FOGSI
GYNAE GAZETTE

ISSUE I

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The **Natural** Progesterone,
The **National** Progesterone**

GOLD STANDARD

In Recurrent Pregnancy Loss

Susten Cap 400 300 200 100 ™

Natural Micronised Progesterone 100 mg/ 200 mg/
300 mg/ 400 mg SLDS Capsule

Worldwide guidelines recommend **NMP 400 mg twice daily** at the time of bleeding in early pregnancy until 16 weeks of gestation[1,3,5]

RCOG 2023 (Green-top Guideline no. 17 on RM)

400 mg micronised vaginal progesterone twice daily at the time of bleeding until 16 weeks of gestation[1]

ESHRE 2022

Vaginal Progesterone improves live birth rate in women with RPL & vaginal blood loss in subsequent pregnancy[2,~]

TGA 2022 (Australia)

NMP 400 mg vaginally b.i.d. from initiation at the first sign of vaginal bleeding during the 1st trimester of pregnancy & continued to at least 16th week of gestation in Threatened Miscarriage cases[3]

FOGSI 2015

NMP 400 mg/day vaginally till 20 weeks of pregnancy[4]

NICE 2021

NMP 400 mg vaginally b.i.d. till 16 weeks to women with vaginal bleeding & previous miscarriage[5,#]

75% Live birth rate with NMP in women with 1 or more previous miscarriages[6,*]

For the use of registered medical practitioner or a hospital or a laboratory only.

Ref.: 1.Regan L, Rai R, Saravelos S, Li TC; Royal College of Obstetricians and Gynaecologists. Recurrent MiscarriageGreen-top Guideline No. 17. BJOG. 2023 Nov;130(12):e9–e39. 2.ESHRE Guideline Group on RPL; Bender Atik R, Christiansen OB, et al. ESHRE guideline: recurrent pregnancy loss: an update in 2022. Hum Reprod Open. 2023 Mar 2;2023(1):hoad002. 3.Australian Public Assessment Report for Utrogestan 200 Accessed on: January 03, 2024 4.FOGSI position statement on the use of progestogens. Available at: http://www.fogsi.org/wp-content/uploads/2015/11/Progesteroneposition-paper-Oct-2015.pdf. Accessed on: February 03, 2024 5.Jacqui Wise, BMJ.2021 Nov 24;375:n2896. 6..Arri Coomarasamy et al., Am J Obstet Gynecol 2020 Aug;223(2):167-176. **NICE:** National Institute for Health and Care Excellence; **RCOG:** Royal College of Obstetricians and Gynaecologists; **FOGSI:** Federation of Obstetric and Gynaecological Societies of India; **ESHRE:** European Society of Human Reproduction and Embryology **RM** : Recurrent Miscarriage ,**RPL:** Recurrent Pregnancy Loss, **NMP :** Natural Micronised Progesterone *For the subgroup of women with a history of 1 or more miscarriage(s) and current pregnancy bleeding, the live birth rate was 75% (689/914) with progesterone vs 70% (619/886) with placebo (rate difference 5%; risk ratio, 1.09, 95% confidence interval, 1.03–1.15; p=.003). The benefit was greater for the subgroup of women with 3 or more previous miscarriages and current pregnancy bleeding; live birth rate was 72% (98/137) with progesterone vs 57% (85/148) with placebo (rate difference 15%; risk ratio, 1.28, 95% confidence interval, 1.08–1.51; p=.004). No short-term safety concerns were identified from the PROMISE and PRISM trials. #vaginal micronised progesterone 400 mg twice daily to women with an intrauterine pregnancy confirmed by a scan, if they have vaginal bleeding and have previously had a miscarriage' and 'if a fetal heartbeat is confirmed, continue progesterone until 16 completed weeks of pregnancy ~Vaginal progesterone may improve live birth rate in women with three or more pregnancy losses and vaginal blood loss in a subsequent pregnancy(Conditional; ⊕⊕⊕◯) ^ Based on following conclusions from consensus document and systematic review/meta-analysis: "Vaginal progesterone therapy represents the gold standard approach for luteal phase support after IVF/ICSI." [Ref: Orvieto R, et al. Optimising Follicular Development, Pituitary Suppression, Triggering and Luteal Phase Support During Assisted Reproductive Technology: A Delphi Consensus. Front. Endocrinol. 2021;12:675670. doi: 10.3389/fendo.2021.675670] Vaginal progesterone is currently the best preterm birth prevention treatment for women with a singleton pregnancy who are asymptomatic but at high risk of preterm birth." AND "We suggest that vaginal progesterone should become the new gold standard comparator." [Ref: Care A, et al. Interventions to prevent spontaneous preterm birth in women with singleton pregnancy who are at high risk: systematic review and network meta-analysis. BMJ 2022;376:e064547. http://dx.doi.org/10.1136/ bmj-2021-064547] * *As per IQVIA & SMSRC report 2023, In NMP Capsules category : Susten Cap. is Ranked 1st brand in terms of sales (Value, Units) & prescriptions by Gynecologists, It is widely available across states

