide.com"

Dydrogesterone

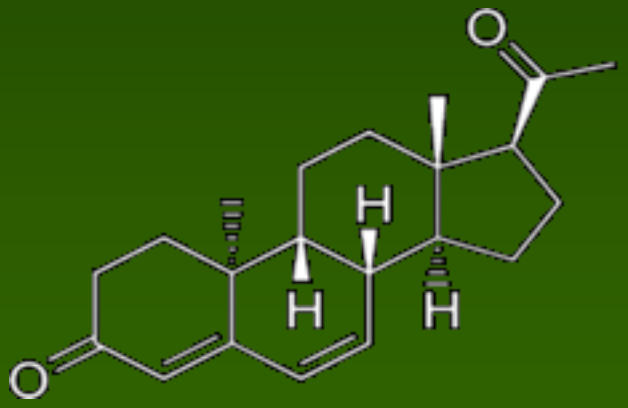
Dydrogesterone

- Stereoisomer of progesterone, with additional double-bond between carbon 6 and 7
- Metabolite 20-Dihydrodydrogesterone progestogenically active

Progesterone



Dydrogesterone



Lotus Study (1)

ART

Human Reproduction, Vol.32, No.5 pp. 1019–1027, 2017
Advanced Access publication on March 1, 2017 doi:10.1093/humrep/dex023

human reproduction ORIGINAL ARTICLE *Infertility*

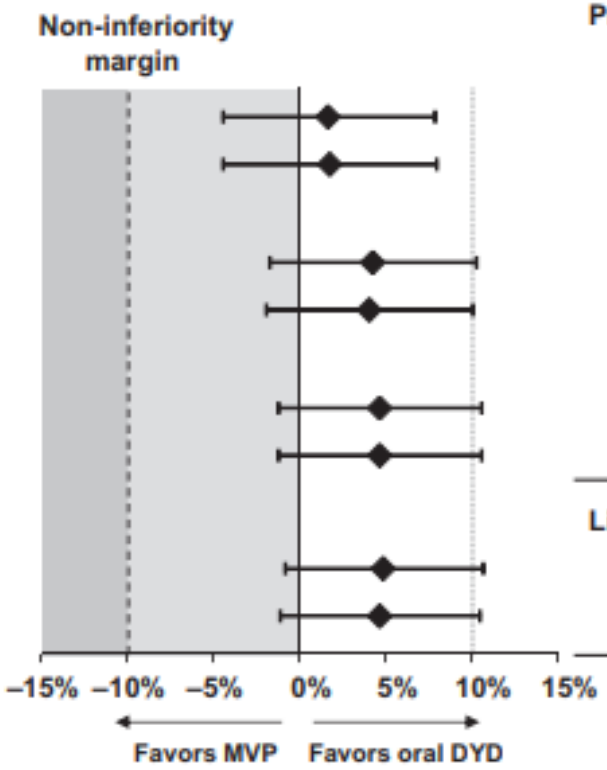
A Phase III randomized controlled trial comparing the efficacy, safety and tolerability of oral dydrogesterone versus micronized vaginal progesterone for luteal support in *in vitro* fertilization

Herman Tournaye , Gennady T. Sukhikh , Elke Kahler and Georg Griesinger

- Double-blind, RCT investigating if dydrogesterone is not inferior to micronised progesterone in IVF
- 497 women randomised to DYD 30mg, 432 to MVP 600mg
- Pregnancy rates at 12 weeks of gestation, 37.6% and 33.1% in DYD & MVP groups respectively (difference 4.7%; 95% CI: −1.2– 10.6%). NS
- Start – day of OPU. Cessation – 12 weeks.

Lotus Study (2)

ART

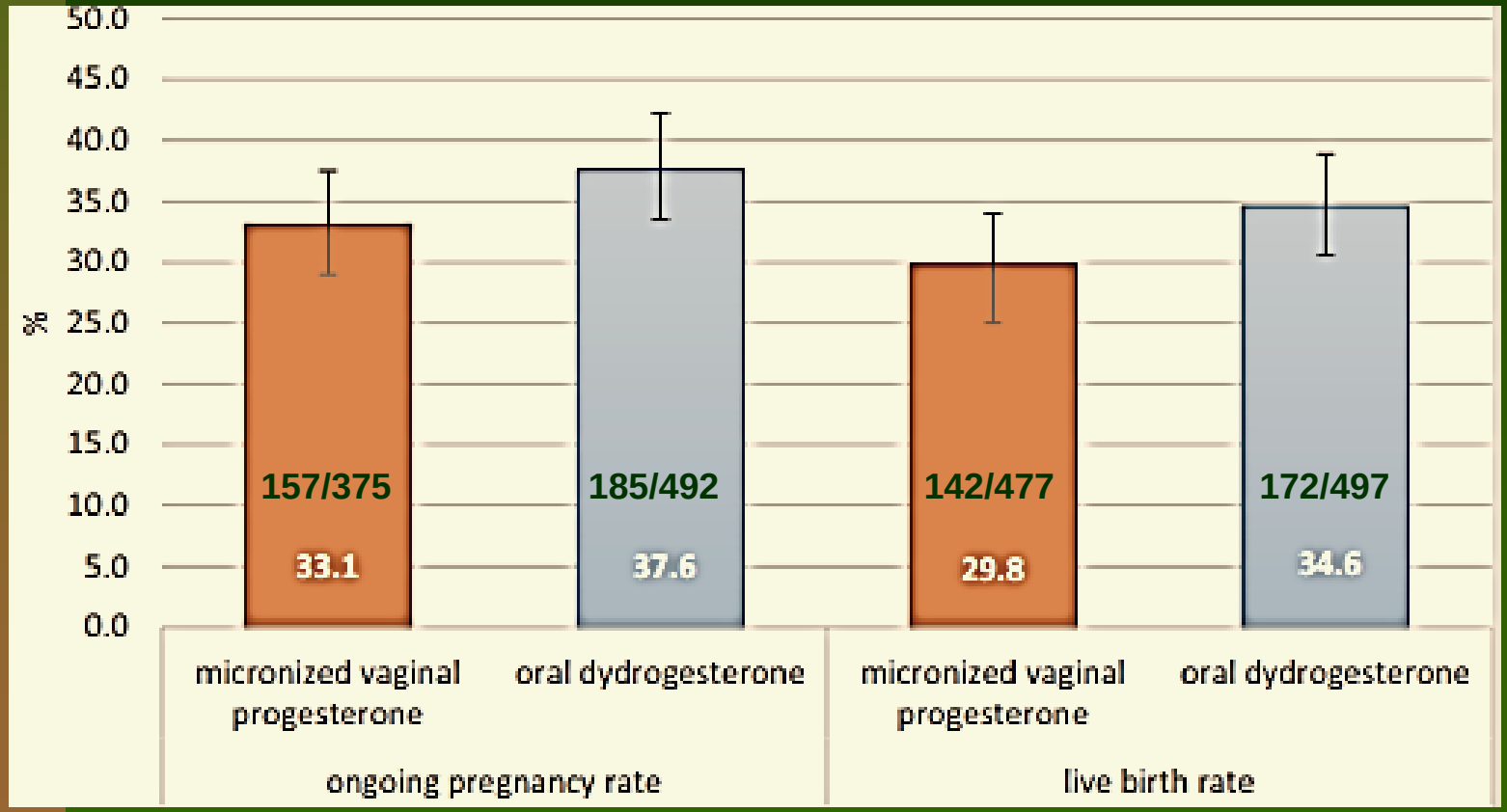


Outcome	% (*n*/*N*)		Difference in pregnancy rate (Oral DYD–MVP)	95% CI
	Oral DYD	MVP		
Pregnancy rate				
4 weeks of gestation				
FAS	47.1 (234/497)	45.5 (217/477)	1.7	–4.4–7.9
PPS	47.2 (232/492)	45.5 (216/475)	1.8	–4.4–8.0
8 weeks of gestation				
FAS	39.6 (197/497)	35.4 (169/477)	4.3	–1.7–10.3
PPS	39.6 (195/492)	35.6 (169/475)	4.1	–1.9–10.1
12 weeks of gestation				
FAS	37.6 (187/497)	33.1 (158/477)	4.7	–1.2–10.6
PPS	37.6 (185/492)	33.1 (157/475)	4.7	–1.2–10.6
Live birth rate				
FAS	34.6 (172/497)	29.8 (142/477)	4.9	–0.8–10.7
PPS	34.6 (170/492)	29.9 (142/475)	4.7	–1.1–10.5

