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REVIEW

A review of conventional and sustained-release formulations of oral natural micronized progesterone in obstetric indications

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Abstract

Background: Exogenous progesterone is a treatment option for obstetric indications associated with reduced progesterone activity. Oral natural micronized progesterone (NMP) is effective, although it requires multiple daily doses and may cause adverse events due to its active metabolites. A sustained-release formulation of NMP (NMP-SR) has been developed to overcome the limitations of conventional oral NMP.

Methods: This narrative review examines the available evidence for oral NMP and NMP-SR in several obstetric indications of interest.

Results: Literature searches identified 17 studies of oral NMP (luteal phase support during assisted reproduction, prevention of threatened miscarriage, prevention of preterm delivery), and clinical studies supporting use of NMP-SR (luteal phase support during intrauterine insemination, maintenance of high-risk pregnancy). Oral NMP was effective for luteal phase support during *in vitro* fertilization and intrauterine insemination, prevention of threatened miscarriage, and prevention of preterm delivery. NMP-SR was comparable to dydrogesterone for luteal phase support during intrauterine insemination and effectively maintained high-risk pregnancies. Oral NMP-SR was well tolerated.

Conclusions: By releasing progesterone gradually and circumventing first-pass metabolism, NMP-SR elicits the desired therapeutic effect with benefits over conventional oral NMP in terms of bioavailability, once-daily dosing and improved tolerability. Oral NMP-SR appears to be a valuable option for treating obstetric conditions associated with insufficient progesterone exposure.

Keywords: high-risk pregnancy, luteal support, natural micronized progesterone, preterm labour, sustained-release formulations, threatened miscarriage.

Citation

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Introduction

Progesterone is essential for the female reproductive cycle, having roles in the menstrual cycle, blastocyst implantation and maintenance of pregnancy.[1,2] During the luteal phase of the menstrual cycle after ovulation, progesterone is secreted by the corpus luteum and instigates secretory transformation of the endometrium into an implantation-receptive state.[2] Progesterone continues to be produced during pregnancy, where it is involved in modulating the maternal immune response, reducing uterine contractility, and regulating the uteroplacental circulation, thus contributing to the maintenance of pregnancy.[1]

Insufficient exposure to progesterone to enable normal secretory transformation of the endometrium and implantation (luteal phase deficiency) is associated with infertility and early pregnancy loss.[2,3] Luteal phase deficiency also occurs following controlled ovarian stimulation used in assisted reproduction, with potentially adverse effects on implantation in this setting.[2] Later, in established pregnancy, a functional withdrawal of progesterone activity within the uterus is associated with onset of labour, whether at term or preterm.[4]

Exogenous progesterone is used to treat various obstetric conditions associated with reduced progesterone activity. Progestogens widely approved for use in pregnancy include natural progesterone and the synthetic progestogens 17-α-hydroxyprogesterone caproate (17OHP-C) and dydrogesterone. Synthetic progestins mimic some of the effects of progesterone but have variable affinities for other steroid receptors (androgen, glucocorticoid, and mineralocorticoid receptors), which result in differential progestogen activity and safety profiles.[5]

The most common routes for delivery of progesterone in the obstetric field are intramuscular (IM), vaginal and oral.[1] 17OHP-C is administered by IM injection[6] and dydrogesterone is administered orally.[7] Since the early 1990s, natural progesterone for exogenous administration has been formulated in micronized particles to enhance its bioavailability after oral administration.[8] Despite this advancement, oral natural micronized progesterone (NMP) requires multiple daily doses due to first-pass metabolism and is associated with adverse events (e.g. drowsiness and/or dizziness) due to active metabolites.[8] A sustained-release formulation (NMP-SR) has been developed to overcome the limitations of oral NMP. NMP-SR has a better tolerability profile than conventional oral NMP and is more bioavailable, permitting once-daily dosing.[9]

This narrative review examines available evidence from clinical studies investigating oral NMP and oral NMP-SR in obstetric indications. Indications of interest were assisted reproduction, recurrent or threatened miscarriage, preterm birth, and high-risk pregnancy.

Literature search

Searches were performed in PubMed and Cochrane Register from inception of each database to 17 September 2019 using the words 'micronized progesterone', 'micronised progesterone', and 'oral'. All records (*n*=295 for 'micronized progesterone' and 'oral'; *n*=29 for 'micronised progesterone' and 'oral') were examined to identify relevant articles for inclusion. Systematic reviews identified in searches were reviewed for additional studies. No restrictions were applied for language or geographical location. The searches identified 17 studies of oral NMP and 3 studies of NMP-SR. Depending on study methodology (e.g. randomized controlled trial (RCT) or observational study), oral NMP or NMP-SR were compared with no treatment, placebo, other progesterone formulations (vaginal, IM), or oral dydrogesterone or were investigated alone. The results were tabulated and are reported narratively per obstetric indication.