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PRESIDENT'S MESSAGE

Dear seniors and colleagues,

I am delighted to introduce the inaugural edition of our newsletter, the Gynae Gazette. This issue addresses the critical topic of preterm birth and its management, with a focus on the combined use of vaginal medications and surgical techniques.

Preterm birth is a major concern in obstetrics, significantly affecting neonatal health. Despite advancements, preventing preterm birth remains a challenge. Recent evidence suggests that utilizing a combination of specific interventions can help reduce its incidence when compared to monotherapy.

Our gazette includes a comprehensive review of recent studies and succinct summaries of key findings, making it easier for busy practitioners to stay informed.

I extend my heartfelt thanks to the editors, reviewers, and contributors for their dedication. Your efforts help us advance our knowledge and improve patient care. Please share your feedback and ideas as we continue this journey together.

Thank you for your support and commitment to FOGSI.

Best wishes,

Dr. Jaydeep Tank

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SECRETARY GENERAL'S MESSAGE

Dear seniors and colleagues,

I am excited to present the first edition of the Gynae Gazette. This new publication addresses the vital issue of preterm birth, focusing on innovative strategies such as the combined use of vaginal interventions with surgical approach.

Preterm birth poses significant challenges in our field, impacting neonatal outcomes. Despite medical advancements, its prevention remains complex. Emerging research indicates that a combined approach may offer better results in reducing preterm birth rates.

The Gynae Gazette provides a thorough review of recent research along with concise summaries to keep you well-informed. Our editorial team has worked tirelessly to deliver valuable insights in an accessible format.

I want to thank our dedicated editors, authors, and reviewers for their hard work. Your contributions are essential to this publication's success. We look forward to your feedback and ideas to enhance future issues.

Thank you for your ongoing support and dedication to FOGSI.

Best wishes,

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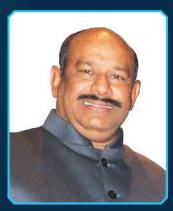

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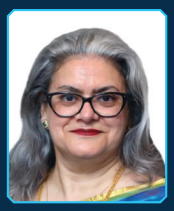

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CLINICAL TALKS

Insights on preventing preterm birth

Introduction

Preterm birth, defined as delivery before 37 weeks of gestation, largely contributes to infant morbidity and mortality. Prematurity claims the lives of nearly 1 million infants every year worldwide.[1] Around 15 million babies are born preterm around the world, and the rate has only been increasing over the last 2 decades in almost all countries, leading to a global preterm birth prevalence rate of 11%.[1] Studies report that an estimated one-third of these cases occur in South Asia.[2] Analysis of the National Family Health Survey round 5 revealed that during 2019–21, approximately 12% of the children were born preterm in India.[2]

While the underlying cause of preterm birth remains largely unknown, several modifiable and nonmodifiable risk factors have been identified (Figure 1).[3] The signs and symptoms of preterm delivery could be subtle (Figure 2).[3,4]

Figure 1: Preterm birth risk factors[3]

Biologic	Socioeconomic	Environmental and lifestyle
Advanced maternal age, diabetes, hypertension, cardiac disease, assisted reproductive technologies, fetal anomalies, inherited conditions, short cervix, multiple pregnancies, underweight/overweight, previous preterm birth or labor, vaginal bleeding or infection, preterm premature rupture of membranes	Poor nutrition, lack of access to healthcare, low income, lack of social support, and education level	Water and air quality, alcohol consumption, smoking, long working hours, and standing for an extended duration

Figure 2: Signs and symptoms indicating the possibility of preterm delivery[3,4]