Lotus Study (3)

(Griesinger et al, 2018)

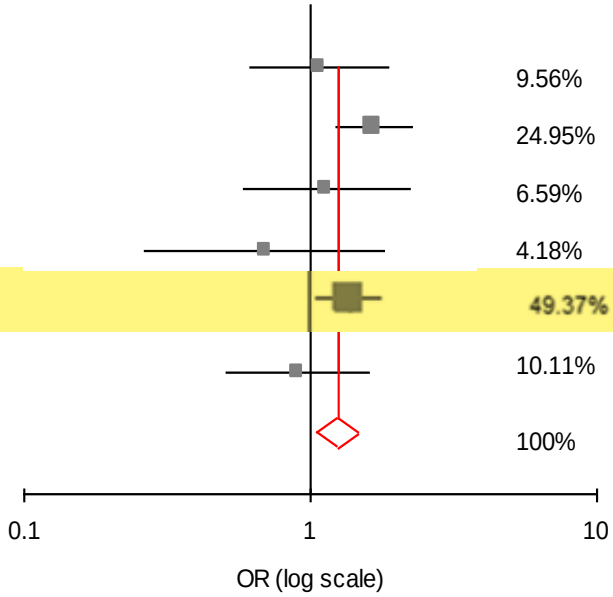
Full assessment analysis (Intention to treat)



DYD vs MVP: Metaanalysis

ART

Study ID	DYD CPR/Total	MVP CPR/Total	Weight %	95% CI
Chakrvarty et al, (2005)	19/79	80/351	9.56%	1.0727 (0.6048 to 1.9027)
Patki & Paw ar (2007)	150/366	91/309	24.95%	1.6636 (1.2065 to 2.294)
Ganesh et al (2011)	23/73	24/83	6.59%	1.1308 (0.5701 to 2.243)
Salehpour et al, (2013)	10/40	13/40	4.18%	0.6923 (0.2612 to 1.8348)
Lotus (2017)	187/497	147/477	49.37%	1.3542 (1.038 to 1.7667)
Saharkiz et al, (2016)	29/96	37/114	10.11%	0.9008 (0.5013 to 1.6186)
META-ANALYSIS:	428/1151	414/1374	100%	1.246 (1.0496 to 1.4792)
	37.2%	30.1%		

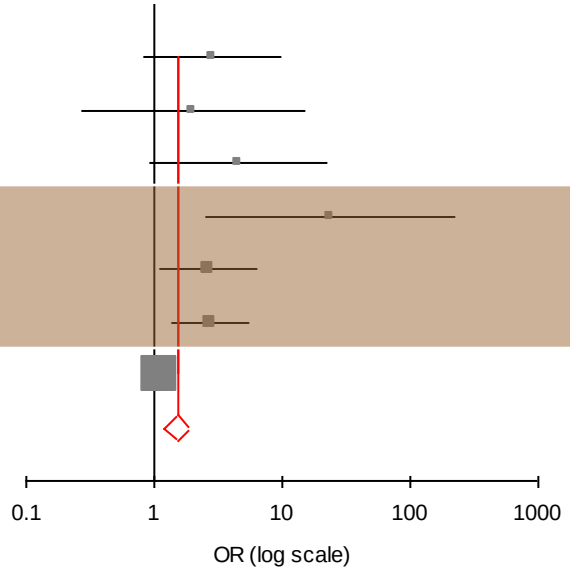


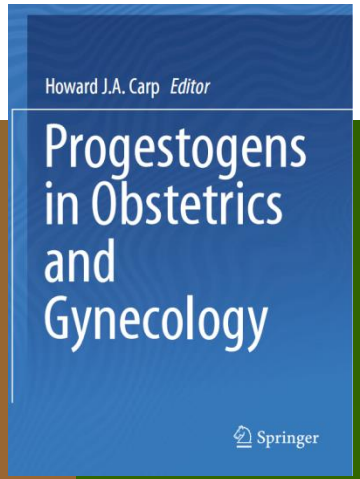
Heterogeneity
Q = 6.11
P = 0.012
I^2 = 18.23% (CI 0%-63.02%)

Updated Metaanalysis on Progesterone Support in RPL (Fixed Effects Model)

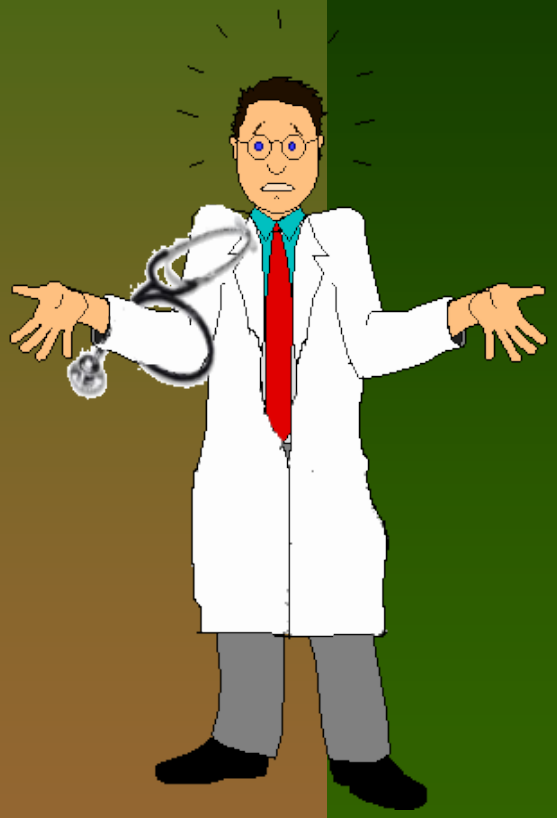
RPL

Study	Progestin	Progestin Births/Total		Control Births/Total		Weight (%)	OR with 95% CI
Sw yer & Daley [1953]	MPA	21/27	78%	11/20	55%	2.53%	2.8636 (0.8086 to 10.1421)
Goldzieher [1964]	17 OHP	6/8	75%	6/10	60%	1.20%	2 (0.2601 to 15.3811)
Le Vine [1964]	Implant	12/15	75%	7/15	47%	1.26%	4.5714 (0.9032 to 23.1367)
Freedman [1970]	DYD	12/18	67%	1/13	8%	0.35%	24 (2.4965 to 230.7247)
El Zibdeh [2005]	DYD	71/82	87%	34/48	70%	5.19%	2.6578 (1.0923 to 6.4669)
Kumar [2014]	DYD	163/175	93%	144/173	83%	8.96%	2.7355 (1.3461 to 5.5591)
Promise [2015]	MP	262/398	66%	271/428	63%	80.50%	1.1161 (0.8388 to 1.485)
META-ANALYSIS:		547/723	**76%**	474/707	**67%**	100%	1.5196 (1.1982 to 1.9274)