Review

Natural micronized progesterone

Historically, the oral route of administration was not used for natural progesterone due to its poor absorption and a marked first-pass effect, which limited its bioavailability.[8] However, it was discovered that the efficiency of oral delivery could be improved by using a micronized form of the hormone.[8] Reducing the particle size of progesterone to <10 µm increased the available surface area and improved the dissolution rate and intestinal absorption.[10] Suspending NMP in oil within a gelatin capsule further improved intestinal absorption.[10]

In pharmacokinetic studies, physiologically relevant plasma progesterone concentrations were achieved and remained elevated for up to 12 hours after administration of ≥100 mg oral NMP in three divided doses.[8]

NMP-SR was developed soon thereafter. Designed on 'EROMAT technology', the sustained-release formulation utilizes a hydrophilic matrix polymer that releases micron-sized particles of progesterone in a controlled manner over 16–24 hours. This gradual release of progesterone, together with a prolonged elimination half-life of 18 hours[11] and high protein binding (90–99%), maintains serum progesterone concentrations in the luteal phase range (i.e. ≥14 ng/mL) with once-daily dosing.[9] After once-daily doses of NMP-SR 200, 300 or 400 mg for 7 days, mean mid-luteal serum progesterone concentrations of 20.6, 36.1 and 46.2 ng/mL, respectively, were measured.[9,12] The controlled release of drug particles during intestinal transit facilitates lymphatic absorption of intact drug into the systemic circulation from the small intestine and direct entry of the drug into the systemic circulation via the mucosal lining of the colon. By circumventing first-pass metabolism, active circulating drug elicits the desired therapeutic effect while minimizing the risk of metabolite-related adverse effects.[9] In this manner, NMP-SR overcomes the limitations of conventional oral NMP.

Luteal phase support during assisted reproduction

In vitro fertilization

Progesterone supplementation is used for luteal support after *in vitro* fertilization (IVF).[2] In this setting, progesterone is predominantly administered as a vaginal preparation, although prescribing preferences may differ by geographical region.[2,13] A meta-analysis of RCTs found that neither the route of administration of progesterone (IM, vaginal, oral) nor progestogen type (micronized progesterone or synthetic) affected the outcome of luteal phase support for assisted reproduction techniques (ARTs), including IVF and intracytoplasmic sperm injection (ICSI), with respect to live birth/ongoing pregnancy, clinical pregnancy, or miscarriage rates.[14]

The results of RCTs evaluating oral NMP after IVF have been mixed (Table 1). Supplementation with oral NMP after IVF significantly increased luteal phase serum progesterone levels and prolonged the duration of the luteal phase compared with no supplementation.[15] Two studies comparing oral and vaginal NMP found similar rates of clinical pregnancy and ongoing pregnancy with either approach,[16,17] although one study reported a significantly lower implantation rate with oral versus vaginal NMP.[17] A prospective randomized study that compared oral NMP and IM progesterone for luteal support in patients undergoing IVF found that, while the implantation rate was lower with oral NMP, the clinical pregnancy rate did not differ significantly.[18] A case–control study reported that a combination of oral plus vaginal NMP provided a similar rate of

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Table 1. Studies evaluating oral natural micronized progesterone and oral natural micronized progesterone sustained release for luteal support during assisted reproduction.

