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Comparing Prophylactic Vaginal Progesterone & Cervical Cerclage In Preventing Preterm Birth: A Systematic Review.

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Abstract: Preterm birth complicates at-risk singleton pregnancies, and this is associated with a poor prognosis for pregnant mothers. When comparing cervical cerclage to vaginal progesterone, the rationale is clear, but its effectiveness remains a mystery.It is the goal of this systematic review to shed further light on this well-known conundrum. To find research on preventive vaginal progesterone usage vs cervical cerclage, PubMed, PubMed Central, Medline, Science Direct, and Google Scholar were searched. There were three randomized control trials, three systematic reviews and meta-analyses, two cohort studies, and two conventional reviews. It was determined that both strategies for managing preterm delivery were equally effective in terms of preterm birth prevention when applied to pregnant women. We found that vaginal progesterone had less side effects than cervical cerclage, but it has no influence on a woman's ability to function and does not improve her life expectancy. The systematic reviews and randomized controlled studies unequivocally confirmed these findings. Cervical cerclage was shown to be more risky than preventive vaginal progesterone in a comprehensive study. However, prophylactic application of cervical cerclage still remains a superior treatment modality if serial transvaginal ultrasound scans are pointing towards cervical shortening. Therefore, more research is required to understand this relationship to identify populations at risk.

Keywords: Preterm birth; Prophylactic Vaginal Progesterone; Cervical Cerclage; pregnancy

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Introduction

Preterm birth (PTB) is the delivery of a child after the 20th week but before the completion of 37th week of pregnancy [1]. It is a prominent cause of prenatal death and morbidity across the world (about 1.1 million annually), and long-term neurodevelopmental disabilities and accounts for about 11% of pregnancies[2]. About 5% of babies are born before 28 weeks (extremely premature), 10 percent are born between 28 to 31 weeks (very premature), and around 85% are born either in the middle of 32 to 33 weeks(moderate) or sandwiched between 34 to 36 weeks (late premature) of pregnancy [3]. Screening and therapy to identify high-risk women for preterm delivery is necessary to reduce the fetomaternal consequences of preterm birth.

There exist no specific causes for preterm birth, but preterm delivery is more likely for the woman under certain circumstances. Studies have shown that advanced maternal age is one of the key risk factors for preterm birth [2]. Additionally, doing harmful things during pregnancy can trigger preterm birth like drug abuse and dependence [4].

Having a previous premature birth can predispose a woman to other premature births in the future [4]. Pregnancies with multiple babies could lead to premature birth[4, 5]. Many Researches has also shown that having fewer than six months between pregnancies can result in higher chances of premature birth [4]. Some infections in the lower reproductive tract or the amniotic fluid can lead to a premature birth[6]. During prenatal period and even before, it is also important to maintain sustainable lifestyles to avoid premature birth. Maintaining a proper diet is important to avoid being underweight or overweight. These circumstances, and others, on their own, do not result in preterm birth. However, they increase the likelihood of its occurrence[7].

In order to avoid preterm labour, the first step is to identify pregnancies that are at risk. A number of factors may be used to identify high-risk situations. One of the best ways to predict preterm delivery is a previous personal history of spontaneous preterm birth (up to 34+0 weeks) or a loss in the middle of the second trimester (from 16+0 weeks on). A transvaginal ultrasound examination conducted between 16 and 24 weeks of pregnancy can detect a cervical length of less than 25 millimetres. In addition, asymptomatic cervical shortening and a prior history of premature pre-labor membrane rupture (P-PROM) or cervical trauma are warning signs of an at-risk pregnancy[8]. Other than these factors, it is also noted that bleeding in the second trimester could also lead to spontaneous preterm birth, so it can be taken as a high-risk pregnancy [9].

Preterm birth can be prevented using a variety of preventive methods. Three tools for preventing preterm birth have been developed in RCTs throughout the last decade. Progesterone, cervical cerclage, and pessary all have a role. There are three ways to provide progesterone: oral, vaginal, and intramuscular (IM). Vaginal progesterone and preterm birth prevention: the OPTIMUM trial is one of three major studies [10]. The effects of progesterone on lowering the risk of preterm birth were shown to be negative [11]. However, a number of investigations have been out, notably the third and biggest PROGRESS project [12].

