Progesterone in Obstetrics

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Back to Basics

- Progesterone – "PROGestational steroid hormone" - an essential hormone needed to maintain pregnancy
- After ovulation, endogenous progesterone is produced by the corpus luteum ,rises sharply and peaks after a week.
- If the ovum is fertilized and implants into the endometrium, the corpus luteum continues to secrete progesterone to prevent endometrial shedding, thereby protecting the developing fetus.

How Progesterone Works ?

- Favorable changes in endometrium for successful implantation & maintenance of pregnancy
- Suppresses immunity to prevent rejection of fetal cells- Nature's natural immunosuppressant
- Induces myometrial quiescence & prevents uterine contraction by suppressing cytokines, PGs & response to oxytocin

Routes Of Progesterone

- Oral - guarantees optimal compliance
  Adverse effects - nausea, headache, breast tenderness, bloating and sleepiness.

- Vaginal - higher concentrations in the uterus but does not reach high and constant blood levels
  Adverse effects – discharge & vaginal irritation in some patients

- Intramuscular - only route which results in optimal blood levels
  Adverse Effects – redness at injection site, pain inflammation & rarely abscess

(tablets, capsules, vaginal pessaries, injections and gels)

Progesterone in RPL & Threatened Miscarriages

FOGSI POSITION STATEMENT 2015

Threatened Miscarriage

- **Oral route** –Dydrogesterone 40 mg loading f/b 20-30mg daily till 7 days after bleeding stops
- **Vaginal route-** micronized progesterone- 400 mg per day till bleeding stops

FOGSI Position Statement 2015

Recurrent Miscarriage

- **Oral Route** – Dydrogesterone 10mg BD till 20 weeks of pregnancy
- **Vaginal route** – Micronized Progesterone 400 mg/day till 20 weeks of pregnancy
- Both (Micronized Progesterone & Dydrogesterone) – derived from plant source, closely related to endogenous progesterone

PROMISE
(PROgesterone in MIScarriagE)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Progesterone in Women with Recurrent Miscarriages

N Engl J Med 2015;373:2141-8.
DOI: 10.1056/NEJMoa1504927

Women with unexplained RM, received either micronized progesterone at a dose of 400 mg (200 mg bd vaginally) or placebo, from soon after a positive UPT (and no later than 6 weeks of gestation) until 12 weeks of gestation

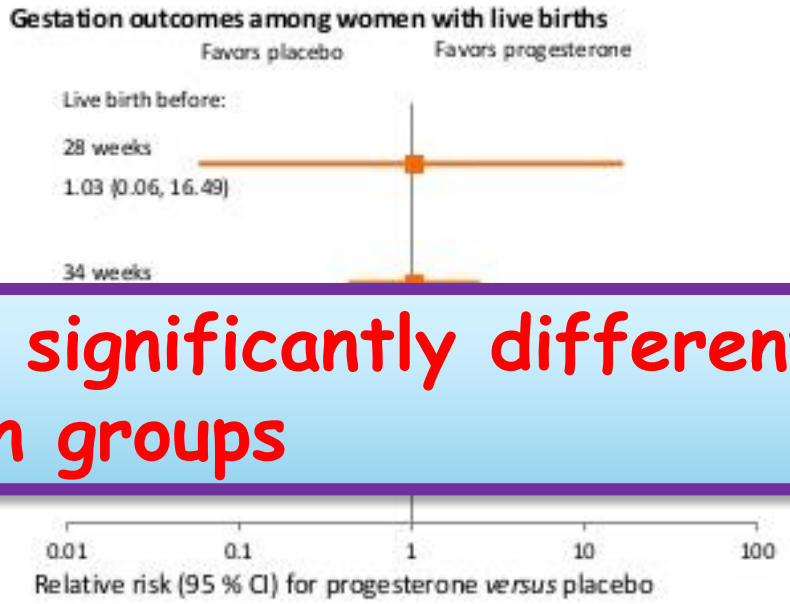
EFFICACY RESULTS

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)

Live birth rate was not significantly different between groups

- ongoing pregnancy (at 12 weeks)
- ectopic pregnancy
- miscarriage
- stillbirth
- neonatal outcomes



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

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

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

Conclusions: No evidence that first-trimester progesterone therapy improves outcomes in women with a history of unexplained RM.

Limitations: did not explore the effect of treatment with other progesterone preparations

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

Ashok Kumar, M.D., Ph.D.,[a] Nargis Begum, M.Sc., Ph.D.,[a] Sudha Prasad, M.D.,[a] Sarita Aggarwal, M.D.,[b] and Shashi Sharma, Ph.D.[c]

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Fertil Steril® 2014;102:1357–63.