Study	Study design/*N*	Ovarian stimulation[a]	Luteal support	Results
***In vitro* fertilization**				
Colwell and Tummon 1991[15]	RCT/39	CC + hMG	Oral NMP 200 mg qds *vs* no luteal support	Serum P levels higher in oral NMP group *vs* no-luteal-support group on days 2, 4 and 11 (all $p<0.001$) Mean ± SD duration of luteal phase longer after oral NMP (17.0 ± 1.3 *vs* 13.7 ± 3.0 days, $p<0.05$) No significant difference in ongoing pregnancy rates (20% *vs* 0%)
Pouly et al. 1996[16]	RCT/283	hMG	Oral NMP (100 mg in am, 200 mg in pm) *vs* vaginal NMP 8% (90 mg/day)	Mean ± SD blood P level higher in oral NMP group *vs* vaginal NMP group on day 8 (50.9 ± 81.9 *vs* 29.9 ± 56.4 ng/mL, $p<0.001$) No differences between oral NMP and vaginal NMP groups for rates of implantation (29.9% *vs* 35.3%), clinical pregnancy on day 30 (25.0% *vs* 28.8%), ongoing pregnancy on day 90 (22.9% *vs* 25.9%), abortion after day 90 (3.0% *vs* 11.1%), deliveries per patient (22.2% *vs* 23.0%) or deliveries per embryo transferred (11.1% *vs* 11.7%)
Friedler et al. 1999[17]	RCT/64	GnRH + hMG	Oral NMP 200 mg qds *vs* vaginal NMP 100 mg bd	No difference in serum P levels between groups in conception cycles Higher serum P levels on days 11 and 15 in oral NMP group *vs* vaginal NMP in nonconception cycles ($p=0.032$) Lower implantation rate with oral NMP *vs* vaginal NMP (10.7% *vs* 30.7%, $p<0.01$) but no significant differences in rates of pregnancy (33.0% *vs* 47.0%), miscarriage (40.0% *vs* 12.5%), or ongoing pregnancy (20.0% *vs* 41.1%)
Licciardi et al. 1999[18]	RCT/43	GnRH downregulation, FSH or hMG, or FSH + hMG	Oral NMP 200 mg tds *vs* IM P 50 mg/day	No difference in serum P levels between groups Lower implantation rate with oral NMP *vs* IM P (18.1% *vs* 40.9%, $p=0.004$) No difference in clinical pregnancy rates (45.8% *vs* 57.9%)
Tomic et al. 2011[19]	Case control/370	GnRH agonist, FSH	Oral NMP 100 mg tds + vaginal NMP 8% (90 mg/day) *vs* vaginal NMP 8% (90 mg/day)	No difference in ongoing pregnancy rate between combination of oral + vaginal NMP *vs* vaginal NMP alone (39.5% *vs* 33.5%, $p=0.48$) but lower abortion rate with combination therapy *vs* monotherapy (6.4% *vs* 15.6%, $p<0.05$)

(Continued)

Table 1. (*Continued*)

Study	Study design/*N*	Ovarian stimulation[a]	Luteal support	Results
Intrauterine insemination				
Güven et al. 2016[22]	OL, OB/591	FSH	Oral NMP 100 mg bd *vs* no luteal support	All patients had unexplained infertility Evaluation of IUI cycles that developed a single follicle Higher clinical pregnancy rate in oral NMP group *vs* no luteal support group (24.3% *vs* 15.0%, p=0.021) Higher live birth rate in oral NMP group *vs* control group (19.8% *vs* 9.8%, p=0.004)
Chi et al. 2016[23]	RET, OB/1779	Not available[b]	Oral NMP *vs* vaginal NMP *vs* DYD[b]	No difference in rates of biochemical pregnancy, clinical pregnancy, early miscarriage, or ectopic pregnancy between recipients of oral NMP *vs* vaginal NMP *vs* DYD
Malhotra and Krishnaprasad 2016[12]	OL, OB/78	CC + hMG	Oral NMP-SR 200 or 300 mg od *vs* oral DYD 10 mg bd	All patients had unexplained infertility In the first cycle, mid-luteal serum P levels of ≥ 14 ng/mL were achieved in 82.2% of oral NMP-SR recipients *vs* 78.8% of DYD recipients Biochemically confirmed pregnancy rate in the first cycle was 11% in oral NMP-SR group *vs* 30% in DYD group
Gopinath and Desai 2014[20]	OL, OB/60	Natural or stimulated (CC ± hMG)	Oral NMP-SR 400 mg/day *vs* oral DYD 10 mg bd	All patients had unexplained infertility In the first cycle, mean serum P levels were maintained at ≥ 14 ng/mL in the mid-luteal phase in 93.3% of patients (oral NMP-SR 90.0% *vs* DYD 96.7%) Overall first-cycle biochemically-confirmed pregnancy rate 5% (oral NMP-SR 6.7% *vs* DYD 3.3%) Possible reasons for the low pregnancy rate were monofollicular development in patients undergoing natural IUI cycles, a trend towards a low-motility fraction, and evaluation of the first cycle only

[a]Subsequent ovulation induction was achieved using administration of human chorionic gonadotropin.
[b]Publication in Chinese; additional details not available in English abstract.
bd, twice daily; CC, clomiphene citrate; DYD, dydrogesterone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hMG, human menopausal gonadotropin; IM, intramuscular; IUI, intrauterine insemination; *N*, number of subjects; NMP, natural micronized progesterone; OB, observational study; OL, open label; P, progesterone; qds, four times daily; RCT, randomized controlled trial; RET, retrospective; SR, sustained release; tds, three times daily.