Suture (purse-string) application at internal Os level provides structural support to the cervix during cervical cerclage. As a result, it serves as a biochemical barrier to prevent infection from spreading and protects the mucous membranes [13]. Studies have shown that history-indicated cerclage is more effective than expectant care in reducing preterm delivery in more than half of the instances in which it has been tested in large randomised controlled trials (n=1292). Preterm deliveries earlier than 35 completed weeks were significantly reduced in women having a background in second-trimester loss and in women having a past of preterm birth when an ultrasound-indicated cerclage was used instead of expectant care [RR 0.57; 95 percent CI 0.33-0.99] [13].

Vaginal or intramuscular administration of progesterone is an option [12]. Nonetheless, unlike intramuscular 17-hydroxyprogesterone caproate, which has been demonstrated in the PROLONG trial to be unsuccessful in preventing premature birth, vaginal progesterone has not been licenced by the FDA for this purpose[14]. Another unresolved issue is the mechanism of action by which progesterone helps prevent PTB as progesterone levels are usually maintained throughout pregnancy and labor[14]. Regarding cervical cerclage, the effect of single vs. double cervical cerclage needs to be explored further [15], especially in high-risk singleton pregnancies. On the other hand, there is room to explore the role of combining any two treatment modalities with being more effective in preventing preterm birth.

When babies are born prematurely, it has a significant impact on their mortality, morbidity, and cost to society[13]. According to a study that involved a French population, longevity and the likelihood of developing medical conditions is lowered where there was a long period of gestation. This problem is usually common in twin or more births. For singleton pregnancies, it is not common to have preterm births [13]. Similarly, it is important to develop a lasting solution for the problem. There has been extensive research on the matter, and scholars and medical practitioners have developed viable solutions to the problem.

In this systematic review, we are examining the efficacy of vaginal progesterone versus cervical cerclage in singleton pregnant women who are considered to be at high risk for preterm birth.

Material and Methods:

In order to determine if vaginal progesterone is more beneficial than preventative history ultrasound-indicated cervical cerclage in preventing preterm birth in at-risk singleton pregnancies, we searched for publications in academic journals that addressed this topic. It was utilised as a guide throughout the study procedure to follow PRISMA 2020 Guidelines for Systematic Reviews and Metaanalyses. PUBMED, PUBMED CENTRAL, Medline, Science Direct, and Google Scholar were combed for articles. Progesterone, cervical cerclage, and the prevention of premature delivery are the main topics. A control vocabulary thesaurus, also known as the MeSH, developed by the National Library of Medicine (NLM) makes it easy to search for articles in the PubMed databases. In the end, the search technique was as follows: " PROPHYLACTIC VAGINAL PROGESTERONE OR VAGINAL PROGESTERONE OR PROGESTERONE PESSARY OR ("Progesterone/administration and dosage"[Majr] OR "Progesterone/adverse effects"[Majr] OR "Progesterone/therapeutic use" AND PROPHYLACTIC CERVICAL CERCLAGE OR MCDONALD STITCH OR MCDONALD SUTURE OR SHIRODKAR STITCH OR ("Cerclage, Cervical/adverse effects"[Majr] OR "Cerclage, Cervical/classification"[Majr] OR "Cerclage, Cervical/history"[Majr] OR "Cerclage, Cervical/therapeutic use"[Majr] OR "Cerclage, Cervical/therapy"[Majr]) AND SPONTANEOUS PRETERM BIRTH OR MID TRIMESTER MISCARRIAGE OR USG EVIDENCE OF SHORT CERVIX(25MM OR LESS) ALONE OR WITH HISTORY OF CERVICAL TRAUMA OR PREPROM IN PREVIOUS PREGNANCY OR ("Pregnancy, High-Risk analysis"[Majr] OR "Pregnancy, High-Risk/statistics and numerical data"[Majr]) AND PREVENTION OF PRETERM BIRTH , PRETERM BIRTH OR PRETERM LABOUR , EARLY DELIVERY OR (PREVENTION OF PRETERM BIRTH , PRETERM BIRTH OR PRETERM LABOUR , EARLY DELIVERY) OR ("Premature Birth/analysis"[Majr] OR when a baby is born prematurely, he or she is given medication. The usage of keywords in other databases is mentioned in Table 1.

Table 1: Access to databases and the resulting search

Databases	**Main points**	**Search resu**
PUBMED	Following the final plan outlined above,	17413
Science Direct	treatment with progesterone or cervical cerclage to premature labour	262
Search Engine Academics(GS)	Premature labour can be avoided using vaginal progeste cervical cerclage.	2040

GS: Google Scholar

Eligibility Criteria

Progesterone, cerclage, or pessary were all included in the title and abstract searches for studies comparing them to a control group or another intervention to prevent premature delivery.