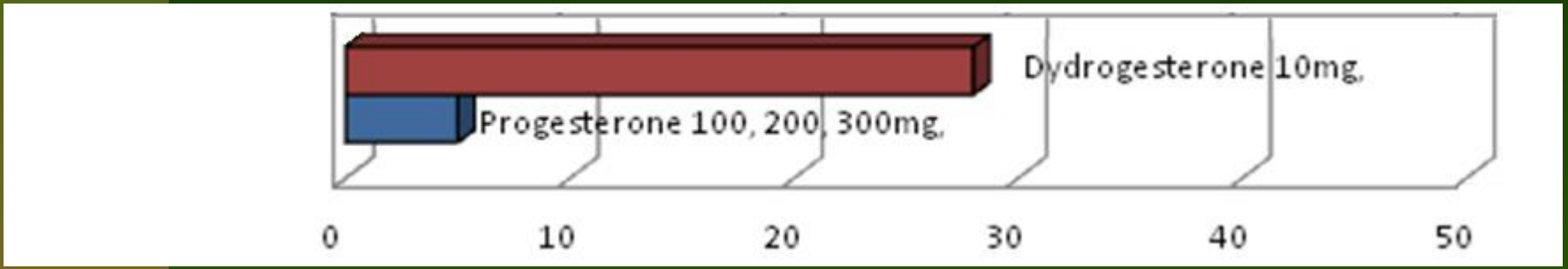
Concerns with DYD



- Not the physiological hormone
- No effect on serum progesterone levels
- Histological endometrial ripening
  - In post menopausal women, 20mg DYD better than 300mg progesterone (King & Whitehead , 1986)
  - In POF, 600mg MVP superior to 20mg DYD (Fatemi et al, 2007)
  - No difference in results in DUB, 20mg DYD vs 90mg vaginal gel (Karakus et al, 2009)

Bioavailability & Receptor Binding

Bioavailability



Adapted from Schindler et al, 2003 & Stanczwyk et al, 2013

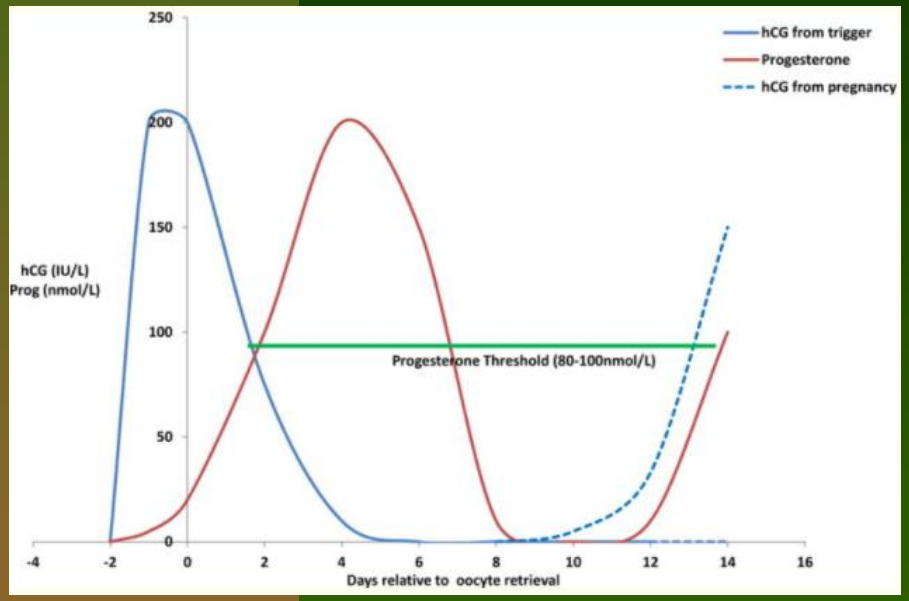
	Progesterone	Dydrogesterone
Receptor Binding	50	75

Adapted from Wiekatz & Kuhl 2005 & Schindler et al, 2008
Progesterone receptor (promegestone = 100%)

Progesterone

When to Start ?

ART



Connell et al, 2016

- Window to start progesterone between evening of OPU & day 3 after oocyte retrieval.
- No difference in starting at OPU, 1 day later (Gao et al, 2018) or 2 days later, (Baruffi et al, 2003; Connell et al, 2016)
- Williams et al, (2001) investigated progesterone initiation on day 3 or 6 after oocyte retrieval and reported a decreased likelihood of pregnancy on day 6 initiation.

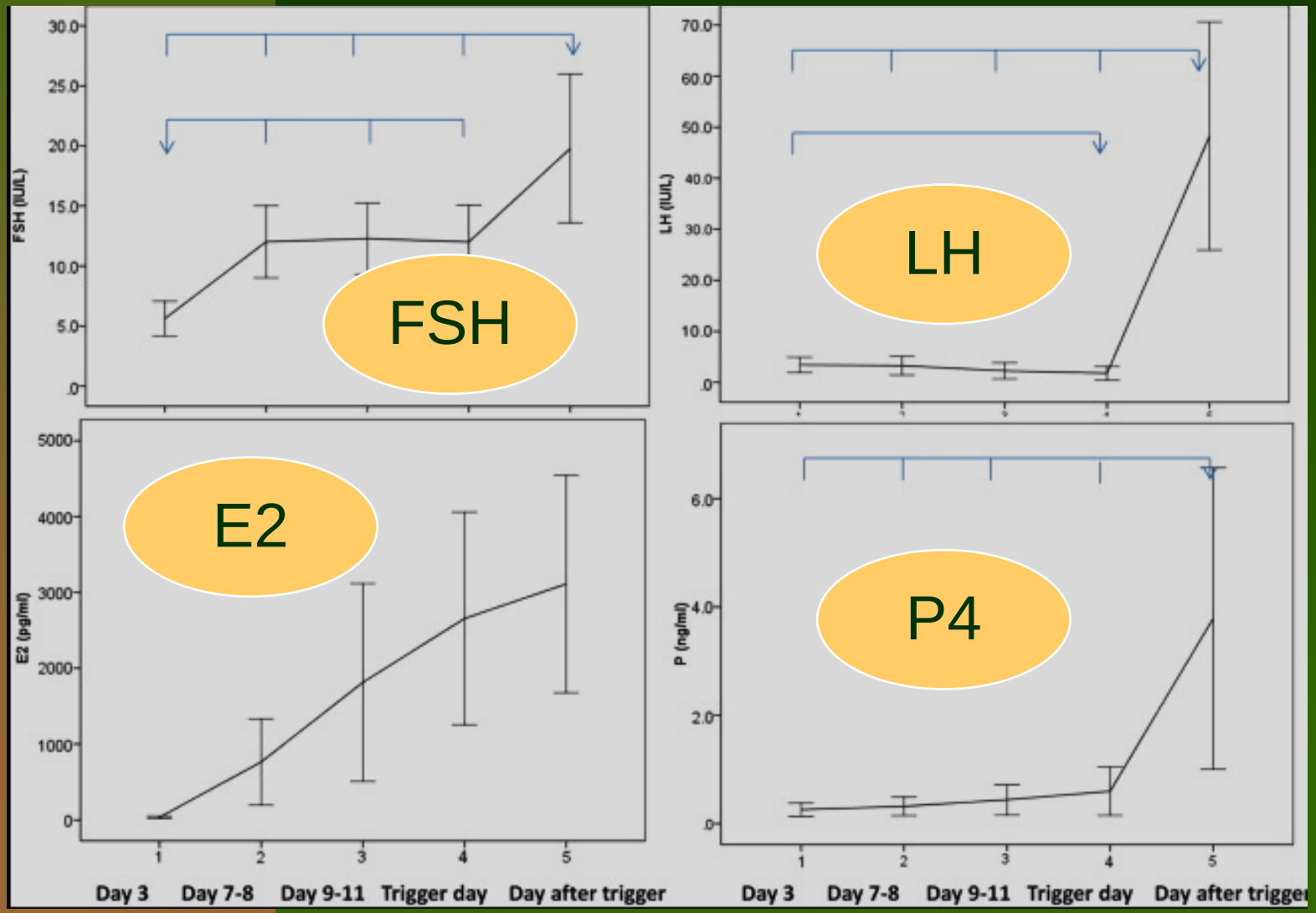
Follicular Phase Progestogen (1)