Contractions	Discharge	Discomfort
Regular contractions (every 10 minutes), which gradually intensify and coincide with changes in the cervix, and cramps resembling menstrual discomfort	Clear vaginal discharge (could also be watery, with mucous, or bloody) could feel like a gush or trickle	Constant dull lower back pain, pelvic or lower abdominal pressure

Preterm birth prevention: Interventions in focus

Some conservative approaches to prevent preterm delivery include screening for periodontal disease, restriction of physical activity, bed rest, antibiotics to target bacterial vaginosis or symptomatic bacteriuria, and lifestyle changes such as smoking cessation.[5] Other common strategies include invasive measures such as cervical stitch (cervical cerclage), cervical pessary, or the administration of vaginal progesterone (Figure 3).[4,5]

Figure 3: Common preventive strategies for preterm birth

Cervical cerclage

The procedure entails suturing the cervix's neck in the presence of regional or general anesthesia to extend mechanical support to the cervix and reduce the chances of preterm delivery.[4,5] Delivery can be delayed by 4–9 weeks following surgical cervix closures.[5] Cerclage may be inserted in different indications as follows:

- **Physical examination-indicated cerclage (emergency/rescue cerclage):** Cerclage is inserted in women with a singleton pregnancy at <24 weeks of gestation when cervical dilation is observed without contractions, intra-amniotic infection, or placental abruption (Aim: To reclose the cervical opening and prevent exposure of amniotic fluid to vaginal bacteria).[5,6]
- **History-indicated cerclage:** It is inserted as a prophylactic when 1 or more pregnancy losses have occurred in the past in the second trimester, related to painless cervical dilation and in the absence of labor or abruptio placentae.[6*]
- **Ultrasound-indicated cerclage:** It is considered for women with a history of preterm birth or pregnancy loss at <34 weeks, and when a planned ultrasound session reveals shortening of the cervix (<25 mm) before 24 weeks of gestation.[5,6*]
- **Complications:** It includes iatrogenic rupture of membranes, intra-amniotic infection, and lacerations at the surgical site.[5]

Cervical pessary

- A pessary is usually administered when the patient is in the lithotomy position, in the absence of anesthesia.[5]
- The deviation in the uterocervical angle resulting from the insertion of the cervical pessary helps relieve pressure on the internal opening of the cervix, thereby preventing premature rupture of membranes and premature labor.[5]
- While this method is associated with more vaginal discharge, it usually does not cause discomfort to the patient.[5]

Progesterone supplementation

- The usefulness of progesterone supplementation in preterm birth prevention is now supported by good-quality evidence.[7]
- Some possible mechanisms suggested include inhibition of prostaglandin synthesis, inducing an anti-inflammatory action, inhibiting the expression of estrogen receptor alpha (ER-α), and reducing sensitivity to estrogen. It also exerts several effects on the myometrium such as induction of cyclic adenosine monophosphate (cAMP) with time-dependent nitric oxide stimulation and prevention of myometrial gap junction formation.[7-9]
- A possible functional withdrawal of progesterone brought about by changes in progesterone receptors and their transcriptional activity at tissue level is another suggested mechanism.[7]
- Among all the available forms, natural progesterone is used for preterm birth prevention and can be administered orally, vaginally, or parenterally.[7]

[*](Aim: Support cervical opening, thereby creating a biochemical blockade and inducing an inflammatory response.)

Considering the differing mechanisms of action and high failure rates associated with each of them (failure rate of cervical cerclage in achieving birth after 37 weeks: 20%, failure rate of progesterone in achieving birth after 34 weeks: 66%, no reduction in the risk of preterm birth with cervical pessary at various time-points including <28 weeks, <32 weeks, and <37 weeks of gestation), and lack of improvement in perinatal outcomes, the combination of progesterone and cervical cerclage has been suggested as an effective option to reduce the rate of preterm birth in women with a short cervix or those with a history of preterm births in multiple studies.[9,10]

Benefits of cerclage and vaginal progesterone combination: Evidence highlights

- The prostaglandin-inhibiting mechanism of progesterone with subsequent lowering of uterine contractions is accentuated following the cervical cerclage procedure.[11]

- Several clinical studies have demonstrated the benefits of combination therapy in various patient subgroups, with improvements in other maternal and perinatal outcomes, as stated below.[10,12-14]

Study population: Patients at high risk with a shortened cervix <25 mm or a history of preterm births[10]

- The combination of vaginal progesterone and cervical cerclage significantly reduced the risk of preterm birth <37 weeks compared to either preventive measure alone.
- The rate of preterm births was significantly reduced with the combination at <34 weeks, <32 weeks, and <28 weeks compared to cerclage alone.
- The risk of preterm births was also significantly lower at <32 and <28 weeks compared to progesterone alone.
- The interval between cerclage and delivery was significantly longer in the combined therapy group than in the cerclage-only-treated group.
- Significantly higher neonatal birth-weight and lower neonatal mortality were reported in the combination group than either treatment alone.