Table 2. Studies evaluating oral natural micronized progesterone for prevention of threatened miscarriage.

Study	Study design/*N*	Treatment	Results
Marinov et al. 2004[25]	RET/68[a]	Oral NMP 200 mg bd for ≥14 days	Oral NMP administered for average of 21 days. Overall, 88% of patients were discharged from hospital with a healthy pregnancy
Turgal et al. 2017[26]	OL, RCT/60[b]	Oral NMP 400 mg/day for 4 weeks *vs* no treatment	Mean placental volume increased more in oral NMP group *vs* control group: 336% (67–1077) *vs* 141% (29–900), p=0.007 No between-group differences in mean change for gestational sac, amniotic sac, or embryonic volumes No difference between oral NMP *vs* control for secondary endpoints including live birth rate (92.9% *vs* 96.4%, p=0.55) and mean gestational age at delivery (38.0 ± 2.8 *vs* 38.5 ± 1.6 weeks, p=0.46)
Siew et al. 2018[27]	OL, RCT/118[c]	Oral NMP 200 mg bd *vs* Oral DYD 10 mg bd, both for 2 weeks	No difference between oral NMP and oral DYD groups for miscarriage rate at ≤16 weeks (10.2% *vs* 15.2%, p=0.581) No difference in extent of bleeding at days 4–10: 89.7% of oral NMP recipient *vs* 96.6% of DYD recipients reported similar/less/resolved bleeding *vs* baseline, p=0.272

[a]Women with first or second consecutive threatened spontaneous abortion in the first trimester. Published in Bulgarian; additional details not available in English abstract.
[b]Women with single intrauterine pregnancy with live embryo at 6–<9 weeks' gestation and vaginal bleeding, with/without abdominal pain, with closed cervix, and no history of recurrent miscarriage.
[c]Women with single intrauterine pregnancy at 6–10 weeks' gestational age and vaginal bleeding, and no history of recurrent miscarriage (≥3 consecutive miscarriages).
bd, twice daily; DYD, dydrogesterone; *N*, number of subjects; NMP, natural micronized progesterone; OL, open label; RCT, randomized controlled trial; RET, retrospective.

ongoing pregnancy but a lower abortion rate to that seen with vaginal NMP alone.[19]

Intrauterine insemination

Intrauterine insemination (IUI) is used in the management of various types of infertility, including mild male infertility, mild endometriosis and unexplained infertility.[20] It is a relatively low-cost treatment and less invasive and psychologically demanding than IVF and ICSI procedures. IUI can be associated with pregnancy rates of 10–20% per cycle.[21]

Use of oral NMP in the IUI setting has been evaluated largely in observational studies (Table 1). A prospective observational analysis of 591 IUI cycles in which a single follicle was developed found that the clinical pregnancy rate was improved with oral NMP compared with no luteal support.[22] A large retrospective analysis of 1,779 patients found no significant difference in pregnancy outcomes (rates of clinical pregnancy, biochemical pregnancy, early miscarriage and ectopic pregnancy) between recipients of oral NMP, dydrogesterone or vaginal NMP.[23]

Two small, open-label, observational studies compared success rates in the first cycle of IUI with progesterone luteal support using NMP-SR or dydrogesterone in women with unexplained infertility (Table 1). Mean serum progesterone levels were maintained at ≥14 ng/mL during the mid-luteal phase in most patients in both treatment groups in both studies.[12,20] First-cycle biochemically confirmed pregnancy rates were 6.7% and 11% per study in patients treated with NMP-SR and 3.3% and 30% per study in patients treated with dydrogesterone. Possible reasons proposed by Gopinath and Desai for low pregnancy rates were monofollicular development in patients undergoing natural IUI cycles, a trend towards a low-motility fraction and evaluation of the first cycle only.[20]

Recurrent or threatened miscarriage

Inadequate production of progesterone in the early part of pregnancy may be a causative factor in some cases of miscarriage. Progesterone supplementation, starting in the first trimester, is frequently prescribed to prevent spontaneous miscarriage and recurrent miscarriage of unknown aetiology.[24]