ART

- Subtle early rises in progesterone can decrease pregnancy rates (Sohn et al, 1999).
- Levels over 1.5ng/ml on the day of hCG trigger can decrease pregnancy rates (Bosch et al, 2012; Xu et al, 2012)
- Micro array studies of gene expression involved in endometrial receptivity & implantation show dysregulation of genes & proteins when exposed to premature elevation in progesterone (Labarta et al, 2011; Li et al, 2011; Van Vaerenbergh et al, 2011).

Follicular Phase Progestogen (2)

ART



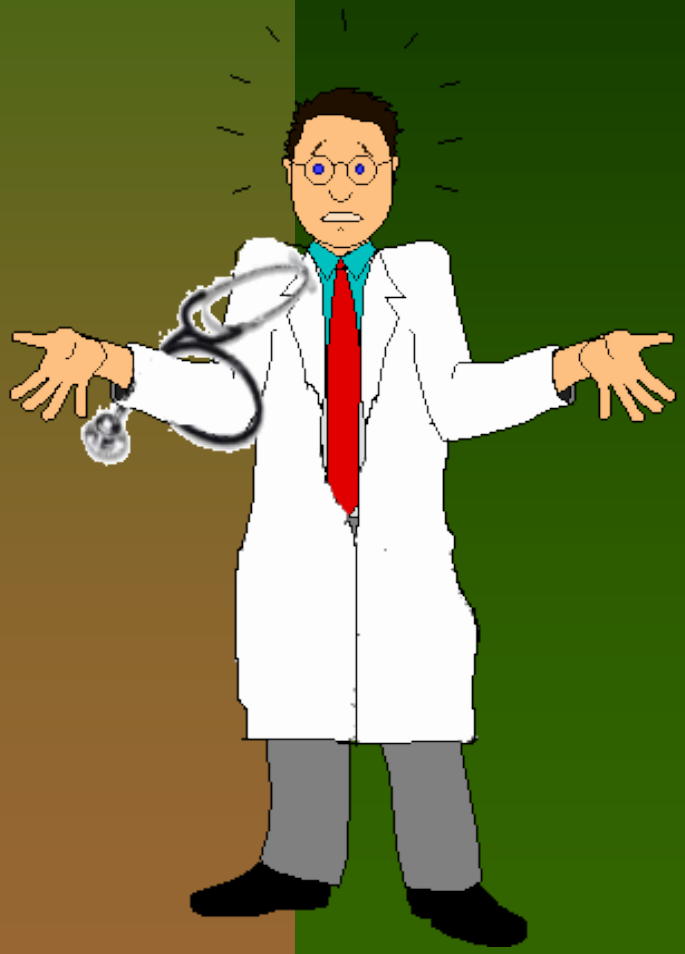
- MPA 10mg od from day 3 with 150-225 iu hMG. (Kuang et al, 2015)
- Freeze all protocol

Follicular Phase Progestogen (3)

ART

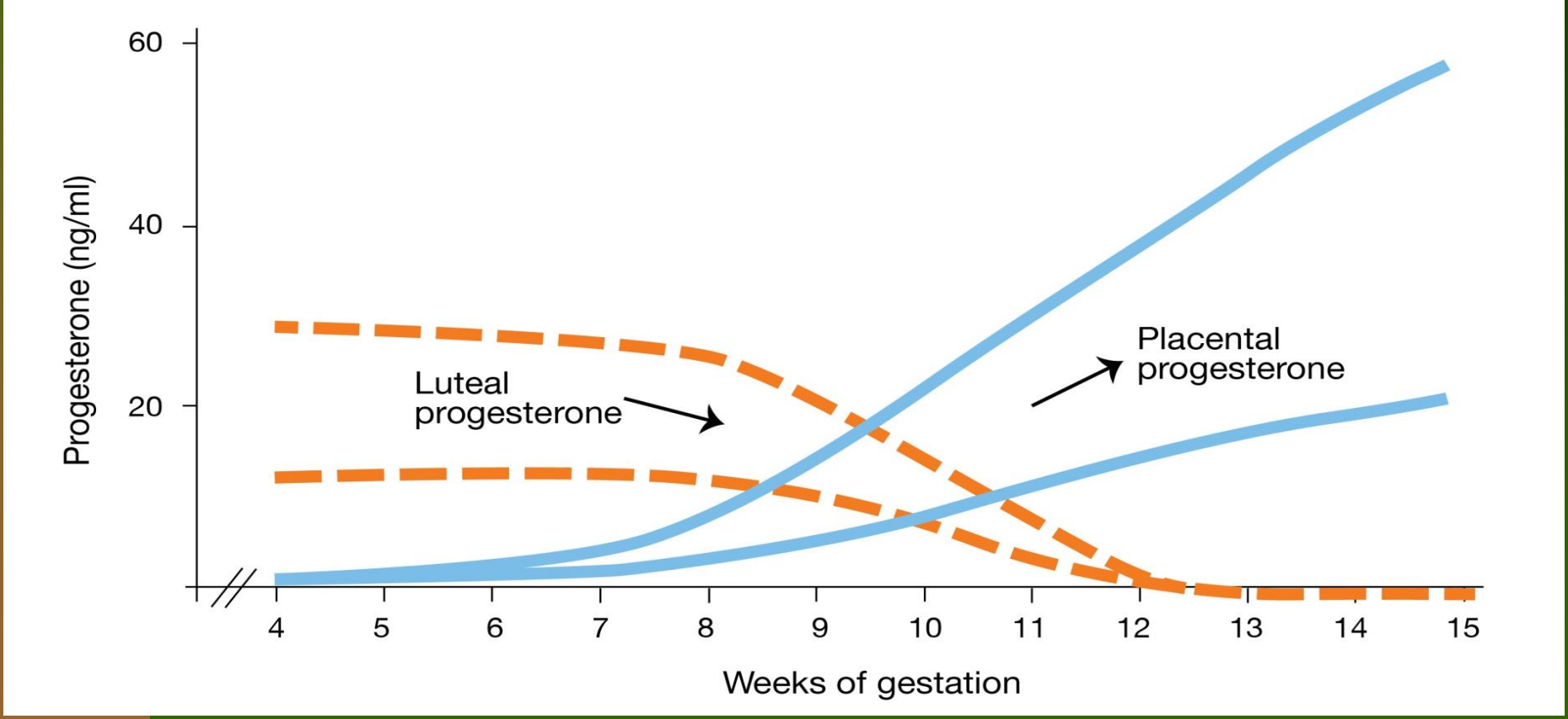
- Yu et al, (2018) DYD 10mg b:d from day 3 → trigger vs MPA
- RCT of 516 patients. 1 cycle freeze all. No significant difference in:- mean number of oocytes retrieved, or clinical pregnancy rate of 1st FET cycle 57.6% after DYD (125/217) & 62.3% (132/212) after MPA group (OR: 0.82, 95% CI: 0.56–1.21)
- Zhu et al, (2015) used oral MP 100mg b:d from day 3 → trigger vs short protocol triptorelin 0.1mg from day 2 → trigger
- Retrospective study on 374 patients .
- No significant difference in mean no. oocytes retrieved, mature oocyte rate or clinical pregnancy rate at 1st FET cycle (54.27% vs 51.65%).