Study population: Women with singleton pregnancies with PEICC due to acute cervical insufficiency[12]

- The combination of adjuvant vaginal progesterone with physical examination-indicated placement of cervical cerclage (PEICC) was associated with a significantly lower spontaneous preterm birth rate at <36 weeks and <32 weeks.
- Low birth-weight of neonates (<2500 g) and frequent neonatal intensive care unit (NICU) admissions were reported in the nonadjuvant group.

Study population: Women with singleton pregnancies at high risk, with transvaginal scans showing a short cervix (<25 mm) at 12 weeks[13]

- A satisfactory outcome (no preterm birth in <37 weeks) was reported in 91% of the women receiving the combination of vaginal progesterone and cervical cerclage, compared to the 61% receiving vaginal progesterone alone.

Study population: Women with evidence of progressive cervical shortening of <20 mm despite cervical cerclage[14]

- At the time of birth, the average gestational age in the progesterone-cerclage group was 36.36 weeks, compared to 32.64 weeks in the cerclage-only group.
- Significantly higher birth weights of infants were also reported in the group receiving the combination compared to the control group.

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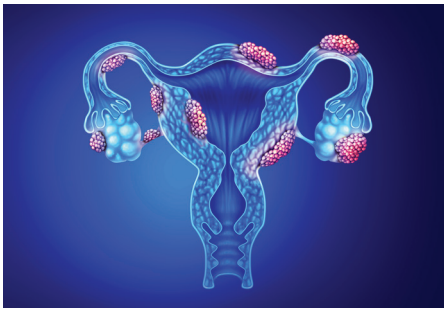
THERAPY IN LIMELIGHT

Postoperative vaginal medication

Impact of adjunctive vaginal progesterone use following McDonald cerclage



The present study assessed the impact of supplementing vaginal progesterone following McDonald cerclage for the prevention of second-trimester spontaneous abortion in patients with singleton pregnancy.[1]

Study methods

Study design

A single-center prospective, open-label, randomized controlled trial was conducted between April 2017 and March 2019.

Patient population

Adult patients with a singleton pregnancy at 12–14 gestational weeks (age: 20–35years), had at least one of the following indications for cerclage at the time of recruitment:

- A history of second-trimester pregnancy loss with painless cervical dilatation
- Prior cerclage placement for cervical insufficiency
- A history of spontaneous preterm delivery (<34 weeks)
- Ultrasonographic evidence of short cervical length (<25 mm)

Interventions

Patients who underwent McDonald cerclage were randomly divided to receive one of the two treatments.

- **Group 1**: Patients received vaginal progesterone pessary (once daily), following cerclage until 37 completed gestational weeks (n = 115).
- **Group 2**: Patients received no medication (n = 112).
- **Follow-up**: Every 2 weeks

Outcomes

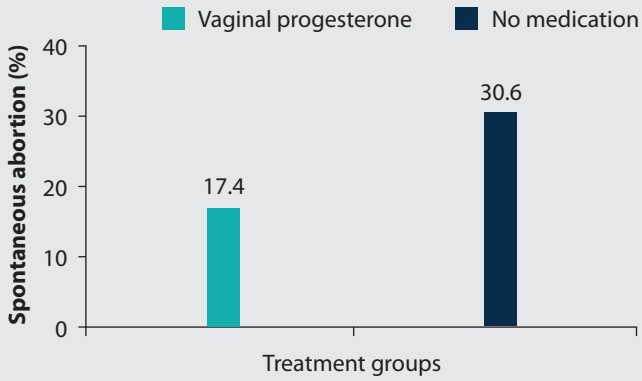
- **Primary:** Rate of spontaneous abortion before 28 weeks
- **Secondary:** Mean gestational age at delivery (weeks), number of preterm deliveries, number of vaginal bleeding episodes before 28 weeks, mean birth-weight, mode of delivery, APGAR score (5 minutes), and number of neonates admitted to the neonatal intensive care unit (NICU).

