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Updates of Progestogens in Preterm Labour Review

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Abstract – Preterm births (PTBs) are among the main source for feto-maternal mortality and short and long term neonatal/infant morbidity around the world. PTBs refer to premature deliveries occurring preceding 259 days of gestation or before 37 gestational weeks (gw).

This condition is prevalent and thusly presents a significant world general medical issue: It has been accounted for that roughly 15 million preterm deliveries universally in 2010, of which 1 million babies died because of PTB related complications. The biological bases and pathways of preterm delivery have just been to some extent clarified. PTB is a complex syndrome and inadequate exploration has been performed on the aetiology.

Many are the possible risk factors (past PTB, cervical effacement and dilatation, infections/inflammations being the major predisposing factors). Predictive, preventive and interventional procedures are expanding to manage patients at high risk for preterm delivery hence improving feto-neonatal results. Progesterone plays a critical part in the upkeep of uterine quiescence (particularly during the latter half of pregnancy) because of the constraint of stimulatory prostaglandin production and contraction related protein gene expression, the suppression of the inflammatory cascade activation and in this manner the spread of ascending infection, the decrease of cervical stroma degradation and gap-junction formation. Also, term and preterm labour onset are related with functional withdrawal of progesterone activity at a uterine level. As a result, progesterone and different progestogens have been tried in clinical preliminaries for preventing PTB. The characteristics of progestogens' pharmacokinetic and pharmacodynamics profile are of extraordinary interest to researchers and clinicians to characterize the ideal medication, route of administration, dosage and exposure-response relationship.

Keywords – Preterm Labour , Progesterone , Tocolysis.

I. INTRODUCTION

Preterm births (PTBs) refer to premature deliveries which occur preceding 259 days of gestation or under 37 gw. The condition is prevalent introducing a significant general medical issue around the world. 15 million preterm deliveries occurred around the world in 2010, representing 1 million infants died as a result of PTB complications [1]. In the USA, 1/8 of the deliveries in recent years were preterm; 85% of which were related with serious perinatal morbidity and mortality [2]. Of 3.1 million worldwide neonatal deaths, 35% were due to PTB complications [3]. Approximately 20% of preterm deliveries were iatrogenic, for foetal and/ or maternal indications (toxaemia, placental abruption, intrauterine growth restriction, placenta praevia, maternal cholestasis, non-reassuring foetal monitoring test and monochorionic-monoamniotic twin pregnancy complications) [4]. Another 20–30% of PTB

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cases were identified with preterm premature rupture of membrane (P-PROM), 20–25% were an aftereffect of intra-amniotic inflammation or infection and 25–30% were related with unexplained (spontaneous) preterm labour(PTL) [5].

Perinatal mortality increments multiple occasions in women with PTB (51.7/1000 births) which is likewise a main source for serious perinatal morbidity, for example, neurodevelopmental insufficiency, cerebral palsy, seizures, visual impairment, deafness, bronchopulmonary dysplasia, retinopathy of prematurity, gastrointestinal complications, cardiovascular and metabolic disorders [6,7]. Also, clinical consideration of preterm infants is costly including enormous expenses for medical services systems and families. Medications that decrease the rate of PTB would significantly affect the clinical, monetary and emotional burden for these children, their families and the medical services systems.

Clinical risk recognizable identification remaining the first and the most significant way to deal with women at risk for preterm delivery and it depends on non-specific variables, past history of PTB, short cervix estimated on transvaginal ultrasound, infection/inflammatory status detection. When women at risk are distinguished, clinicians can apply the accessible methodologies to prevent this event.

Progesterone assumes a critical part in the support of uterine quiescence (during the latter half of pregnancy) because of a decline in stimulatory prostaglandin production, inhibition of contraction related protein gene expression, suppression of the cytokine inflammatory response in this manner preventing rising infection dissemination, just as a decrease in gap junction development and cervical stroma degradation. Progesterone alters not just oestrogen synthesis in foetal membranes and the placenta, yet additionally foetal endocrine-intervened impacts. It diminishes the quantity of oxytocin receptors and supresses the initiation of the pro-inflammatory cascade. Also, term and preterm labour onsets are both basically connected with functional withdrawal of progesterone activity at a uterine level [8].