When To Stop?



- What is your objective?
- Clinical Pregnancy Rate
- Live Birth Rate

Luteal Placental Shift



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

When To Stop (Evidence)?

ART

- Nyboe Andersen et al, (2002) RCT 385 patients. MVP 600mg.
- MVP stopped when βhCG positive, 78.7% delivered, if continued until 9 weeks 82.4% delivered (NS)
- Conclusion – LPS can stop with positive βhCG
- Aboulghar et al, (2008) RCT on continuation until 9weeks or discontinuation of P4 support on 1st ultrasound with positive fetal heart activity. No significant differences in miscarriages or threatened miscarriage between groups. Conclusion - no advantage to continuing progesterone support beyond the time of first ultrasound viability study

Does Progesterone Prevent Recurrent Miscarriage? (Coomarasamy,et al, 2015)

RPL

The NEW ENGLAND JOURNAL of MEDICINE

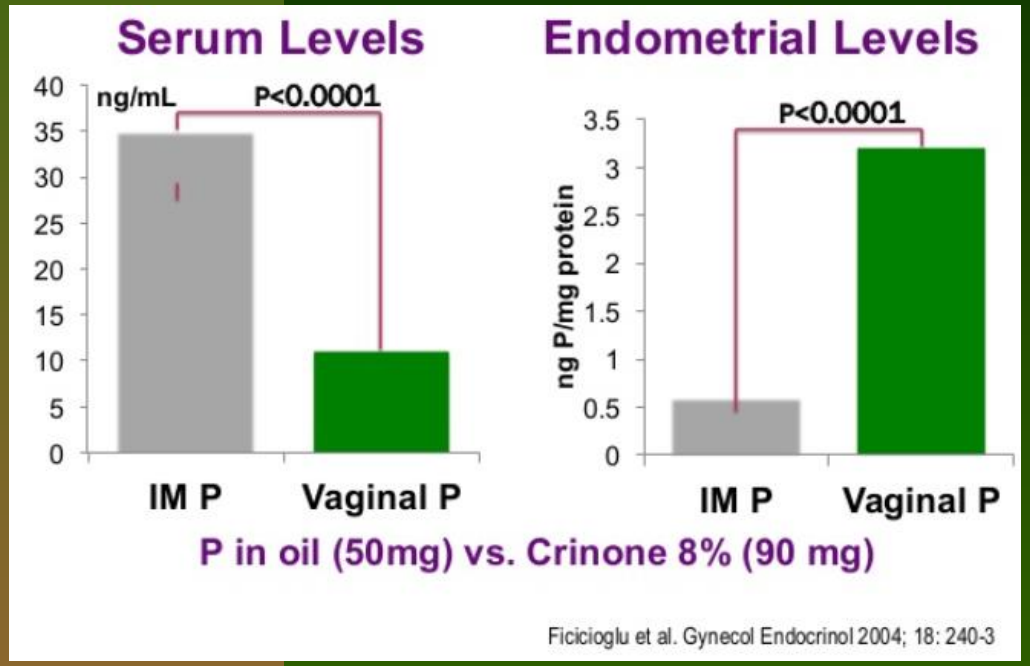
ORIGINAL ARTICLE

A Randomized Trial of Progesterone in Women with Recurrent Miscarriages

- Coomarasamy,et al, (2015) Double-blind, RCT investigating if VMP from positive β hCG increases LBR in women with RPL
- 404 women treated, 432 placebo. 65.8% LBR after VMP vs 63.3% in placebo group (RR 1.04; 95% CI 0.94 - 1.15)
- Stephenson et al, (2016) RCT of 116 women. VMP 200-400mg from day 3 after LH surge. LBR higher in women prescribed VMP 68% (86/126) vs 51% (19/37); OR = 2.1 (95% CI, 1.0-4.4).

IM or Vaginal? (1)

ART



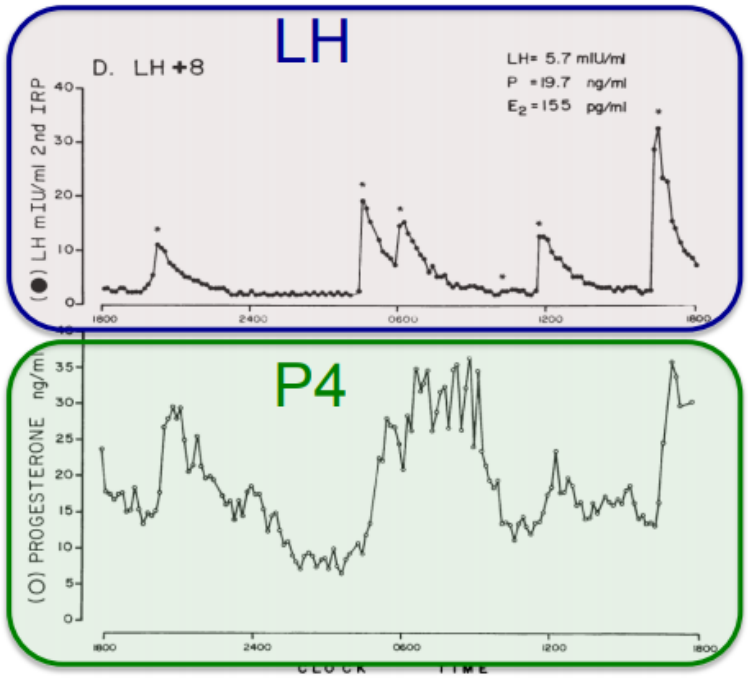
- Concn. is 14 times higher in endometrium compared to serum levels following MVP. Ratio is 1:1 with IM progesterone (Cincinelli et al, 2000)
- IM progesterone conferred the most benefit compared with oral or vaginal use. (Pritts & Atwood, 2002) However, 2 of the 5 included studies used 100 to 200 mg MVP daily.