Important findings

- Patients in the progesterone-treated group demonstrated a significantly lower rate of spontaneous abortion before 28 weeks when compared to the nonprogesterone group ($p = 0.016$; Figure 1).
- At the time of delivery, mean gestational age was significantly higher in patients treated with progesterone than those receiving no medication ($p < 0.001$).

- In comparison to the vaginal progesterone-treated group, preterm delivery (28–37 weeks) was significantly higher in Group 2 (12.7% *vs.* 36%; $p = 0.005$).
  - The mean birth-weight of preterm neonates was significantly higher in progesterone-treated patients than in those receiving no medication (2952.05 ± 364.2 *vs.* 2620.88 ± 286.3; $p = 0.002$).
  - The number of newborns with a 5-minute APGAR score <7 was lower in the progesterone-treated group compared to those in Group 2 (8 *vs.* 20; $p = 0.008$).
  - The frequency of NICU admissions was lower among newborns treated with progesterone, compared to those in Group 2 (8 *vs.* 15; $p = 0.044$).
- The rate of vaginal bleeding episodes before 28 weeks was similar in both groups.

Figure 1: Frequency of spontaneous abortion in the treatment groups



Utilizing vaginal progesterone post-McDonald cerclage significantly reduced the occurrence of abortion before 28 weeks, resulting in positive neonatal outcomes.

Postoperative vaginal progesterone in ultrasound-indicated cerclage: Preventing preterm birth

The present study evaluated pregnancy outcomes based on postoperative vaginal progesterone use in patients who underwent ultrasound-indicated cerclage.[2]

Study methods

Study design

This single-center retrospective study was conducted between January 2005 and June 2017.

Patient population

A total of 86 patients who underwent ultrasound-indicated cerclage had the following indications for cerclage:

- Singleton pregnancies
- Incidentally found short cervical length under 20 mm in screening transvaginal ultrasound
- Cerclage performed between $16^{0/7}$ and $23^{6/7}$ weeks' gestational age
- Intact membranes
- Absence of regular uterine contractions
- No history of prophylactic cerclage during the current pregnancy period

Interventions

Patients were divided into 2 groups.

- **Group 1:** Patients received vaginal progesterone (200 mg/day) within 1 week of the cerclage surgery and continued until 34–36 weeks of gestation (n = 45).
- **Group 2:** Patients received no medication (control group, n = 41).

Outcomes

- **Primary:** Rate of preterm delivery before 34 weeks of gestation
- **Secondary:** Gestational age at delivery, number of preterm deliveries, and neonatal outcomes including birth-weight, APGAR score, and NICU admission

Important findings

Maternal outcomes

- Patients receiving adjunctive vaginal progesterone therapy demonstrated significantly lower rates of preterm delivery <34 weeks of gestation when compared to those receiving no medication ($p = 0.021$; Figure 1).
- In comparison to control group, median gestational age was significantly longer in vaginal progesterone-treated patients (37.3 weeks *vs.* 38.3 weeks; $p = 0.020$; Figure 2).
- Vaginal progesterone use post-cerclage independently lowers the risk of preterm delivery before 34 and 37 weeks.

Figure 1: Frequency of preterm delivery in the treatment groups

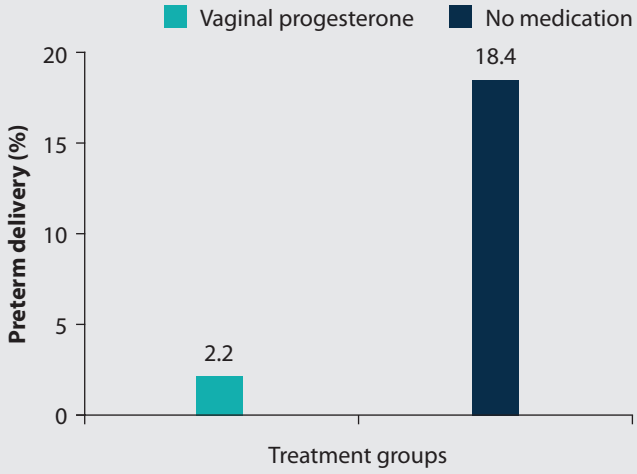
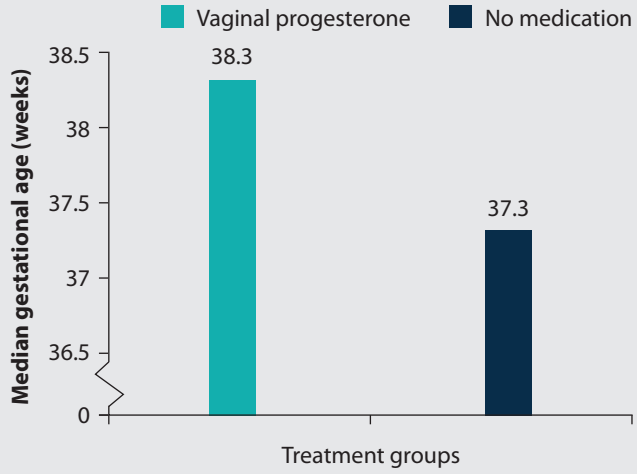