A few studies have evaluated the use of oral NMP in the setting of threatened spontaneous miscarriage in the first trimester (Table 2). A retrospective cohort study found that 88% of women with a threatened spontaneous miscarriage treated with oral NMP 200 mg twice daily were discharged home with a healthy pregnancy.[25] An RCT (n=60) that evaluated first-trimester placental and fetal volumes showed that oral NMP 400 mg/day had beneficial effects in terms of significantly increasing placental volume compared to no treatment, although no significant difference was seen in the live birth rate or perinatal complications (assessed as secondary endpoints).[26] Finally, a recent comparative RCT (n=118) found that oral NMP 200 mg twice daily was as effective as dydrogesterone 10 mg twice daily at reducing bleeding and rates of miscarriage.[27]

Preterm birth

Progesterone supplementation is one of the treatment options for the prevention of preterm birth. Meta-analyses have confirmed that progesterone is effective at reducing the risk of preterm birth before 34 weeks and before 37 weeks in women with singleton pregnancies and a history of a previous preterm birth and at reducing the risk of preterm birth before 34 weeks in women with a short cervix.[28,29] No significant differences were found between natural progesterone (oral/vaginal) and IM 17OHP-C[28] or between routes of administration (oral, vaginal and IM).[29]

Studies evaluating oral NMP for the prevention of preterm birth are summarized in Table 3. Three RCTs compared oral NMP with placebo for the prevention of preterm delivery (PTD) in women with a history of previous spontaneous PTD. Two of these studies (n=150 and n=212) found that oral NMP significantly reduced the rate of PTD and increased the mean gestational age at delivery compared with placebo.[30,31] The third study (n=33) found numerical improvements in these parameters with oral NMP compared with placebo but the differences did not achieve statistical significance, likely because the study was underpowered.[32] A meta-analysis of these same three studies demonstrated a significantly decreased risk of preterm birth at <37 weeks' gestation (relative risk (RR) 0.68; 95% CI 0.55–0.84) and at <34 weeks' gestation (RR 0.55; 95% CI 0.43–0.71) and increased gestational age of delivery (mean difference 1.71 weeks; 95% CI 1.11–2.30) with oral NMP compared with placebo.[33] A noncomparative observational study (n=345) also suggested that oral NMP may be effective at preventing PTD.[34] A small retrospective analysis comparing different routes of administration of progesterone in women at high risk for preterm labour (n=30) found a numerically lower rate of PTD with vaginal progesterone than with oral NMP but no statistical comparison was performed.[35]

Studies investigating oral NMP as maintenance tocolysis are few (Table 3). A small RCT from France reported no differences between oral NMP and placebo in terms of pregnancy prolongation; however, adjuvant oral NMP significantly reduced the requirement for intravenous β-mimetic (ritrodrine) and shortened the mean hospital stay by 4.2 days.[36] A RCT from India in 90 women with arrested preterm labour found that maintenance tocolysis with oral NMP significantly prolonged the latency period (days gained until delivery) and significantly reduced the number of preterm births compared with placebo.[37]

High-risk pregnancy

Use of oral NMP-SR has been evaluated across a range of high-risk pregnancies, including but not limited to patients with a poor obstetric history, history of preterm birth, threatened miscarriage or habitual abortion (Table 4). A retrospective, multicentre, case–cohort analysis included 185 consecutive women with a high-risk pregnancy who received oral NMP-SR supplementation.[38] The most common indications were a history of first (n=36, 19.5%) or second (n=37, 20.0%) trimester loss, short/incompetent cervix (n=22, 11.9%), primary (n=22, 11.9%) or secondary (n=12, 5.9%) prophylaxis for preterm birth, and threatened miscarriage with/without spotting (n=19, 10.3%). Fifty women had a history of ≥2 pregnancy losses (28 unexplained recurrent pregnancy losses and 22 spontaneous losses). Oral NMP-SR was generally administered at a dose of 300 mg in women with previous pregnancy loss, cervical risk factors, or threatened miscarriage and at a dose of 200–300 mg in women with a history of preterm birth or those who had premature contractions. Treatment was usually initiated between 16 and 26 weeks of pregnancy and continued until 34 weeks. Mean treatment duration was 19±1 weeks in patients with cervical risk factors, 18±5 weeks in cases of unexplained recurrent pregnancy loss and 10±1 weeks in those with threatened miscarriage. In all treated cases, pregnancy was maintained at the 34-week assessment, with no adverse outcomes.

