Progesterone supplementation for preventing preterm birth: a systematic review and meta-analysis

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Aim. The aim of this study is to assess the role of progesterone in preterm birth prevention.

Methods. A MEDLINE search (from 1966 to the present; date of last search January 2005) was performed – using the key words progesterone, pregnancy, preterm birth, preterm labor, and randomized, controlled trial – in order to identify randomized, controlled trials in which progesterone (either intramuscular or vaginal administration) was compared with placebo or no treatment. Data were extracted and a meta-analysis was performed.

Results. Seven randomized, controlled trials were identified. Women who received progesterone were statistically significantly less likely to give birth before 37 weeks (seven studies, 1020 women, RR = 0.58, 95% CI = 0.48–0.70), to have an infant with birth weight of ≤2.5 kg (six studies, 872 infants, RR = 0.62, 95% CI = 0.49–0.78), or to have an infant diagnosed with intraventricular hemorrhage (one study, 458 infants, RR = 0.25, 95% CI = 0.08–0.82).

Conclusions. For progesterone supplementation to be advocated for women at the risk of preterm birth, the prolongation of gestation demonstrated in this meta-analysis must translate into improved infant outcomes, including a reduction in mortality. There is currently insufficient information to allow recommendations regarding the optimal dose, route, and timing of administration of progesterone supplementation.

Key words: perinatal morbidity and mortality; preterm birth; progesterone; randomized trial; systematic review

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Preterm birth before 37-week gestation is a common obstetric problem, accounting for 7.9% of all births in Australia in 2000, with 2.7% of births being before 34-week gestation (1). Data are similar for the US, with recent data, showing a preterm birth rate of 12.1% (2). Of these infants, 1.96% were born before 32-week gestation, with the majority of preterm infants (10.14%) born between 32- and 36-week gestation (2). However, mortality rates are greater for infants born preterm, with over 50% of the perinatal mortality occurring in infants born before 32-week gestation (1). Data from the US show that 1% of infants born between 32- and 36-week gestation will not survive their first year (2). For those infants who are born preterm and survive, there is an increased risk of need for hospitalization within the first year of life (3) and adverse outcome, including cerebral palsy or other long-term disabilities (4).

While the exact mechanism of the onset of labor in humans is complex (5–8), progesterone has a role in maintaining pregnancy (9–11). This includes the maintenance of early pregnancy, with removal of the corpus luteum associated
with pregnancy loss before the establishment of placental progesterone production (12). Pharmacological withdrawal of progesterone by administering 3-beta-hydroxysteroid dehydrogenase inhibitors or mifepristone (RU486) is associated with the onset of labor, and progesterone has been used clinically in order to facilitate the termination of pregnancy (13, 14). By contrast, women undergoing assisted reproductive techniques have been administered progesterone preparations in order to maintain pregnancy (15). Progesterone is thought to contribute to the maintenance of pregnancy, by maintaining uterine quiescence (16, 17), which is postulated to occur through the suppression of the calcium–calmodulin–myosin light chain kinase system, reducing calcium flux and altering the resting potential of uterine smooth muscle (8, 9).

In many animal species, changes that precede the onset of labor related to connective tissue remodelling in the cervix are associated with a decrease in maternal progesterone concentrations and an increase in estrogen (5, 8, 17, 18). These changes have not been documented to occur in women before labor or birth; there are no apparent changes to circulating steroid hormone levels (8, 11, 17, 19, 20). While there may be no changes detectable biochemically, it is has been suggested that there may be a ‘functional’ withdrawal of progesterone, mediated through changes in receptor expression (11, 17, 21, 22).

Recent reports of the clinical use of progesterone supplementation for women at the risk of preterm birth (23, 24) have rekindled an interest in the use of progesterone in this setting, which dates back to the 1960s (25). Our aim is to assess the role of progesterone in preterm birth prevention by using the best available evidence from the current randomized, controlled trial literature.

Participants and methods

Types of studies

Published randomized, controlled trials in which progesterone (either intramuscular or vaginal administration) was compared with placebo or no treatment. Quasi-randomized studies (where randomization was performed, using date of birth, hospital number, odd or even number allocation, or weekday of admission) were included.