Progesterone Pulsatility

(Filicori et al, 1984)

Physiology: production of progesterone = 25 mg/day

P4: pulsatile production under the control of LH:



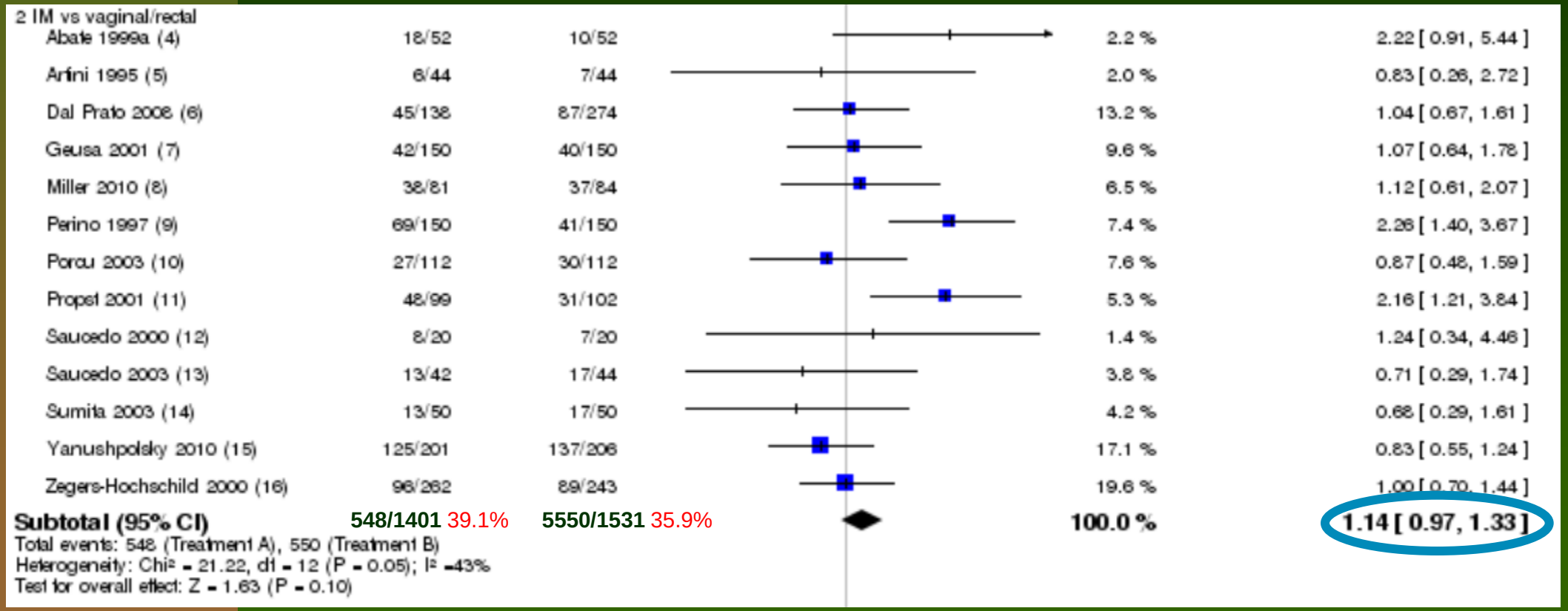
Day LH +8

IM or Vaginal? (2)

(Van Der Linden et al, 2015)

ART

Clinical Pregnancy Rate



IM or Vaginal? (3)

(Van Der Linden et al, 2015)

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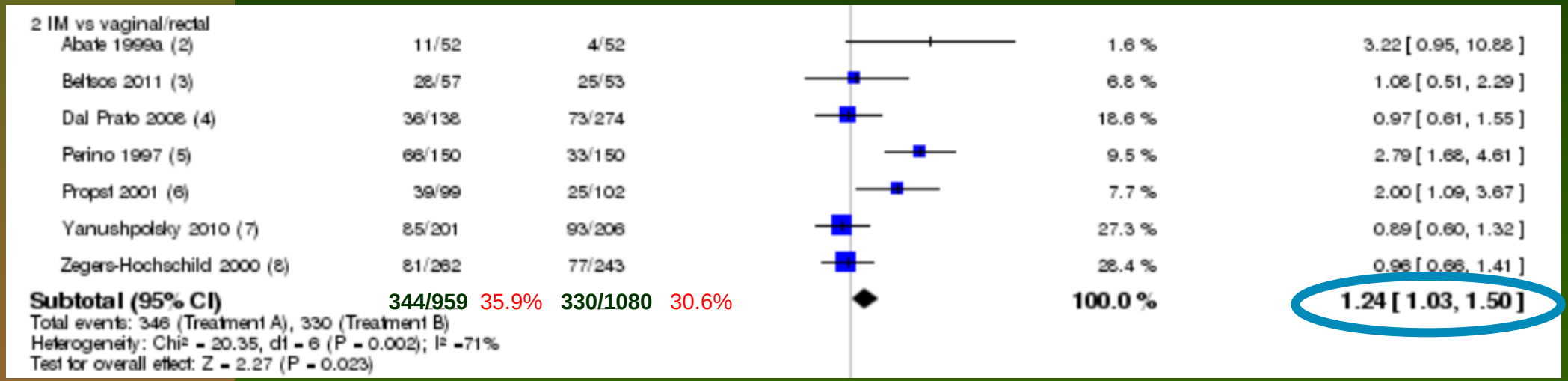
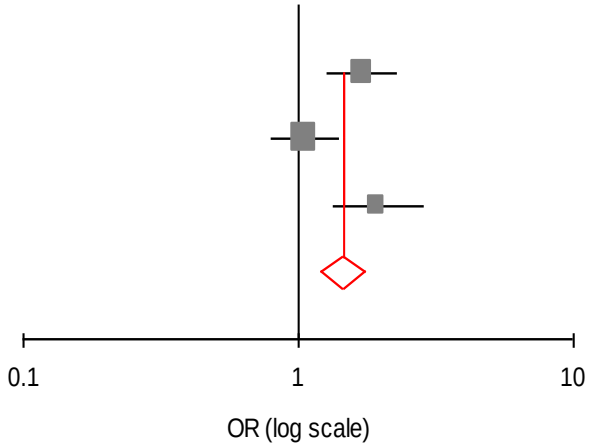
Live Birth Rate



IM or Vaginal in Freeze All Cycles

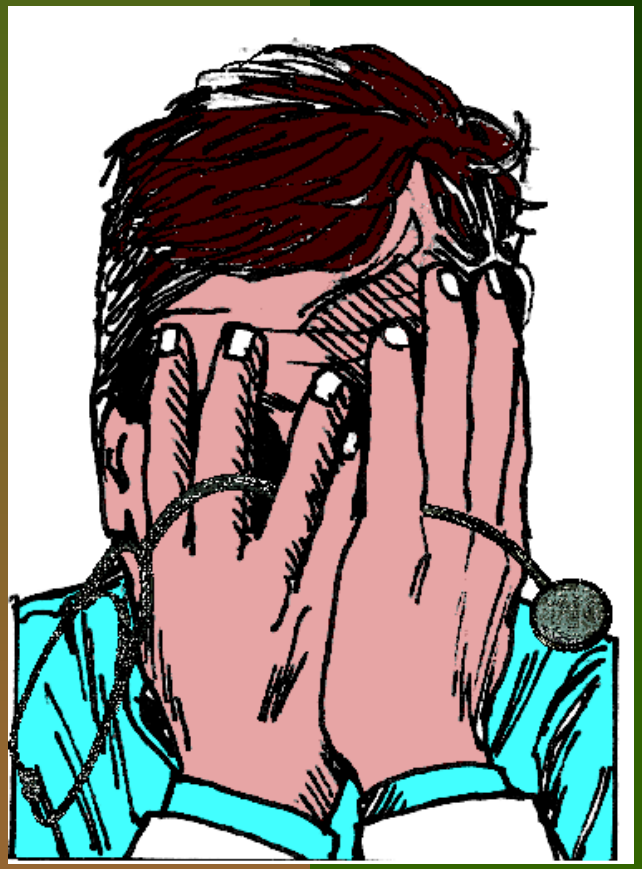
ART

Study ID	!M Progesterone Pregnancies/total	MVP Pregnancies/Total	Weight %	OR with 95% CI
Faser et al, 2012	225/440	110/289	35.29%	1.703 (1.2588 to 2.3038)
Shapiro et al, 2014	421/682	144/238	44.43%	1.0529 (0.7782 to 1.4246)
Devine et al, 2017	123/218	84/210	20.28%	1.9421 (1.3221 to 2.8529)
META-ANALYSIS:	769/1340 57.3%	338/737 52.6%	100%	1.4626 (1.2152 to 1.7604)