Safety

The most common adverse events reported in studies of oral NMP in obstetric indications were drowsiness/somnolence and dizziness.[16,27,31] In the largest placebo-controlled trial of oral NMP, somnolence occurred in 41.6% of oral NMP recipients *versus* 19.7% of placebo recipients (p=0.002) and dizziness in 29.1% *versus* 9.8% (p=0.002).[31] Studies of oral NMP-SR have reported considerably lower rates of adverse events: 4.3%[38] and 6.7%[12] for drowsiness and 3.2% for dizziness.[38]

The low incidence of adverse events associated with NMP-SR is further supported by a prescription-event monitoring study conducted in India.[39] The study evaluated 153 patients with a poor obstetric history (50%), unexplained fertility (43.8%) or secondary amenorrhea (5.9%) who received oral NMP-SR 300 or 400 mg once daily after natural or stimulated ART cycles. Oral NMP-SR was well tolerated. Incidences of adverse effects were low (hyperemesis: 1.3%; drowsiness: 0.6%; giddiness: 0.6%) and events were generally mild and transient.

Only a few direct comparisons of oral NMP with other agents have been published. Oral NMP was associated with more drowsiness and giddiness but less nausea compared with

Table 3. Studies evaluating oral natural micronized progesterone for prevention of preterm birth.

Study	Design/*N*	Type of patients	Treatment/timing	Results
Prevention of preterm birth				
Rai et al. 2009[30]	DB, RCT/150	History of sPTD 20–<37 weeks Singleton pregnancy	Oral NMP 100 mg bd *vs* placebo From 18–24 to 36 weeks or delivery	Rate of PTD (<37 weeks) lower with oral NMP *vs* placebo (39.2% *vs* 59.5%, *p*=0.002) Mean ± SD gestational age at delivery greater with oral NMP *vs* placebo (36.1 ± 2.66 *vs* 34.0 ± 3.25 weeks, *p*<0.001) Oral NMP prevented sPTD between 28–<32 weeks (2.7% *vs* 20.3%; RR 0.20, 95% CI 0.05–0.73, *p*=0.001) but not between 32 and <34 weeks (RR 0.86, 95% CI 0.60–1.22, *p*=0.85) or between 34 and <37 weeks (RR 0.83, 95% CI 0.48–1.45, *p*=1.00) [RR of PTD with oral NMP *vs* placebo with gestational age ≥37 weeks as reference] Among patients requiring tocolysis, mean tocolysis-to-delivery interval longer with oral NMP *vs* placebo (49.7 *vs* 26.8 hours, *p*=0.058)
Ashoush et al. 2017[31]	DB, RCT/212	History of sPTD <37 weeks Singleton pregnancy	Oral NMP 100 mg qds *vs* placebo From 14–18 to 37 weeks or delivery	Risk of sPTD (<37 weeks) lower with oral NMP *vs* placebo (44.7% *vs* 63.7%; RR 0.7, 95% CI 054–0.92, *p*=0.01) Mean ± SD gestational age at delivery greater with oral NMP *vs* placebo (35.4 ± 2.7 *vs* 33.9 ± 2.9 weeks, *p*=0.01) Patients who required tocolysis had a longer mean tocolysis-to-delivery interval (87 ± 45.5 *vs* 36 ± 14.2 hours, *p*<0.001)
Glover et al. 2011[32]	DB, RCT/33	History sPTD >20 to <37 weeks Singleton pregnancy	Oral NMP 400 mg/day *vs* placebo From 16–19 to 33 weeks	Rate of sPTD (<37 weeks) numerically lower with oral NMP *vs* placebo, but statistical significance not achieved (26.3% [5/19] *vs* 57.1% [8/14]; RR 0.55, 95% CI 0.26–1.16, *p*=0.15) Mean ± SD gestational age at delivery not significantly longer with oral NMP *vs* placebo (37.0 ± 2.7 *vs* 35.9 ± 3.8 weeks, *p*=0.3)
Boelig et al. 2019[33]	Meta-analysis[30–32] /386	History of sPTD <37 weeks Singleton pregnancy	Oral NMP *vs* placebo	Risk of preterm birth decreased at <37 weeks' gestation (relative risk [RR] 0.68; 95% CI 0.55–0.84) and at <34 weeks' gestation (RR 0.55; 95% CI 0.43–0.71) with oral NMP *vs* placebo Increased gestational age at delivery (mean difference 1.71 weeks; 95% CI 1.11–2.30) with oral NMP *vs* placebo
Tariq et al. 2017[34]	OB/345	History of PTD Singleton (95%) or multiple pregnancy	Oral NMP 400 mg/day From 15–20 weeks to delivery	Oral NMP prevented PTD (< 37 weeks) in 67% of patients, and PTD occurred in 33% of patients despite treatment Mean gestational age at time of delivery 37.51 ± 1.34 weeks
Natu et al. 2017[35]	RET/30	High risk for preterm labour (history of preterm labour or abortion; infection or multiple gestation in current pregnancy) Singleton or multiple pregnancy	Oral NMP *vs* vaginal progesterone suppository From first trimester[a]	PTD rate was 40% (6/15) with oral NMP *vs* 26.7% (4/15) with vaginal progesterone; statistical analysis was not performed

