COMMENTARY

# Did the NICE guideline for progesterone treatment of threatened miscarriage get it right?

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## Abstract

In November 2021, NICE updated its clinical guideline that covers the management of threatened miscarriage in the first trimester. They recommended offering vaginal micronised progesterone twice daily until 16 completed weeks of pregnancy in those with a previous miscarriage. However, the duration of treatment is not evidence based. In the major clinical trial that informed the guideline, there was no benefit in starting progesterone after 9 weeks and the full effect of progesterone was present at 12 weeks of pregnancy. There are theoretical risks impacting offspring health in later life after maternal pharmaceutical progesterone treatment. As the effect of progesterone seems to be complete by 12 weeks of gestation, we should consider carefully whether to follow the guidance and treat up to 16 weeks of pregnancy.

## Lay summary

In November 2021, new guidelines were published about the management of bleeding in early pregnancy. If someone who has had a previous miscarriage starts bleeding, they should now be treated with progesterone as this slightly reduces the chance of miscarriage. The guideline says progesterone should be given if the pregnancy is in the womb, and potentially normal, until 16 weeks of pregnancy. However, in the big studies looking at progesterone's effect in reducing miscarriage the beneficial effects of progesterone were complete by 12 weeks of pregnancy. At that stage, it is the placenta and not the mother's ovary that makes the progesterone to support the pregnancy. We do not know the long-term effects of giving extra progesterone during pregnancy on the offspring. Some research has raised the possibility that there might be some adverse effects if progesterone is given for too long. Maybe the guidance should have suggested stopping at 12 weeks rather than 16 weeks of pregnancy.

**Key Words:** ▶ luteal support ▶ gestation ▶ pessary ▶ bleeding ▶ pregnancy

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## Commentary

The NICE guideline (NG126) 'Ectopic pregnancy and miscarriage: diagnosis and initial management' was updated on 24 November 2021 (https://www.nice.org.uk/guidance/ng126). The major change in this guideline was in the management of threatened miscarriage. NICE now recommend to 'offer vaginal micronised progesterone 400 mg twice daily to women with an intrauterine pregnancy confirmed by a scan, if they have vaginal bleeding and

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have previously had a miscarriage' and 'if a fetal heartbeat is confirmed, continue progesterone until 16 completed weeks of pregnancy'. They recognised that this was an off-label use of vaginal micronised progesterone.

In the evidence review used to develop this recommendation, the study providing the highest weight (98.8%) to the metanalysis was the PRISM trial (Coomarasamy *et al.* 2019). PRISM was a multicentre double-blind randomised placebo-controlled clinical trial where women (age 16–39) with early pregnancy bleeding and a potentially viable pregnancy were randomised to progesterone treatment or matched placebo. It is the PRISM trial protocol, which required a scan-confirmed intrauterine pregnancy and treatment with 400 mg twice daily vaginal micronised progesterone up until 16 weeks of pregnancy, that informed the NICE guidance.

Although the primary analysis of that trial did not show that progesterone therapy resulted in a significantly higher incidence of live births (RR: 1.03, 95% CI: 1.00–1.07, $P = 0.08$) a planned subgroup analysis suggested a benefit in those with ≥3 miscarriages (RR: 1.28, 95% CI: 1.08–1.51). However, the majority (55.4%) of trial participants had no previous miscarriage and there was absolutely no benefit of progesterone in this group (live birth: placebo 74.5%, progesterone 74.2%; RR: 0.99, 95% CI: 0.95–1.04). When the group without a previous miscarriage was removed, *post hoc* analysis showed if there was any number of previous miscarriages there was a significant benefit of progesterone therapy (livebirth: placebo 70%, progesterone 75%; RR 1.09, 95% CI 1.03–1.15, $P = 0.003$). The committee felt that the important size effect and *post hoc* subgroup analysis were robust enough to inform the recommendation (https://www.nice.org.uk/guidance/ng126/evidence/evidence-review-c-pdf-10889099534).

The source of progesterone support for pregnancy is endocrine, coming from the corpus luteum of the maternal ovary, until 9 weeks of gestation and uterine, coming from the fetal placenta, after 9 weeks of gestation (Duncan 2021). There was no good evidence base for the duration of progesterone treatment in threatened miscarriage. In the PRISM trial (Coomarasamy *et al.* 2019), the treatment window until 16 weeks was chosen based on a consensus of UK clinicians with the premise that if there is a deficit in progesterone production it might be from the placenta as well as the corpus luteum of the maternal ovary (https://www.nice.org.uk/guidance/ng126/evidence/evidence-review-c-pdf-10889099534).