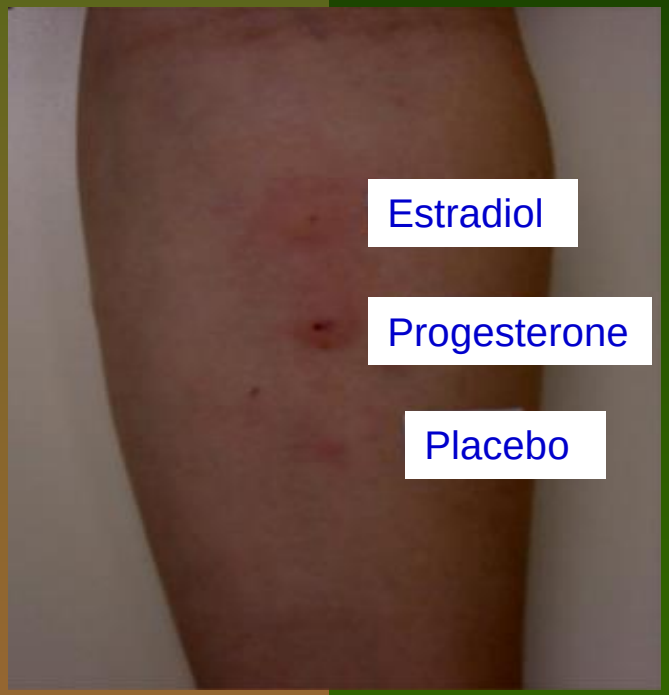
Vehicle

IM Progesterone in Oil



- Side effects include:- Extreme pain, swelling, itching and other local reactions at injection site, abscesses formation, hypersensitivity reactions, cough, dyspnea, tiredness, dizziness, genital itching, & increased risk of gestational diabetes, mood swings, headaches, bloating, abdominal pain, perineal pain, constipation, diarrhea, nausea, vomiting, joint pain, depression, decreased sex drive, nervousness, sleepiness, breast enlargement, breast pain, dysuria, polyuria, UTI, vaginal discharge, fever, flu-like symptoms, back pain, leg pain, sleep disorder, upper respiratory infection, asthma, acne and pruritus. (FDA, 2006).
- Concerns regarding vehicle - castor oil may induce contractions by stimulating release of prostaglandins. (Brancazio et al., 1988; O'Sullivan 2010) Arachis oil (Peanut) in peanut allergy

Micronized Progesterone: Side Effects



- Beyond 1st trimester may reveal gravidic cholestasis. (UK Label)
- Nausea, headache & sleepiness. May interfere with driving ability
- Problems with patient compliance.
- Uncomfortable if there is bleeding or discharge & may be washed out if bleeding is severe.
- Irritation, discharge & allergies in 10.5% (Chakravarty et al, 2005)
- OR of 3.7 (95% CI, 2.3-6.0) for hypospadias (Carmichael et al, 2005)

Dose

Relative Doses

Compound	Dose
Duphaston	30mg
Crinone	90mg
Utrogestan	600mg
Endometrin	300mg
Prometrium	600mg
Cyclogest	800mg

Compound	Vehicle
Gestone	100mg
Proluton	250mg
Prontogest	100mg
Prolutex	25mg

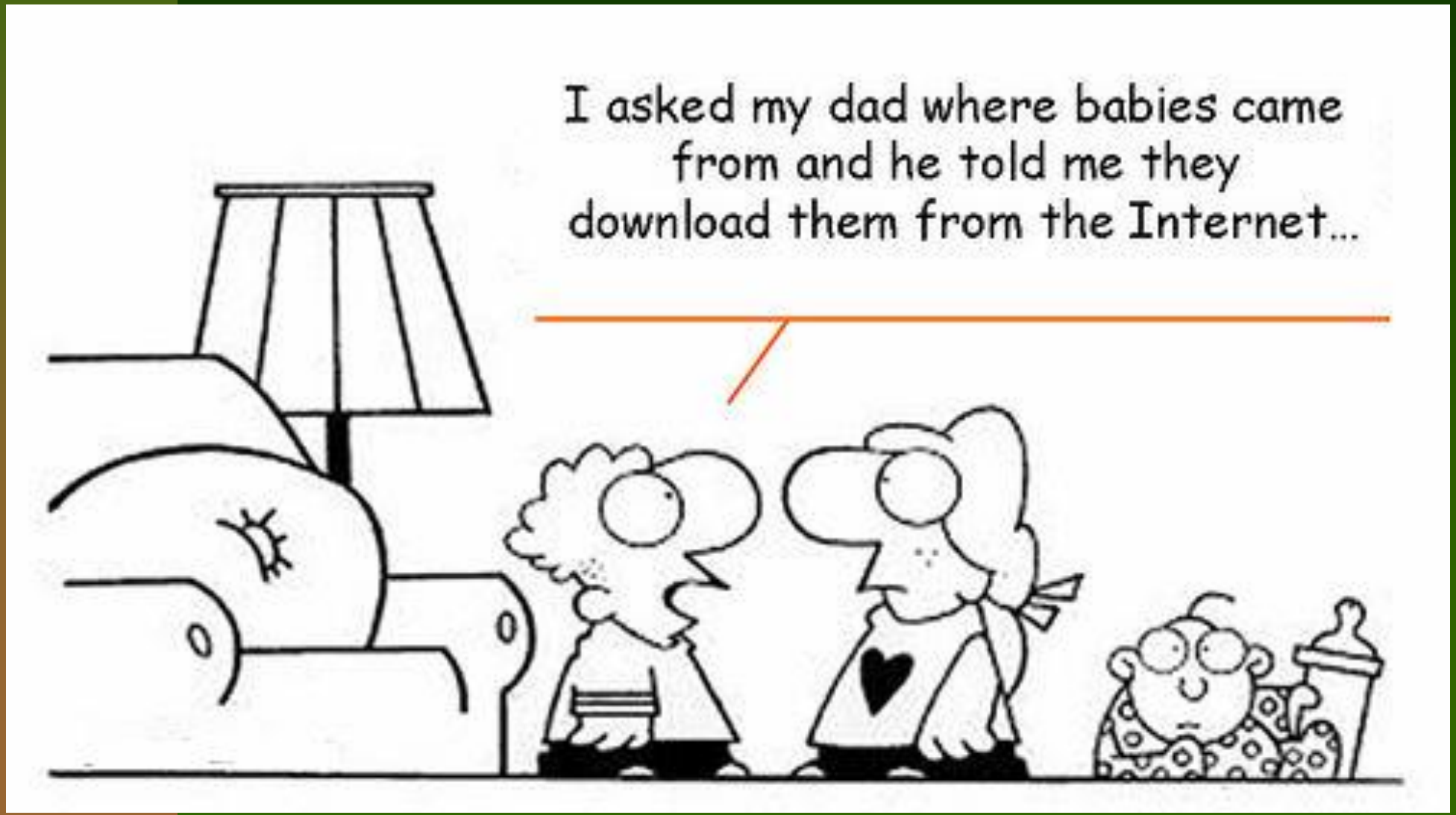
Increasing Dose in Frozen-Thawed Cycles

(Orvieto et al, 2007; Alsbjerg et al, 2013)