Types of participants

Women with a singleton pregnancy in which progesterone was administered for the prevention of preterm birth were the participants.

Types of outcome measures

The outcomes sought were those considered of importance for women and infants born preterm and were the following.

Adverse outcomes for the infant/child. Neonatal respiratory disease (as defined by trial authors), need for assisted ventilation, oxygen therapy required at 36 weeks post-menstrual age, preterm birth less than 37-week gestation, stillbirth or infant death (excluding lethal congenital anomalies), Apgar score of ≤7 at 5 min of age, birth weight of <2500 g, seizures, cord pH ≤ 7.18, intraventricular hemorrhage, air leak syndrome, need for surfactant therapy, nitric oxide for respiratory support, patent ductus arteriosus requiring treatment, proven necrotizing enterocolitis, proven systemic infection, retinopathy of prematurity, seizures, altered level of consciousness (stupor, decreased response to pain, or coma), need for tube feeding, admission to the neonatal intensive care unit, and neurodisability at childhood follow-up.

Adverse outcomes for the woman. Defined as length of antenatal hospital stay, tocolytic therapy, antenatal corticosteroid therapy, side-effects of progesterone supplementation (including headache, nausea, breast tenderness, coughing and irritation injection site), antepartum hemorrhage, pre-eclampsia, preterm labor, ruptured membranes, pre-labor ruptured membranes at term, choioamnionitis, antibiotic use during labor, postpartum hemorrhage, antibiotic use after birth, length of postnatal hospital stay, maternal death, not breast feeding at 4 months postpartum or any other serious maternal complication, maternal emotional well-being (as defined by trial authors), maternal preferences for treatment, and satisfaction with care.

Costs of health care. As defined by trial authors.

Search strategies for the identification of studies

This review used the search strategy developed by the Cochrane Pregnancy and Childbirth Group of the Cochrane Collaboration, and involved searching the group’s specialized register of controlled trials (CENTRAL). In addition, a MEDLINE search (from 1966 to the present) was performed, using the key words progesterone, pregnancy, preterm birth, preterm labor, and randomized, controlled trial (date last searched January 2005). A manual search was performed of the reference list of all identified studies.

Methods of the review

Identified trials were evaluated for appropriateness for inclusion and methodological quality without considering their results, according to pre-stated eligibility criteria. Eligible trials were assessed, using the following criteria for assessment of quality:

- Generation of random allocation sequence: adequate, inadequate, and unclear.
- Allocation concealment: A = adequate, B = unclear, and C = inadequate.
- Blinding of participants: yes, no, inadequate, and no information.
- Blinding of caregivers: yes, no, inadequate, and no information.
- Blinding of outcome assessment: yes, no, inadequate, and no information.
- Completeness of follow-up data (including any differential loss of participants from each group): A = <3% of participants excluded, B = 3–9.9% of participants
excluded, C = 10–19.9% of participants excluded; D = 20% or more excluded, and E = unclear.

- Intention to treat (analysis of participants in original randomized group).

Data were extracted from the original studies, with data from various trials combined if considered to be sufficiently similar by the reviewers. Meta-analyses were performed by using relative risks (RR) and 95% confidence intervals (95% CI) for binary outcomes, and weighted mean differences for continuous outcomes. Planned subgroup analyses were by means of dose and frequency of progesterone administration and mode of administration (intramuscular versus intravaginal). Sensitivity analyses were performed in order to take account of any differences in use, only in women considered to be at ‘high’ risk of preterm birth, and study quality (in this case for quasi-randomized trials and adequate allocation concealment).