(Continued)

Table 3. (*Continued*)

Study	Design/*N*	Type of patients	Treatment/timing	Results
Maintenance tocolysis				
Noblot et al. 1991[36]	DB, RCT/44	Arrested preterm labour (tocolysis with ritrodrine)	Oral NMP 400 mg qds × 24 h then tds *vs* placebo From start of tocolysis to 35 weeks or delivery	Pregnancy prolongation (6.0 *vs* 6.4 weeks) or number of deliveries before 37 weeks (6 *vs* 8) not different between oral NMP and placebo Total ritrodrine dose (863 *vs* 1370 mg; $p<0.05$) and number of days of hospitalization (13.6 *vs* 17.8; $p<0.05$) lower with oral NMP *vs* placebo
Choudhary et al. 2014[37]	DB, RCT/90	Arrested preterm labour (successful tocolysis with nifedipine) Singleton pregnancy	Oral NMP 200 mg/day *vs* placebo From 48 hours after tocolysis to 37 weeks or delivery	Mean ± SD latency period (days gained until delivery) longer with oral NMP *vs* placebo (33.29 ± 22.16 *vs* 23.07 ± 15.42 days, $p=0.013$) Rate of PTD lower with oral NMP *vs* placebo (33% *vs* 58%, $p=0.034$)

[a]Dosing regimens and duration not specified further.
bd, twice daily; CI, confidence interval; DB, double blind; *N*, number of patients; NMP, natural micronized progesterone; OB, observational; PTD, preterm delivery; qds, four times daily; RCT, randomized controlled trial; RET, retrospective; RR, relative risk; SD, standard deviation; sPTD, spontaneous PTD; tds, three times daily.

Table 4. Studies evaluating natural micronized progesterone sustained release for high-risk pregnancy.

Study	Study design/*N*	Treatment	Results
Prabhat and Korukonda 2018[38]	RET/185[a]	Mean oral NMP-SR dose: • 271.4 mg for mean 18 weeks for unexplained RPL • 262.5 mg for mean 19 weeks for cervical factor • 311.1 mg for mean 10 weeks for threatened miscarriage (spotting or prior history)	In all 185 cases, pregnancy was maintained at week 34 assessment with no adverse outcomes Two cases of spotting were managed symptomatically

[a]Women with first ($n=36$) or second ($n=37$) trimester loss, cervical factor ($n=22$), still birth ($n=15$), threatened PTB ± spotting ($n=19$), placenta previa ($n=5$), PTB primary prophylaxis ($n=22$), PTB secondary prophylaxis ($n=12$), elderly primi ($n=2$), polyhydramnios ($n=3$), uterine fibroid ($n=3$), twin ($n=7$), septate uterus ($n=2$).
N, number of subjects; NMP-SR, natural micronized progesterone sustained release; PTB, preterm birth; RET, retrospective; RPL, recurrent pregnancy loss.

dydrogesterone[27] and with more drowsiness/somnolence but less vaginal irritation compared with vaginal progesterone.[16,17,19]

In a retrospective analysis, NMP-SR and dydrogesterone were both well tolerated in women who underwent stimulated IUI for unexplained fertility.[12] Among 45 women treated with NMP-SR and 33 women treated with dydrogesterone, 3 drowsiness events and 1 nausea event were reported with NMP-SR and 4 nausea events and 1 drowsiness event were reported with dydrogesterone.