Figure 2: Median gestational age in the treatment groups



Neonatal outcomes

The neonatal outcomes noted between the treatment groups are as follows:

- Birth-weight (postoperative vaginal progesterone: 3235 g *vs.* control: 3063 g)
- 5-minute APGAR score <7 (postoperative vaginal progesterone: 5.9 *vs.* control: 6.3)
- NICU admission (postoperative vaginal progesterone: 17.8 *vs.* control: 22.2)

Adjunctive vaginal progesterone use significantly reduced the rate of preterm birth before 34 and 37 weeks of gestation in patients who underwent ultrasound-indicated cerclage.

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RESEARCH SNAPSHOTS

Impact of combined fertility interventions

Combining cervical cerclage and progesterone supplementation represents a promising strategy for reducing the incidence of preterm births among women at risk.[1] Cervical cerclage involves placement of a stitch around the cervix to provide mechanical support and prevent premature cervical dilation.[2] Progesterone supplementation, on the other hand, may help in maintaining uterine quiescence and cervical integrity, reducing the risk of preterm birth.[3] Clinical studies demonstrating the impact of combined progesterone and cervical cerclage are discussed in detail below.

Vaginal progesterone and cervical cerclage in preventing preterm birth: A combined approach

The present study aimed to evaluate the effectiveness of vaginal progesterone in combination with cervical cerclage for the prevention of preterm birth in comparison to single therapy.[1]

Study methods

Study design

The study is a systematic review and meta-analysis including 11 randomized and pseudo-randomized control trials, nonrandomized experimental control trials, and cohort studies.

Patient population

The study included patients with singleton pregnancies who had shorter cervical length (<25 mm) and a history of preterm birth.

Interventions

Patients were subjected to either cerclage, progesterone, or a combined treatment.

Outcomes

- **Primary:** Preterm birth <37 weeks gestation
- **Secondary:** Preterm birth <28 weeks, <32 weeks, and <34 weeks gestation; neonatal outcomes including neonatal intensive care unit (NICU) admission, intubation, birth weight, neonatal mortality, and gestational age at delivery; maternal outcomes including number of days between intervention and delivery, preterm premature rupture of membranes (PPROM), and cesarean section

Important findings

Preterm birth <37 weeks

- Patients receiving combination treatment demonstrated significantly lower rates of preterm birth <37 weeks when compared to treatment with cerclage (risk ratio [RR] 0.45, 95% confidence interval [CI] 0.29–0.71) or progesterone alone (RR 0.75, 95% CI 0.58–0.96).

- The rate of preterm birth in patients receiving combination therapy was significantly lower than in those receiving single therapy (Figure 1).

Obstetric outcomes

- Patients receiving combined vaginal progesterone and cervical cerclage exhibited significantly lower rates of preterm birth <34 weeks, <32 weeks, and <28 weeks than those receiving single therapy (Table 1).
- The combined therapy group exhibited a significantly longer gestational age at delivery compared to the cerclage-only group (mean difference: 0.91 weeks; 95% CI 0.65–1.17) and the progesterone-only group (mean difference: 2.13 weeks; 95% CI 1.35–2.91).