Both clinical trials and non-clinical trials-related publications were included in the selection process.

Relevant papers from the last 10 years were included in this review. This analysis does not include articles about animal research in general. Patients of the reproductive age group are taken into account.

Studies that were carried out on pregnant women with identified congenital abnormalities or intrauterine fetal death or in active preterm labor were also excluded while doing this review.

To prevent bias in our discussion, we used these inclusion and exclusion criteria to choose those papers that were relevant to our study issue.

Results

It was found that 19715 articles were retrieved from a methodological search strategy described in the technique section above. In addition, papers were weeded out based on their eligibility and accessibility to the full text. There were only 10 items available, and this article was a quality control measure based on the research characteristics.

The Cochrane risk-of-bias tool was used for studies including randomized control trials. The Joanna Bricks Institute (JBI) Critical Appraisal tool and AMSTAR checklist were used for systematic evaluations of cohort studies. Three SR/MA, two cohort studies, two conventional reviews, and three randomized control trials made up the finished study. All of the studies are of good quality with a low risk of bias. The type of interventions included in the studies included progesterone, cerclage, and placebo doses. The studies varied in different aspects; however, the studies had a similar goal. We can see a tabulated summary of the below in Table 2.

Table 2: A tabulated summary of the articles Abbreviations: n= Number of patients, RDS= Respiratory Distress Syndrome, NICU= Neonatal ICU

S.NO	Author	Study Design	Methodology	Outcome
1	[9]	RCT	200 mg micronized Progester 60) vs Placebo (n= 49) Once daily starting from 16-26 weeks till 36 weeks	Those patients who have a his bleeding in the second trimeste were given progesterone or had no effect in avoiding premature delivery.
2	[16]	RCT	400 mg vaginal Progesterone vs 400 mg vaginal Proge plus cervical pessary (n= 72) Vaginal progesterone: once da Continued till 37 weeks	The combination treatme cervical pessary plus progesterone was less effec reducing the adverse effe pregnancy and neonatal ou compared to the monotherap vaginal progesterone alone.
3	[17]	RCT	Study of 200 mg of progesterone n=618) vs. (n=610): vaginal progesterone admi every day. From 22-24 weeks till 34 wee	The study found no eviden vaginal progesterone had protective effect on preterm c or poor newborn outcomes. On a follow-up visit at the age there were no long-term health repercussions.
4	[1]	MA and SI	There were fourteen studies that were reviewed fo evaluation. Subjects received proge (n=1259) Vs placebo (n=2653)	The review concluded the supp role progesterone in preterm bi prevention specifically in the w with one risk factor.
5	[18]	SR	Total # of studies included review: n= 40 (11311 pregnant women)	The review concluded the sup role of per vaginal progesteron preterm birth prevention as neonatal mortality in at risk sin pregnancies.

				However, there was no advantage for women with cervix.
6	[11]	IPD	Includes five RCTs (n=775)	Vaginal progesterone subst decreases the risk of preterm d and Bad outcomes for infants mothers with short cervixes who are otherwise healthy thro pregnancy, according to the rev
7	[17]	TR	In the progesterone group percent (42/402) and 10.6 percent (41/388) of t women studied were found to elevated progesterone (adjusted RR, 0.98; 95 percent CI, 0.64–1.49; P= respectively.	Women with a short cervix advantage from vaginal proges according to the two organ mentioned above.
8	[13]	TR	N= 7861 women Interventions studied progesterone and cervical cerclage.	Vascular progesterone has shown to minimise the risk of admission and early preterm d significantly.
9	[12]	CS	Cervical cerclage (n=142) Vaginal progesterone(n=59) Cervical pessary (n=42)	With a short cervix, pregnant can use any of the three treatm options to prevent preterm lab
10	[19]	RS	N= 267 Cervical cerclage (n= 116) Vaginal progesterone (n= 151	Cervical cerclage, as compa vaginal progesterone, extends pregnancy by roughly 39 days does not prevent premature del

RCT: Randomized Controlled Trial; MA: Meta-analysis; SR: systematic review; TR: Traditional review; RS: Retrospective study; CS: cohort study; IPD: Individual patient data

Discussion

Causes and Possible Effects of Preterm Birth

Preterm birth is a multifactorial condition that could be triggered by a variety of risk factors [1]. The key preventive measure for PTB lies in the correct identification of risk factor that could increase the incidence of preterm birth in a pregnancy[1]. Preterm birth is more likely when there is vaginal bleeding in the second trimester, according to Salim et al. [9] or past history of cervical trauma/ preterm birth [8]. Hezelgrave et al., on the other hand, posit that preterm birth may be based on a short cervical length[14].