However, there is evidence for the duration of treatment that comes from the PRISM trial itself (Coomarasamy *et al.* 2019). Overall, there was a 75% live birth at ≥34 weeks in the progesterone arm and a 72% live birth at ≥34 weeks in the placebo arm. This 3% difference between groups was seen at ongoing pregnancy rates at 12 weeks gestation (83% progesterone and 80% placebo). This suggests that any effect was fully manifest before 12 weeks gestation. Indeed, if treatment was started ≥9 weeks of gestation, there was no effect of progesterone supplementation (RR: 0.98, 95% CI: 0.94–1.03). If treatment was started <9 weeks gestation, progesterone supplementation did have an effect (RR: 1.15, 95% CI: 1.03–1.28; $P = 0.012$). This suggests that the effect might be before the luteoplacental shift at 9 weeks of gestation (Coomarasamy *et al.* 2019).

There is further evidence from the PROMISE trial where vaginal micronised progesterone (400 mg twice daily) was given from a positive pregnancy test until 12 weeks of gestation in those with recurrent miscarriage (Coomarasamy *et al.* 2015). That trial did not show a significant difference for live birth after 24 completed weeks of pregnancy (RR: 1.04, 95% CI 0.94: –1.15, $P = 0.45$). In fact there was no difference at all in the subgroup of those with $n = 3$ previous miscarriages (live birth: placebo 67.4%, progesterone 67.9%; RR: 1.01 95% CI: 0.89–1.14, $P = 0.91$). It was powered to detect a 10% increase in live birth after progesterone treatment. Although in all subgroup analysis, the difference of 2.5% between the progesterone group (65.8%) and control (63.3%) was not significant it was similar to that seen in the PRISM trial (Coomarasamy *et al.* 2019). Interestingly that difference was already manifest at 8 weeks gestation (placebo 78.0% and progesterone 81.9%). This also suggests that any effect of progesterone supplementation in early pregnancy to prevent miscarriage might occur before the luteoplacental shift at 9 weeks gestation.

Although the effect might be manifest before the luteoplacental shift and thus be complete by 12 weeks of gestation are there any problems with continuing progesterone treatment until 16 weeks? Although there have been some concerns about progestogens increasing the risk of hypospadias in some studies (Carmichael *et al.* 2005), this was not seen in the PRISM and PROMISE studies and it is likely that natural progesterone is not associated with an increase in congenital abnormalities (Coomarasamy *et al.* 2015, 2019). However, prenatal fetal exposure to steroids is a Goldilocks phenomenon where too much or too little hormone is detrimental and it has to be just right. There is evidence of fetal programming of adult disease by excess estrogens, androgens and glucocorticoids, which are all normal hormones present during pregnancy (Diamanti-Kandarakis *et al.* 2009).

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Progesterone may be no different. There is animal data suggesting fetal effects of natural progesterone on neural function. In a clinically realistic ovine study, administration of natural progesterone to the mother, until the equivalent developmental stage of 15–16 weeks in humans, increased male fetal progesterone concentrations (Siemienowicz *et al.* 2020). Progesterone receptors were found in the developing brain, and maternal progesterone treatment had functional effects on the male fetal hypothalamus and pituitary (Siemienowicz *et al.* 2020). In population studies of autism spectrum disorder (ASD) to examine if there was a link to *in vitro* fertilisation (IVF), it was reported that there was no association with IVF but maternal progesterone hormone treatment was associated with an increased risk of ASD (RR: 1.51, 95% CI: 1.22–1.86) (Davidovitch *et al.* 2018). A small case-control study linked maternal progesterone exposure to the sexual orientation of offspring (Reinisch *et al.* 2017).

The effect of progesterone on neural function is well recognised although its effect on the developing brain is not well researched. In the animal study (Siemienowicz *et al.* 2020), long-term data are not available and the human studies may have recall bias, different progesterone preparations and are limited to the association rather than causation. However, there is a biologically plausible potential impact of maternal therapeutic progesterone supplementation and a longer-term impact on offspring health, not evident at birth. It, therefore, seems sensible to limit pharmaceutical progesterone exposure in early pregnancy to those pregnancies that may benefit for as short a time as possible. NICE have made a considered call about the utility of progesterone supplementation in threatened miscarriage with those with a previous miscarriage based on *post hoc* analysis. Perhaps the duration of progesterone supplementation should also be considered using *post hoc* analysis, and in this regard, there is no reason to use progesterone supplementation until 16 weeks and theoretical reasons why it might be harmful.

Treatment with progesterone should be for as short a duration as is required to see maximum effects. It is possible that progesterone supplementation may not have many effects after the luteoplacental shift at 9 weeks gestation. In threatened miscarriage, it is likely that there are no ongoing effects beyond 12 weeks of gestation when progesterone support has switched to the placenta. We need to reconsider the guidance on continuing pharmacological progesterone treatment until 16 completed weeks of pregnancy.

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