ART

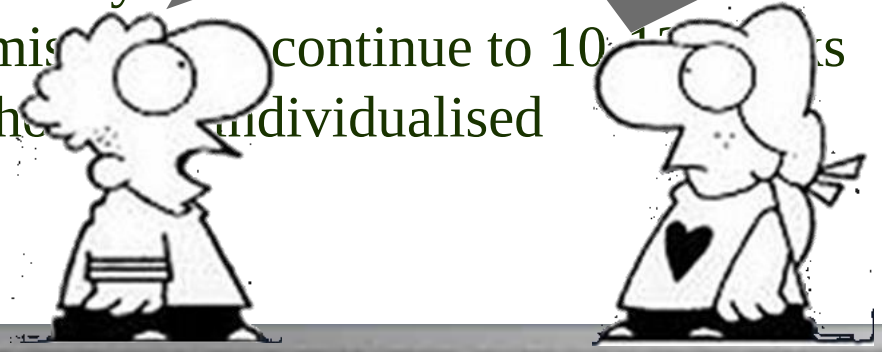
- Comparing outcomes after IM progesterone or VMP for luteal support

	Orvieto et al, 2007			Alsbjerg et al, 2013		
	IM 50mg VMP 200mg	IM 100mg VMP 400mg	p	VMG 90mg	MVG 180mg	p
CPR	5/63 7.9%	12/29 41.4%	<0.001	43/161 26.7%	71/185 38.4%	0.021
Live Births				14/161 8.7%	38/185 20.51%	**0.002**


I asked my dad where babies came from and he told me they download them from the Internet...

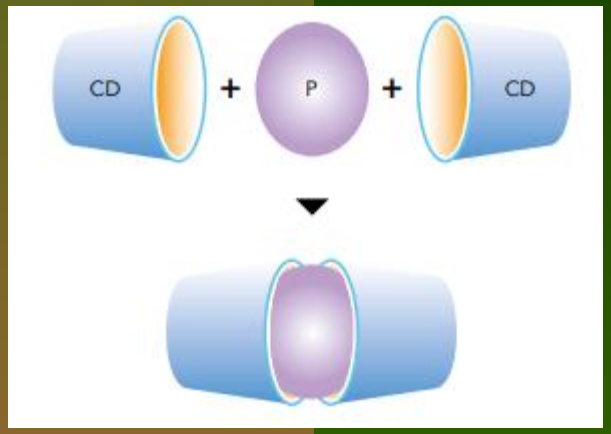
- Luteal phase progestog
  live birth rates, but
- Progestogens are
  ovulation protoc
- Dydrogesterone h
  and prevention of m
- If side effects of proges
- Start on day of OPU c
- Stop at pregnancy te
- To prevent mis continue to 10
- Treatment sh individualised

Thank You For Listening



Subcutaneous / Rectal Progesterone

ART



- SC route. Progesterone made water soluble be enclosing in cyclodextran with hydrophilic exterior & hydrophobic interior
- 2 studies of 1465 participants OR 0.92 (CI 0.74, 1.14) (Van Der Linden et al, 2015)
- 2 studies of rectal administration. 328 patients (OR 1.58 95% CI 1.004 – 2.496)
- Aghsa et al, (2012) Cyclogest 800mg, Krief et al, (2016) MVP 600mg

Dydrogesterone Exposure & CHD (2)

(Zaqout et al. 2015)

- Questionnaire included maternal age, previous pregnancies, consanguinity, family history of CHD & latest pregnancy
- Detailed history regarding usage of medications during pregnancy including dydrogesterone.
- No information when medication started

Lesions	Not exposed		Exposed		Total
VSD	37	29%	19	28%	56
ASD	23	18%	14	18.6%	37
TOF	11	8.6%	7	9.3%	18
TGA	6	4.7%	8	10.6%	14
PDA	11	8.6%	5	6.6%	16
VPS	12	9.4%	5	6.6%	17
AVSD	4	3.1%	2	2.6%	6
DORV	4	3.1%	2	2.6%	6
TAPVD	3	2.3%	1	1.3%	4
CoA	5	3.9%	5	6.6%	10
AoS	4	3.1%	2	2.6%	6
PA	3	2.3%	0	0%	3
Shone complex	1	0.8%	4	5.3%	5
TA	3	2.3%	1	1.3%	4
Total	127		75		202

	Value	df	*P* value
Pearson Chi-square	10.384	13	0.662

CHD in Gaza Strip

(Abed et al, 2014)

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Full Length Research Article

COMPARATIVE STUDY OF MAJOR CONGENITAL BIRTH DEFECTS IN CHILDREN OF 0-2 YEARS OF AGE IN THE GAZA STRIP, PALESTINE

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- In the Gaza strip, congenital malformations are the first leading cause of infant deaths. We collected the records of children between 0 and 2 years admitted with major structural birth defects (BD) in the major pediatric hospitals of the Gaza Strip. Congenital heart diseases (CHD) are the most common reported BD.

Estrogen

Estrogen Support (1)

- Lower pregnancy rates observed with lower luteal phase estradiol to progesterone ratios (Sharara & McClamrock, 1999).
- Early metaanalyses (Kolibianakis et al, 2008; Jee et al, 2010) showed no statistically significant differences in CPR between patients receiving additional estradiol to progesterone alone.
- Elgindy et al. (2010) randomized 270 patients undergoing ICSI in long agonist protocols to 3 arms. All patients received intramuscular progesterone (100 mg daily). No estrogen, oral estradiol valerate 6 mg daily & estradiol valerate 6 mg PV.
- No difference in CPR between progesterone only, & oral E2, but higher pregnancy rates were observed in patients supplemented with vaginal estradiol valerate 6 mg daily.

Estrogen Support (2)

- Lin et al, (2013) RCT of 402 patients undergoing IVF with GnRH-agonists. 2 groups. IM progesterone (60 mg/day) & oral estradiol valerate (6 mg od) or IM progesterone alone. No differences with respect to CPR, live-birth rate, or miscarriage rate.
- Supplementation of progesterone with oral estrogen did not influence live births or ongoing pregnancy rates, but benefit from transdermal or oral & transdermal estrogen supplementation is suggested.
- Findings for supplementation of progesterone with vaginal oestrogen were inconsistent (Van der Linden et al, 2015).

Estrogen Support

(Zhang et al, 2015; Van Der Linden et al, 2015)

Study name	Statistics for each study					
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Var (2011)	2.476	1.316	4.658	2.812	0.005	12.33
Moini (2011)	1.614	0.721	3.613	1.164	0.244	10.52
Elgindy (2010)	1.629	0.949	2.795	1.772	0.076	13.31
Engmann (2008)	0.577	0.310	1.073	-1.738	0.082	12.45
Ceyhan (2008)	0.941	0.337	2.631	-0.116	0.908	8.49
Drakakis (2007)	3.300	1.042	10.447	2.031	0.042	7.53
Gorkemli (2004)	4.387	2.276	8.454	4.418	0.000	12.07
Farhi (2000)	1.665	0.990	2.798	1.924	0.054	13.53
Lewin (1994)	0.903	0.373	2.186	-0.225	0.822	9.77
Pooled odds ratio (by random effect model)	1.617	1.059	2.471	2.224	0.026	

0.

Q = 25.45 (df = 8) with p=0.001, I-square = 68.57