Results

Description of studies

The search identified seven randomized, controlled trials, all of which met the inclusion criteria. Six studies compared intramuscular 17α-hydroxyprogesterone caproate with placebo (24–29) (Table I). A single trial compared vaginal progesterone with placebo (23) (Table II). Doses and frequency of progesterone administration varied from 100 mg daily (23) to 250 mg three times per week (26), 250 mg once per week (24, 27, 29), 500 mg once per week (25), or 1000 mg once per week (28). Likewise, timing during pregnancy of progesterone administration varied, with some women administered progesterone before 20-week gestation (24,25,27–29), continuing treatment to an upper limit of gestational age varying from 32 weeks (26) to 34 weeks (23), 36 weeks (24, 25, 28), or 37 weeks gestation (27, 29). Six studies involved progesterone supplementation in women with a prior history of preterm birth or considered to be ‘at risk’ of preterm birth (23–27,29), and one trial recruited from an unselected population (28). There was limited reporting of the pre-specified neonatal outcomes, and reporting of maternal outcomes overall was poor.

Quality assessment of the studies

The overall quality of the identified studies varied from good to fair. The studies by LeVine (25) and Yemini et al. (29) both used a quasi-randomization system with women being allocated alternately to each group with the identification of groups showed at the conclusion of the study (25), or based on medical record number (29). Allocation concealment was assessed as adequate in the trials by Johnson et al. (27), Meis et al. (24), and da Fonseca et al. (23); inadequate in the trials by LeVine (25) and Yemini et al. (29); and unclear in the trials by Papiernik-Berkhauer (26) and Hauth et al. (28).

Intramuscular progesterone versus placebo

Women who were administered intramuscular progesterone were significantly less likely to give birth before 37-week gestation (six studies, 878 women, RR = 0.59, 95% CI = 0.49–0.72), to have an infant with birth weight of <2.5 kg (six studies, 872 infants, RR = 0.62, 95% CI = 0.49–0.78), or to have an infant with a diagnosis of intraventricular hemorrhage (one study, 458 infants, RR = 0.25, 95% CI = 0.08–0.82), compared with placebo. There were no statistically significant differences for the few other reported infant outcomes, including perinatal death (Table III). There were no longer-term infant outcomes reported.

Maternal outcomes of need for tocolytic therapy, antenatal corticosteroids, and chorioamnionitis were reported in only one trial (24), for which there were no statistically significant differences between treatment groups identified (Table IV).

Intravaginal progesterone versus placebo

A single study of 157 women compared daily intravaginal progesterone with placebo, with only information reported for birth before 37-week gestation (23). For this outcome, women who received progesterone were less likely to give birth before 37 weeks (one study, 142 women, 10/72 progesterone versus 20/70 placebo, RR = 0.49, 95% CI = 0.25–0.96).

All women receiving progesterone versus placebo

The only clinical outcome available for all women receiving progesterone regardless of the route of administration was for preterm birth of <37-week gestation. For this outcome, women who received progesterone were statistically significantly less likely to give birth before 37 weeks (seven studies, 1020 women, RR = 0.58, 95% CI = 0.48–0.70).

Sensitivity analysis for supplementation in women with a history of prior preterm birth or considered to be ‘at risk’ of preterm birth

When the literature is confined to trials, in which progesterone supplementation was used in
Table I. Study characteristics – intramuscular progesterone versus placebo