A positive association was described between dydrogesterone exposure during the first trimester of pregnancy and congenital heart disease in the newborn,[40] although other authors have argued that weaknesses in the study design preclude ascribing a causal relationship.[41] Natural progesterone may have metabolic advantages compared with synthetic progestogens. Oral NMP in 200, 600 and 1200 mg single doses had no effect on mood/performance compared with placebo.[42] In contrast to levonorgestrel and medroxyprogesterone acetate, which significantly decreased high-density lipoprotein cholesterol subfractions, oral NMP had no apparent effect.[43] Oral NMP administered at doses of 50, 100 or 200 mg daily with oral micronized 17-β-oestradiol for 4 months in postmenopausal women had no effect on liver enzymes or on circulating levels of lipoprotein A, an independent risk factor for cardiovascular disease in women.[44]

Discussion

Endogenous progesterone is essential for the establishment and maintenance of pregnancy. As such, exogenous progesterone is used therapeutically for obstetric indications associated with low progesterone levels, including luteal phase support during ART, management of threatened spontaneous miscarriage, prevention of some cases of PTD, and treatment of patients with high-risk pregnancies (unexplained poor obstetric history or at risk of PTD). In regions without specialist IVF/ICSI facilities, IUI may be a practical approach to enhance fertility. It is a simpler and less intrusive procedure than other ART methods, is widely available, and can be a successful and safe option in selected patients.[21] Studies suggest that oral NMP and NMP-SR may be effective and feasible options in this setting.

Route of administration is an important aspect of any therapy as it may influence treatment adherence and treatment satisfaction. In obstetric indications, natural progesterone can be administered by IM, vaginal and oral routes. From the patient's perspective, oral administration is less painful than IM injection and may be more practical and convenient than intravaginal administration. In some countries, including India, women are notably reluctant to use intravaginal medications, particularly during pregnancy, and prefer to take oral medication (personal communication, Reena J Wani). A preference for oral progesterone over vaginal suppositories has previously been reported.[45] Among oral progestogen options for use in pregnancy, NMP-SR represents an important advance, providing better bioavailability and improved tolerability than conventional oral NMP. A once-daily dose of NMP-SR maintains serum progesterone concentrations in the luteal phase range (i.e. ≥14 ng/mL), which compares favourably with the multidose regimens required with conventional oral NMP and dydrogesterone. A once-daily oral regimen of NMP-SR is convenient for patients and may enhance treatment efficacy through better adherence.

In terms of safety and tolerability, oral progestogen preparations avoid the local effects associated with IM injections or intravaginal administration. The sustained-release kinetics of the NMP-SR formulation and absorption of intact progesterone in the distal part of the gastrointestinal tract avoids drug loss through first-pass metabolism and minimizes any central side effects caused by the formation of active metabolites.[9] Drowsiness, the most common adverse event with conventional oral NMP, is much less frequent with NMP-SR.

NMP-SR has been available in India for more than 7 years and is increasingly becoming physicians' treatment of choice for obstetric indications. A real-world national survey of 925 Indian gynaecologists found that 23% reported oral NMP-SR as their preferred choice for managing luteal phase defects, 11% as their preferred choice for luteal phase support during ART and 10% as their preferred choice for prevention of PTD, while 56% reported that NMP-SR was their preferred choice for all three indications.[9] In women with a poor obstetric history associated with luteal phase deficiency, 58% of the clinicians preferred to use vaginal progesterone, 36% oral NMP-SR, and 6% dydrogesterone. Thus, oral NMP-SR has an important role in managing obstetric conditions in India. Given the established efficacy of oral NMP during more than 30 years' use and the enhanced pharmacokinetics and safety profile of NMP-SR, global interest in NMP-SR might be expected in the near future.

The review is limited by the relatively small number of studies, modest sample sizes in some studies and low quality of evidence of some studies. Only about half of reviewed studies (55%) were RCTs, although observational studies have value in terms of reflecting the real-world standard of care. As searches were limited to the PubMed and Cochrane databases, it is possible that some studies of oral NMP and NMP-SR were not identified. To minimize this possibility, search terms were purposely broad and reference lists of all retrieved records were checked individually.

Conclusion

In conclusion, this literature review documents the efficacy of oral formulations of NMP for the management of obstetric conditions associated with insufficient progesterone exposure. Conventional NMP was effective for luteal phase support during ART and for the prevention of miscarriage and preterm birth. Oral NMP-SR showed promising results in selected areas where studies are available (luteal phase support during IUI and management of high-risk pregnancy). Additional studies would be useful in these indications and others where data are currently lacking. Conventional oral NMP and NMP-SR both have the advantage of being natural progesterone. NMP-SR provides benefits over oral NMP in terms of once-daily dosing, which can facilitate patient compliance, and has an improved tolerability profile. Oral NMP-SR appears to be a valuable option in the therapeutic armamentarium for the treatment of obstetric conditions associated with insufficient progesterone exposure.

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