Prematurity is one of the leading causes of health issues in infants and children in the short and long run. The most determinantal effects include problems related to respiratory system like respiratory distress syndrome (RDS) or development of chronic lung issues and long term neurological issues like mental and developmental delays [1].

In order to avoid these consequences, the effects of different prophycatic treatment options have been studied. Three major interventions have been established, each of which has been shown to have mixed results on different women [13]. In this systematic review, we focussed on particularly two of the treatment modalities, namely, vaginal progesterone and cervical cerclage.

Effectiveness of Prophylactic Vaginal Progesterone

Progesterone has been demonstrated to reduce the chances of preterm delivery in women who are in high-risk pregnancies [16]. Preterm births in singleton at-risk pregnancies and those with a history of preterm deliveries have demonstrated consistent benefits with this therapy [18].

Inflammation causes labour to begin, hence progesterone has an anti-inflammatory effect [17]. A functional withdrawal of progesterone from the tissues caused by changes in progesterone receptors may induce spontaneous labor[16]. The half-life of naturally occurring progesterone, which is used to prevent premature birth, is 13 hours. There are no side effects and it is absorbed fast. Despite the recommendation of the American College of Obstetricians and Gynaecologists, research have revealed that progesterone supplementation should only be used in singleton preterm pregnancies with a history of spontaneous preterm births. - At this point in the pregnancy, progesterone is proving to be useful [16].

In a certain study, eighteen experiments were carried out against a control experiment on the efficacy of progesterone. Women with past preterm births, women with short cervices, and women with particular risk factors are included in the study cohort [18]. Progesterone substantially lowered the risk of preterm delivery from less than 33 weeks to less than 37 weeks, according to an examination of the results.

A study by A. Care and S.Jackson in 2021 compared the effects of cervical cerclage vs progesterone in women with a single risk factor of short cervical length. The results of this study didn't support any benefit of cerclage over progesterone in preterm birth prevention [20].

In another RCT, the effect of progesterone therapy for the prevention of preterm birth as a secondary outcome has been observed especially in a group of women with the history of first trimester recurrent pregnancy loss. Results showed positive role of progesterone in reducing the risk of further miscarriages but no significant reduction in the occurrence of preterm birth[21].

On the other hand,another study revealed that in comparison to the control group, those who took progesterone even if they had previously given birth prematurely had a considerably lower risk of preterm delivery [22]. Using vaginal progesterone in individuals with short cervices reduced the incidence of preterm delivery before the 33rd week of pregnancy, according to another research [23]. Patients who had vaginal therapy instead of placebo saw higher results, according to the same research. Additionally, this treatment led to a reduction in neonatal and perinatal deaths [5]. The newborns whose mothers received progesterone treatment also suffered less from respiratory distress syndrome.

In general, studies have shown singleton pregnancies are better and easier than twins. For singleton pregnancies, vaginal progesterone was connected to a significant decrease in premature deliveries between 33 and 28 weeks of pregnancy. Another benefit was that it prevented respiratory distress syndrome (RDS), newborn composite morbidity, and death. The medicine did not substantially prevent preterm deliveries in twin pregnancies before 33 weeks, however it did dramatically lower the chance of composite neonatal morbidity and death.

Clinically given progesterone has least risk of congenital malformations in fetus. To avoid premature delivery, preventive progesterone should be given to pregnant women with a history of preterm birth and a short cervix, according to research by Fonseca [13]. This intervention should be administered at mid-pregnancy after a diagnosis by a scan.

Effectiveness of Cervical Cerclage

Another method that has been proven to work is cervical cerclage. This technique involves a surgical procedure carried out during pregnancy that uses sutures to strengthen the cervix for women who are proven to have short cervices [12]. This procedure can either be done through the vaginal or abdominal route, which is a less common method[14]. This procedure is usually recommended when the cervix is likely to open before the term gestation period is complete. This

method is, however, not applicable for everyone. It is associated with side effects, and it is not always guaranteed to work.

Before 37 weeks, the cervix is closed, long, and strong. As the pregnancy progresses, it opens up gradually as it prepares for the birth of the child. However, if the cervix is too short, it may lead to preterm birth. Patients with a history of pregnancy loss in the second trimester coupled with painless cervical dilatation and no labour might consider this sort of treatment [24]. The painless cervical dilatation that occurs during the second trimester may also apply to patients who have had cerclage in the past. Patients with painless cervical dilatation in the second trimester have also benefited from this treatment. It is possible to use cervical cerclage prior to the 24-week gestational period in singleton pregnancies with a cervical length of less than 25 millimetres[24, 25].