<table>
<thead>
<tr>
<th>Study identification</th>
<th>Study characteristics</th>
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</table>
| LeVine (25)          | Methods: trial conducted in Chicago, USA; recruitment prior to 16 weeks  
Participants: 30 women with a history of three consecutive spontaneous abortions, with no symptoms of threatened abortion in the current pregnancy  
Interventions: weekly intramuscular injection of either 500 mg 17α-hydroxyprogesterone caproate or placebo from before 16-week gestation until 36-week gestation or birth if earlier  
Sample size: not calculated  
Outcomes: preterm birth before 37-week gestation; birth weight of less than 2.5 kg; perinatal death  
Outcome data: all women  
Randomization: alternate allocation to either ‘group A’ or ‘group B’  
Allocation concealment: group identification showed at the conclusion of the study  
Losses to follow-up: none  
Blinding: participants and caregivers |
| Papiernik-Berkhauer (26) | Methods: trial performed in Paris, France; recruitment from 28 weeks  
Participants: ninety nine women with a ‘high preterm risk score’  
Interventions: every three days intramuscular injection of either 250 mg 17α-hydroxyprogesterone caproate or placebo from 28-week gestation until 32-week gestation  
Sample size: not calculated  
Outcomes: preterm birth before 37-week gestation; birth weight of <2.5 kg; perinatal death  
Outcome data: all women  
Randomization: unclear  
Allocation concealment: unclear  
Losses to follow-up: none  
Blinding: participants and caregivers |
| Johnson et al. (27) | Methods: trial performed in Baltimore, USA; recruitment from ‘booking’ until 24-week gestation  
Participants: 50 women with a history of two previous spontaneous abortions or previous preterm birth before 36-week gestation  
Interventions: weekly intramuscular injection of either 250 mg 17α-hydroxyprogesterone caproate or placebo from ‘booking’ until 37-week gestation, or birth if earlier  
Sample size: not calculated  
Outcomes: preterm birth before 37-week gestation; birth weight of <2.5 kg; perinatal death  
Outcome data: 43 women  
Randomization: in a ‘randomized, double-blind fashion’  
Allocation concealment: next of identical drug packages  
Blinding: participants and caregivers |
| Hauth et al. (28) | Methods: trial performed in Lackland Airforce Base, Texas, USA; recruitment from 16- to 20-week gestational age  
Participants: 168 women on active military duty  
Interventions: weekly intramuscular injection of either 1000 mg 17α-hydroxyprogesterone caproate or placebo from 16 to 20 weeks until 36-week gestation, or birth if earlier  
Sample size: not calculated  
Outcomes: preterm birth before 37-week gestation; birth weight of <2.5 kg; perinatal death  
Outcome data: all women  
Randomization: stated to be a ‘randomized, double-blind investigation’  
Allocation concealment: not stated  
Blinding: participants and caregivers |
| Yemini et al. (29) | Methods: trial performed in Rehovot, Israel; unclear at what gestational age recruitment commenced  
Participants: 80 women with a history of at least two previous preterm births or two spontaneous miscarriages, or a combination of these, exclusion women with multiple pregnancy, diabetes, chronic renal disease, chronic hypertension, distress syndrome; anemia; apnoea or bradycardia; sepsis; patent ductus arteriosus  
Sample size: not calculated  
Outcome data: 79 women  
Randomization: medical record number  
Allocation concealment: not stated  
Blinding: participants and caregivers |
| Meis et al. (24) | Methods: trial performed by the Maternal-Fetal Medicine Network, USA; randomization between 16- and 20-week gestation  
Participants: 463 women with a history of previous spontaneous preterm birth; exclusion women with multiple pregnancy, known fetal anomaly, progesterone or heparin treatment during pregnancy, current or planned cervical cerclage, hypertension, seizure disorder  
Interventions: weekly intramuscular injection of either 250 mg 17α-hydroxyprogesterone caproate or placebo from 16 to 20 weeks until 36-week gestation, or birth if earlier  
Sample size: 500 women |
women with a history of prior preterm birth or in other ways considered to be ‘at risk’ of preterm birth (23–27,29), the use of progesterone was associated with a reduction in the risk of birth before 37 weeks (six studies, 852 women, RR = 0.57, 95% CI = 0.47–0.69), infant birth weight of <2.5 kg (five studies, 704 infants, RR = 0.60, 95% CI = 0.47–0.77), and perinatal death (five studies, 708 infants, RR = 0.53, 95% CI = 0.27–1.07) (Table V). The magnitude of this risk reduction was similar to the analysis involving all studies.

Sensitivity analysis for trial quality

On the basis of quasi-randomization methods, the studies by LeVine (25) and Yemini et al. (29) were excluded and a sensitivity analysis was performed. Women who were administered progesterone remained less likely to give birth preterm (five studies, 911 participants, RR = 0.60, 95% CI = 0.49–0.73), to have an infant with birthweight of <2.5 kg (four studies, 763 participants, RR = 0.63, 95% CI = 0.49–0.81), or to have an infant with a diagnosis of intraventricular hemorrhage (one study, 458 infants, RR = 0.25, 95% CI = 0.08–0.82), compared with placebo.