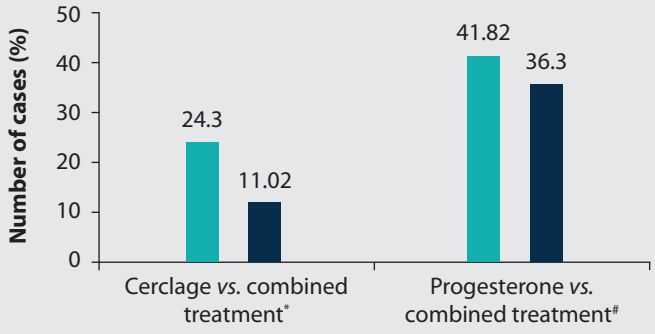
Neonatal outcomes

- In patients receiving combination treatment, birth weight was significantly higher when compared to cerclage-only (mean difference 304.99 g; 95% CI 225.38–384.60) and progesterone only (mean difference 296.78 g; 95% CI 238.06–355.50).
- Neonatal mortality was significantly lower in patients receiving combined treatment than single therapy (cerclage-only [RR 0.24, 95% CI 0.09–0.63] and progesterone-only [RR 0.40, 95% CI 0.22–0.75], Figure 2).
- In terms of NICU admission rate, no significant difference was noted between the single and combination therapy group.

Maternal outcomes

- No significant difference in the cesarean delivery rate was noted between the cervical cerclage group and the combined therapy group; no data is available for progesterone *vs.* combined therapy.
- In comparison to the progesterone-treated group, no significant difference was noted in the PPROM rate in the combined therapy group; no data is available for cerclage *vs.* combined therapy.

Figure 1: Rate of preterm birth following single *vs.* combination therapy

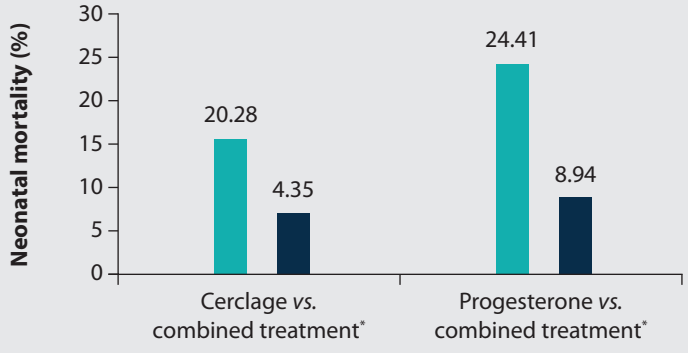


*$p = 0.0005$; #$p = 0.02$.

Table 1: Preterm birth rate in single therapy *vs.* combination therapy

Outcome	Cerclage-only group *vs.* combined therapy (%)	*p*-value	Progesterone-only group *vs.* combined therapy (%)	*p*-value
Birth <34 weeks	19.57 *vs.* 10.61	0.003	18.64 *vs.* 20.83	0.92
Birth <32 weeks	19.19 *vs.* 5	0.05	41.56 *vs.* 15.07	0.0006
Birth <28 weeks	20.81 *vs.* 10.86	0.01	31.63 *vs.* 10.19	0.0007

Figure 2: Neonatal mortality rate following single *vs.* combination therapy



*$p = 0.004$.

The combinatorial approach of utilizing cervical cerclage and vaginal progesterone significantly reduced preterm birth compared to single therapy.

Impact of vaginal progesterone and cervical cerclage on preterm labor prevention and perinatal outcome

The present study aimed to determine the effectiveness of progesterone supplementation, cervical cerclage, or the combination to prevent preterm labor and assess their impact on the perinatal outcome.[4]

Study methods

Study design

A single-center randomized clinical study was conducted between April 2013 and June 2014.

Patient population

A total of 126 pregnant women at high risk of preterm labor and meeting the follow criteria were included in the study:

- Singleton pregnancy
- History of spontaneous preterm labor
- Twin or triplet gestations
- Sonographic cervical length <25mm in mid-trimester
- Gestational age at the antenatal visit of 12–16 weeks

Interventions

Patients were randomly divided into 1 of the 3 groups.

- **Group 1**: Patients received vaginal progesterone (n = 42).
- **Group 2**: Patients were subjected to cervical cerclage (n = 41).
- **Group 3**: Patients received both vaginal progesterone and cervical cerclage (n = 43).
- **Follow-up**: Every 2 weeks till delivery.

