



DR CHARLEY ZHENG, GYNAECOLOGIST AND FERTILITY

# Progesterone for miscarriage an update

## Aetiology

90% of miscarriages are due to chromosomal aneuploidies in the fetus. Anatomical pathologies, acquired thrombophilias, metabolic conditions, endocrine disorders, infections, male factors as well as lifestyle factors all influence and are known causes of miscarriage. Autoimmunity may be a cause – but this is controversial. As more miscarriages occur – and especially in a younger woman – aneuploidy becomes less likely as the cause of the miscarriages.

## Why progesterone?

Progesterone is critical for successful implantation and maintenance of pregnancy. It decidualises the endometrium and has immunomodulatory effects to facilitate implantation. It is readily available and costs approximately \$100/ month in Australia. In its micronized form (natural progesterone) given vaginally, it is safe. Oral synthetic progesterone may interact with androgenic receptors, concerns were raised with female foetuses, but larger studies following initial concerns dispelled this worry.

## Who?

Miscarriage is a stressful period for a couple, and often the woman will place great emphasis and remember this event for the rest of her life. Clinicians often are compelled to treat the woman, whether it's to prevent a recurrent miscarriage, or when a threatened miscarriage is looming. In assisted reproduction, due to defective corpus lutea – progesterone is always given as luteal phase support in a fresh IVF cycle – or otherwise as a part of a programmed hormone replacement cycle due to a lack of corpus luteum. Vaginal progesterone works locally, and it is not known what is an adequate amount needed based on serum measurements.

## New insights

In 2015, the long-awaited PROMISE Trial was published in the NEJM. It was a double blinded multicentre RCT, and convincingly proved that progesterone did not increase live births >24 weeks for patients with unexplained recurrent miscarriage. With 400 patients in each arm, this was the largest RCT conducted to date and carries the most weight in all metaanalysis within this field.

It followed then that the Royal Australian College of Obstetricians and Gynaecologists, as well as the European Society of Human Reproduction and Embryology in its guidelines in 2017 did not support the use of progesterone in recurrent miscarriage.

Roll forward another year to 2018. Another large double blinded RCT (350 in each arm), though this time from a single centre (Ismail 2018), the primary outcome though was miscarriage rate. They demonstrated with a relatively tight confidence interval, that there was a reduction in miscarriage rate from 23.3% to 12% ( $P < 0.001$ ). The live birth rate was a secondary outcome, but also did show statistical improvement. This now combined in a new 2018 Cochrane review refuted the PROMISE trial outcomes, and support is revived for progesterone. Both the PROMISE trial and Ismail 2018 used vaginal estrogen. Interestingly, Ismail's trial started progesterone in the luteal phase even before a confirmed pregnancy.

In May 2019, the PRISM trial outcomes were released. This trial by the same authors as PROMISE evaluated progesterone for threatened miscarriage. This again was a very well designed RCT, achieving the power calculations needed and with clearly defined end points. 2000 patients participated in each arm. Again, this trial did not show any statistical difference in the live birth rates. Subgroup analysis however did suggest a benefit for women with recurrent miscarriage who had a threatened miscarriage.



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## Summary of recent large Randomised Controlled Trials and Systematic Reviews

Trial Name	Trial Details	Results	Findings
2015 Coomarasamy PROMISE	Double blind, placebo controlled RCT  836 women with unexpl RMC	Live birth rate was 65.8% (prog) vs 63.3 (placebo) CI 0.94-1.14 (P=0.45)	Main discussion:  - When should Prog be started  - What route?/dose
2018 Ismail Periconceptional progesterone treatment in women with unexplained RMC	Double blind, placebo controlled RCT  700 women with unexpl RMC	Miscarriage rate 12.2% (Prog) Vs 23.3% (placebo) CI: 0.24-0.58 (P<0.001)	The Progesterone was started before conception.
2019 Coomarasamy PRISM	Double blind, placebo controlled RCT 4153 women with bleeding in early pregnancy (<12weeks)	Live birth rate (>34 weeks) was 75% (prog) vs 72% (placebo) CI 1-1.08 (P=0.08)	Miscarriage rate again no difference. In subgroup analysis, those with > 3 past miscarriages was 72% vs 57% CI 1.08-1.51
2018 Haas Cochrane – Progesterone for preventing miscarriage	Cochrane Systematic review. 2556 women, 13 trials dating back to 1953	Live birth rate increased with progesterone RR 1.11 (CI 1.00 – 1.24)  Miscarriage rate reduced 19.4% vs 26.3% CI (0.51-0.92)	High clinical heterogeneity -68%. But not statistical heterogeneity. May not show same difference if PRISM data was now added

## Conclusions

Because most miscarriages are due to chromosomal aneuploidy, progesterone support would not help most miscarriages. In physiologically abnormal states, such as in assisted reproductive treatments, hypothyroidism/hyperprolactinemia (including breast feeding), there is benefit in progesterone supplementation.

In my interpretation of the data we have to date, I would suggest still considering progesterone support starting prior to conception in those with unexplained recurrent miscarriage. And most definitely in those with recurrent miscarriage who experiences bleeding. In the absence of any known harm, it is reasonable to counsel our patients and give them this choice.

### Dr Charley Zheng

Dr Charley Zheng is an obstetrician, gynaecologist and fertility specialist with interests in advanced laparoscopy, endometriosis, poor responders (IVF), recurrent miscarriage and medical problems in pregnancy.

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