On the basis of adequate allocation concealment, the studies by LeVine (25), Papiernik-Berkhauer (26), Hauth et al. (28), and Yemini et al. (29) were excluded and a sensitivity analysis was performed. Women who were administered progesterone remained less likely to give birth before 37 weeks (three studies, 644 participants, RR = 0.61, 95% CI = 0.50–0.74), to have an infant with birthweight of <2.5 kg (two studies, 496 participants, RR = 0.65, 95% CI = 0.50–0.84), and to have an infant with a diagnosis of intraventricular hemorrhage (one study, 458 infants, RR = 0.25, 95% CI = 0.08–0.82), compared with placebo. In the two trials with adequate allocation concealment, reporting infant death, there was a significant reduction in the risk of death (two studies, 503 participants, RR = 0.48, 95% CI = 0.23–0.98) with the use of progesterone.

Planned subgroup analyses

The weekly dose of progesterone administered was arbitrarily divided into those studies with <500 mg per week (24, 27, 29), and those with ≥500 mg per week (23, 25, 26, 28). There were no statistically significant differences identified between the higher and lower cumulative weekly dose of progesterone for preterm birth (seven studies, 587 participants, RR = 1.41, 95% CI = 0.55–3.61), infant birth weight of <2.5 kg (six studies, 503 participants, RR = 1.28, 95% CI = 0.47–3.51), or perinatal death (six studies, 507 participants, RR = 1.37, 95% CI = 0.40–4.69) (Table VI).

The gestational age at which treatment with progesterone commenced was arbitrarily divided into those studies that commenced supplementation before 20 weeks (24, 25, 27–29) and those after 20-week gestation (23, 26). There were no statistically significant differences identified between earlier and

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Table II. Study characteristics – intravaginal progesterone versus placebo

<table>
<thead>
<tr>
<th>Study identification</th>
<th>Study characteristics</th>
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<tbody>
<tr>
<td>da Fonseca et al. (23)</td>
<td>Methods: trial performed in Sao Paulo, Brazil; randomization from 24 weeks</td>
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<td></td>
<td>Participants: 157 women considered to be at ‘high risk’ for preterm birth because of history of previous preterm birth, cervical suture, uterine malformation</td>
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<tr>
<td></td>
<td>Interventions: nightly intravaginal pessary of either 100 mg progesterone or placebo from 24 weeks until 28-week gestation, or birth if earlier</td>
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<tr>
<td></td>
<td>Sample size: 96 women</td>
</tr>
<tr>
<td></td>
<td>Outcomes: preterm birth before 37-week gestation</td>
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<tr>
<td></td>
<td>Outcome data: 15 women excluded after randomization; outcome data available for 142 women</td>
</tr>
<tr>
<td></td>
<td>Randomization: random number table</td>
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<tr>
<td></td>
<td>Allocation concealment: sequential sealed opaque envelopes; allocation to either drug A or drug B; allocation of groups revealed after last woman birthed</td>
</tr>
<tr>
<td></td>
<td>Blinding: participants and caregivers</td>
</tr>
</tbody>
</table>
later commencement of therapy for preterm birth (seven studies, 587 participants, RR = 0.95, 95% CI = 0.38–2.40), infant birthweight of <2.5 kg (six studies, 503 participants, RR = 0.92, 95% CI = 0.34–2.51), or perinatal death (six studies, 507 participants, RR = 0.24, 95% CI = 0.05–1.12) (Table VII).

Discussion

Meta-analysis of the available randomized, controlled trial literature shows that the use of progesterone for women at the risk of preterm birth is associated with a significant reduction in the risk of preterm birth before 37-week gestation and infant birthweight of <2.5 kg. While promising, these results should prompt the further evaluation necessary and not be interpreted as supportive of the widespread adoption of progesterone supplementation for women considered to be at the risk of preterm birth, as has been advocated by some (30).

Obstetric practice and particularly neonatal care have changed dramatically over the past 25 years, and maternal and infant outcomes from studies relating to preterm birth performed in the 1960s, 1970s, and even 1980s are not directly comparable with those from more recent trials. If the literature is confined to contemporary studies, there were two identified (23,24), although both have limitations in informing best clinical practice. The study by da Fonseca and colleagues only reported the clinical outcome preterm birth before 37-week gestation and preterm birth before 34 weeks (23). While Meis and colleagues reported more widely on infant outcomes (24), the high rate of preterm birth for women in the control group (54.9%) questions whether these findings are truly representative of the obstetric population who have had a previous preterm birth (31). It has been suggested that the high rate of preterm birth in women in the control group may have reflected the use of castor oil in the placebo agent (32).