Women with unexplained RM, received either DYDROGESTRONE 20 mg/day or placebo, from confirmation of pregnancy until 20 weeks of gestation

Efficacy Results
Kumar et al. 2014

Pregnancy outcome

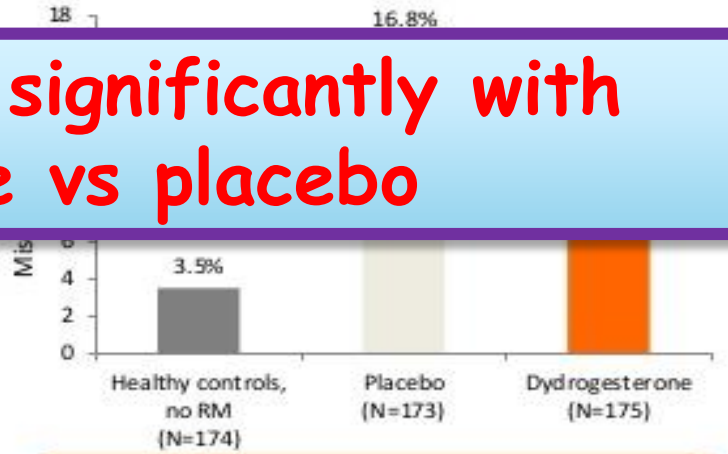
Miscarriage rate decreased significantly with use of dydrogesterone *versus* placebo

- 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

Miscarriage rate decreased significantly with use of Dydroesterone vs placebo

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

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

Safety of Progesterone

- Available evidence strongly supports safety of progesterone in pregnancy
- No reported teratogenecity or serious maternal side effects
- PREDICT trial – no difference in neuro developmental milestones between progesterone & placebo group
- Caution - cardiovascular disease, liver disease & cholestasis

Conclusion

- no evidence of harm
- some evidence of benefit (not from huge multicentric trials)
- Clinician's discretion - until strong evidence is available
- No role of progesterone supplementation in normal healthy pregnant women for prevention of miscarriage

Preterm Labour

Predictors of preterm labour-

- Prev h/o PTL
- Multiple pregnancy
- Advanced maternal age
- Obesity
- Uterine abnormalities
- STDs

History of spontaneous preterm birth - one of the strongest predictors

Progesterone in Preterm Labour

- "GATE KEEPER" of pregnancy
- Functional Withdrawal, leads to ripening of cervix
- Significant role in prevention than in treatment

NICE recommendations

- Consider prophylactic vaginal progesterone

- h/o spontaneous preterm birth (up to 34+0 weeks of pregnancy) or mid trimester loss (from 16+0 weeks of pregnancy onwards)

or

- CL of 25 mm or less on tvs between 16+0 and 24+0 weeks of pregnancy

- Offer as an alternative to cervical cerclage who have both, discuss risk & benefits of both options

- Start treatment between 16+0 & 24+0 weeks

NICE RECOMMENDATIONS

Consider prophylactic Cervical Cerclage when CL, between 16-24 weeks is 25mm or less

AND

- Preterm Prelabour ROM (P-PROM) in a previous pregnancy

or

- History of Cervical trauma

SMFM guidelines (AJOG 2012)

Population	Recommendation regarding use of progestogens
Asymptomatic	
Singletons without prior SPTB and unknown or normal TVU CL	No evidence of effectiveness
Singletons with prior SPTB	17P 250 mg IM weekly from 16-20 wk until 36 wk
Singletons without prior SPTB but CL ≤20 mm at ≤24 wk	Vaginal progesterone 90-mg gel or 200-mg suppository daily from diagnosis of short CL until 36 wk
Multiple gestations	No evidence of effectiveness
Symptomatic	
PTL	No evidence of effectiveness
PPROM	No evidence of effectiveness

Which molecule to prefer in which conditions?

N. Micronized Progesterone

Or

17-Hydroxyprogesterone Caproate (17-OHPC) (synthetic)

	Progesterone	17-Hydroxyprogesterone Caproate
Clinical indications		
History of preterm birth	Yes	Yes
Short cervical length	Yes	No

Dose of 17-OHPC- 250 mg or 500 mg ??

No data to provide guidance on Optimal dose

MFMU trial by Meiss et al 2003– 250 mg weekly 17OHPC, reduced recurrent spontaneous PTB by 33%

AJOG,FEB 2014 – Effectiveness of 17-OHPC may be influenced by plasma concentration, higher PTB with lower concentration

Planned Study- To compare effect of 250 & 500 mg doses

7-31-2019 cinictrials.gov

Relationship between Plasma Concentration of 17-hydroxyprogesterone caproate (17-OHPC) and Preterm Birth

Protocol version 3.2

PTL in MULTIPLE PREGNANCY

- Recent Systemic Review & Meta analysis including STOPPIT trial - Progesterone supplementation does not prevent preterm birth in Multiple Pregnancy

- One meta analysis showed benefit in Multiple Pregnancy with short cervix <=25mm.

  Numbers were small hence further research is needed

17OHPC:Side Effects & Precautions

- Thrombosis & thromboembolism – Discontinue
- Allergic Reaction – consider discontinuing
- Decreased Glucose Tolerance- Monitor PreDiabetic & Diabetic
- Fluid Retention–increased monitoring- Preeclampsia, Cardiac & Renal dysfunction
- Depression – Monitor women with h/o depression, Discontinue if depression occurs

Conclusion

- Due to huge financial burden involved ,using progesterone to prevent preterm labour in women with definite history of sPTB & those with accidental short CL on routine screen would be a safer bet as it is cheap, easily available & without any serious threat to mother or fetus

- Further randomized trials - are needed in Multiple birth


Thank
you