Outcomes

- **Primary**: Spontaneous delivery <37 weeks gestation
- **Secondary**: Spontaneous delivery ≤34 weeks gestation and neonatal morbidity parameters including birth-weight, APGAR score, and NICU admission

Important findings: Women with multifetal (twin and triplet) gestations

- The combination group showed a significantly higher mean gestational age at delivery for multifetal gestations compared to those receiving progesterone or cerclage ($p = 0.0001$).
- Patients with multifetal gestations receiving a combination of vaginal progesterone and cervical cerclage demonstrated significantly lower rates of preterm delivery <37 weeks and <34 weeks than Group 1 and Group 2 ($p = 0.019$ and $p = 0.024$, respectively).
- In women with multifetal gestations:
  - The mean birth weight was significantly higher in the combination group compared to Group 1 and Group 2 ($p = 0.043$).
  - The mean APGAR score was significantly higher in those receiving the combination compared to individual treatments ($p = 0.013$).
  - The number of NICU admissions was significantly lower in the combination group compared to individual treatments ($p = 0.006$).

The combined use of vaginal progesterone and cervical cerclage significantly reduced the risk of preterm labor in twin and triplet pregnancies, as evidenced by a longer mean gestational age at delivery and improved composite perinatal outcomes.

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GUIDELINE QUICK READS

Some guidelines recommend the use of cervical cerclage and vaginal progesterone combination for certain conditions.[1,2]

Prediction and prevention of spontaneous preterm birth, American College of Obstetricians Practice Bulletin Number 234[1]

- A short cervix in the second trimester and a previous preterm delivery are some of the strongest risk factors for preterm birth that can have an additive effect.
- Both cervical cerclage and vaginal progesterone have demonstrated benefits in patients with singleton pregnancy, a history of preterm birth, and a short cervix.
- The high risk of preterm birth should be communicated to patients with singleton pregnancy, a preterm birth history, and a short cervix not administering progesterone. Vaginal progesterone and cerclage should be suggested as effective treatment options, and the uncertainty regarding the best-suited management approach should be discussed.
- Women with a singleton gestation, history of preterm birth, a short second trimester cervix, and on progesterone supplementation should be informed that they have a higher risk of preterm birth, and hence cerclage could be offered in addition to the ongoing administration of progesterone.

Guidelines for obstetrical practice in Japan: Japanese Society of Obstetrics and Gynecology and Japan Association of Obstetricians and Gynecologists 2014 edition[2]

In order to treat women suspected of having cervical incompetency

- Close, cautious monitoring similar to that followed for women experiencing threatened abortion or preterm labor is recommended.
- Therapeutic cervical cerclage use is suggested.
- Prophylactic cervical cerclage can be suggested soon after ≥12 weeks of gestation.
- Progesterone supplementation can be considered, as it is an effective adjunct to cervical cerclage.

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EXPERT OUTLOOK

Preterm birth is associated with high infant and maternal morbidity and mortality, necessitating timely intervention with preventive treatments in high-risk patients.[1]

Cervical cerclage (aimed to provide mechanical support and help maintain a long, closed cervix) and progesterone (aimed to induce an anti-inflammatory action with positive changes in the myometrium) are some of the common approaches important for maintaining pregnancy until term.[1]

The combination of these two interventions provides an additive effect and reduces the risk of preterm birth significantly.[1]

Common clinical scenarios we come across in routine practice with demonstrated efficacy of the cervical cerclage-vaginal progesterone combination are discussed below.

Patient population	Outcome of combined therapy
In women with singleton, nonanomalous pregnancies without a history of spontaneous preterm birth with cerclage placement[2]	▸▸ Adjuvant vaginal progesterone reduces the risk of preterm birth. ▸▸ The risk of infection is also generally low with the combination.
In women with cervical cerclage failure[3]	▸▸ Rescue adjuvant vaginal progesterone usually prolongs pregnancy. ▸▸ It produces positive neonatal outcomes, such as a higher birth weight.
In women with extremely short cervical length (<10 mm), no history of preterm birth, and already receiving progesterone for the treatment of a shortened cervix[4]	▸▸ The placement of a cervical cerclage increases the time to delivery.
In women with twin gestations, with a history of spontaneous preterm births and a short cervical length mid-trimester[5]	▸▸ Improvement in gestational age is observed. ▸▸ Favorable neonatal outcomes are noted (high APGAR score and body weight, along with a low frequency of NICU admissions).

APGAR: Appearance, pulse, grimace, activity and respiration; NICU: Neonatal intensive care unit.

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