An important question that was not answered by the meta-analysis relates to whether the prolongation of gestational age through progesterone supplementation translates into reduced perinatal mortality and improved infant health. Information about the health of the infants was poorly reported in the available literature, with most outcomes reported only in a single trial, or, at best, two trials. The total sample size of those studies reporting infant outcomes (536 infants) was underpowered in order to detect clinically significant differences in important outcomes, such as perinatal mortality and neonatal respiratory distress syndrome.

In the only trial that separated perinatal mortality into its individual components of stillbirth and neonatal death (24), there was a
Table VI. Subgroup analysis comparing total weekly dose of progesterone of <500 mg versus ≥500 mg per week

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies (n)</th>
<th>Participants (n)</th>
<th>Relative risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth (&lt;37 weeks)</td>
<td>7</td>
<td>587</td>
<td>1.41</td>
<td>0.55–3.61</td>
</tr>
<tr>
<td>Birthweight of &lt;2.5 kg</td>
<td>6</td>
<td>503</td>
<td>1.28</td>
<td>0.47–3.51</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>6</td>
<td>507</td>
<td>1.37</td>
<td>0.40–4.69</td>
</tr>
</tbody>
</table>

non-statistically significant trend to a reduction in neonatal death (RR = 0.44, 95% CI = 0.17–1.13), but an increase in stillbirths (RR = 1.50, 95% CI = 0.31–7.34). Interestingly, the two high-quality trials for adequate allocation concealment (24, 27), which reported perinatal mortality, did show a reduction in death with the use of progesterone. The non-significant increase in stillbirth raises concern that prolongation of pregnancy may exacerbate the fetal inflammatory response syndrome, increasing the risk of adverse outcomes. However, the formulation of progesterone used may be of importance, with the suggestion that medroxyprogesterone acetate may protect against inflammatory-induced outcomes, including preterm birth (33). This warrants further exploration in larger studies powered to detect whether these differences truly exist.

Information from animal models suggests that progesterone levels influence fetal behavior in sheep (34), with increased levels suppressing activity and arousal states (35, 36). Further information is required about any potential effects in the human fetus relating to the suppression of behavior and activity states and to potential sedative effects in the infant.

Maternal outcomes related to progesterone therapy were poorly reported in the literature, including side-effects associated with treatment, maternal views, preferences for care, and satisfaction with care. Further large trials are required in order to provide reliable information on these issues (31, 37).

The American College of Obstetricians and Gynecologists has issued a committee opinion relating to the use of progesterone supplementation for women at the risk of preterm birth highlighting the need for further trials that address the optimal route of administration of progesterone (38). Our meta-analysis was unable to inform the optimal route of administration, with only a single study reporting vaginal use of progesterone (23). Available pharmacokinetic data for progesterone relate to its use in other areas of women’s health care, including assisted reproduction (39–42), in menopausal women (43), post-menopausal women (44, 45), and in women with endometrial carcinoma (46). Serum progesterone levels following vaginal administration are lower than those after intramuscular administration (41, 42). There is limited data available to inform the optimal route of administration in women in later pregnancy. Further information is required about dosage and timing of administration. Our meta-analysis did not suggest a difference in effect related to cumulative dose of progesterone administered, or the gestational age at which treatment commenced.

Conclusions

While the use of progesterone supplementation to women at an increased risk of preterm birth is promising before its widespread use in clinical practice can be recommended, further large, randomized trials are required in order to assess more fully the benefits and potential risks to women and their infants. The optimal dose, route, and timing of administration need elucidation (31, 37, 38). For progesterone supplementation to be advocated for women at the risk of preterm birth, the prolongation of gestation demonstrated in this meta-analysis must translate into improved infant outcomes, including a reduction in mortality.

References


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