However, there are situations under which this technique is inapplicable. In such situations, other interventions like vaginal progesterone can be applied. One such instance is when the amniotic sac leaks or ruptures prematurely, before 37 weeks of pregnancy. Another instance is when the patient is in active preterm labor. Additionally, in cases where there is vaginal bleeding or where the patient has an intrauterine infection, it is advisable to avoid this technique. It was also important to consider the risks associated with cervical cerclage.

In the past, the criteria for establishing whether a patient could suffer from spontaneous preterm birth was based on the mother's characteristics, for example, race, age, lifestyle, and obesity [13]. However, such risk systems that base their findings on these maternal aspects have been unreliable and show a low detection rate. An alternative is using transvaginal ultrasounds of the cervical length at the 20th to the 24th week of pregnancy[26]. This has proven to be a more efficient technique to identify high-risk groups in singleton and twin pregnancies [13].

Comparison of Efficacy

The running theme in solving the problem with preterm birth, regardless of the technique used, is first identifying the risk of preterm birth. We have established that there are aggravating factors but there is no conclusive evidence of an at-risk pregnancy. Many scholars and practitioners have found that the most effective way would not be to consider the risk factors like pre-existing conditions or a history of preterm births. The most effective way is through transvaginal ultrasound. Transvaginal ultrasound is also called an endovascular ultrasound. It is the examination of the female reproductive organs using high-frequency sound waves to create images. This helps doctors to diagnose any condition that may exist.

From the analysis above, we have provided that cervical cerclage effectively controls preterm birth. Both vaginal progesterone and cervical cerclage have proved effective in controlling preterm birth. There is minimal evidence that any intervention is more effective than the other. According to a 2016 OPPTIMUM study based on results of a randomized test, it was apparent that vaginal progesterone, compared to cervical cerclage, suggested no difference in their effectiveness[17]. In a more recent analysis by Jarde et al. in 2019, it was established that vaginal progesterone was more effective than cervical cerclage in women with a history of preterm birth[18]. Progesterone also proved more effective in preventing preterm births overall. On these parameters, vaginal progesterone can be considered a more effective technique. However, a treatment that involves combining the two techniques must be considered as it is likely to yield the best results.

The patient's health and preferences will play a role in determining the best course of action. Even in twin pregnancies, women with short cervixes of less than or equal to 25mm should be given progesterone on a regular basis, according to data from IPD-MA [9]. Although progesterone may help prevent preterm birth in women who already have symptoms, additional study is needed to confirm this.

Limitations of the Study

The research was carried out based on an analysis of existing secondary data. Therefore, there are no first-hand results of the outcome of any of the experiments under the current conditions. Further, the cohorts based on collected were for a small population base. Diversity may not have been achieved. Additionally, most of the studies involved small groups, and therefore, there is no guarantee that the outcome will translate to the rest of the population. Hence, to adequately answer the question of which is the more effective intervention, there is a need to carry out an analysis that will cross check of both techniques with best results.

Conclusions

Preterm birth reduction remains one of the biggest obstetric challenges. For this purpose, this study was conducted to compare the effectiveness of vaginal progesterone with cervical cerclage. From research, it is apparent that both techniques are applicable for singleton pregnancies. However, there are some risks associated with each. Cervical cerclage seems to attract more risks than vaginal progesterone use. Vaginal progesterone is a preferred technique based on its applicability for singleton pregnancies. Vaginal progesterone intervention has gained more popularity over the cervical cerclage method because it allows patients a more conservative solution to their problem. However, if the length of the cervix continues to shorten, then preventive cervical cerclage must be done to extend the gestation period. Most studies have stated that cervical cerclage effectively prevents spontaneous preterm birth compared to other treatments.

Further research is needed to develop and grow the knowledge on this matter. Several things need to be finetuned. Among them is the system to be used in identifying the at-risk patient. This will make it easier to identify patients in need of care early enough and begin treatment to prevent premature births and other associated conditions. The information gathered from research and experimentation on the matter can ensure that patients receive effective medical interventions for their situations. It is also useful in determining the weaknesses in the field and assessing the failures of the present system to come up with more effective solutions.

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. The study on humans was conducted in accordance with the ethical rules of the Helsinki Declaration and Good Clinical Practice.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

None.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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