The assortment of scientific writing is growing with publications on the role of progesterone in obstetrical care, particularly in PTL prevention in such manner, progestogens have been to a great extent read in clinical preliminaries for the counteraction of PTBs somewhat recently. Scientists and clinicians have exhibited incredible premium in describing the pharmacokinetic and pharmacodynamics profile of progestogens to characterize and design the best preventive strategies.

This review centres around the components whereby progestogens might decrease the PTL risk, the ideal preparation, dosage and route of administration. Progesterone is the most studied prophylactic agent for the prevention of PTBs and the improvement of neonatal outcome, yet there is an absence of consistency in the detailed advantageous impacts. The various outcomes might be because of the multifactorial aetiology of PTL activation, the different patient cohorts enlisted in clinical preliminaries and the utilization of various types and routes of administration of progesterone and progestogens.

II. Role of Progesterone in Obstetrics

Progesterone is a hormone which assumes a well-recognized fundamental part during the process of reproduction. It is utilized in the treatment of various gynaecological pathologies (endometrial hyperplasia, dysfunctional uterine bleeding, amenorrhea, luteal phase insufficiency, pre-menstrual syndrome, contraceptive use) and obstetrical conditions (assisted reproductive techniques, compromised threatened miscarriage, prevention of RPL, history of past preterm delivery, threatened PTL).

The role of progesterone in the support of pregnancy includes the balance of maternal immune response [9, 10, 11], the suppression of the pro-inflammatory cascade [12], the inhibition of uterine contractility [13, 14, 15], and its helpful impacts on utero-placental perfusion [16, 17]. The physiological parts of progestogens activities have been generally revealed, particularly for progesterone itself (P4) and the synthetic molecule of 17-alpha hydroxyprogesterone caproate (17-OHP-C). Progestogens inhibits IFN-gamma and TNF-alpha, yet increment IL-4 production [18]. Dydrogesterone has been related with more elevated levels of IL-10 and expanded progesterone-induced blocking factor (PIBF) [18, 19], hence showing a critical anti-inflammatory role.

Vaginal micronized progesterone essentially decreases metalloproteinase expression (both of MMP-9 and MMP-2) and lipopolysaccharide (LPS) activity on foetal membranes, suggesting a potential protective system in the avoidance of infection related PTB [20]. Concerning impacts on the myometrium, progesterone has been displayed to have a tocolytic activity both in vitro and in vivo all through pregnancy, diminishing myometrial oxytocin receptor concentration. Early examinations distributed during the 1960s and 1970s exhibited a decrease of PTBs in different high risk population of pregnant patients where 17-OHP-C was administered intramuscularly [9, 10, 11, 12]. During the 1990s the interest in the connection between progesterone/progestogens and PTL grew and the scientific writing expanded.

As of now, we realize that the impacts of progesterone/progestogen treatment are dose dependant and identified with the route of administration, albeit now and then dependent on controversial clinical information's. Some authors have proposed that 17-OHP-C represses myometrial contractility in a portion subordinate way [21], while others have noticed no impact of 17-OHP-C in miscarriage prevention, yet exhibited a decrease in the rate of PTBs and low birth-weight babies [22].

III. Routes of Administration: Key Differences

Albeit the pharmacokinetics and pharmacodynamics of progesterone have been examined beginning around 1935, when progesterone was first synthesized, the ideal variation to utilize stays questionable in view of the different routes of administration, doses and biochemical structure. The rate of absorption is reliant upon which drug structure is being utilized and the blood stream at the site of administration. Progesterone can be administration by a wide range of routes: orally, vaginally, intramuscularly, per rectum, and by transdermal patches.

Some data got from animal models has proposed that vaginal progesterone may extraordinarily change the inflammatory milieu of both the cervix and the endometrium, with ensuing significant potential clinical benefits [23]. Different examinations have likewise upheld the vaginal route of administration in contrast with intramuscular infusion. There is likewise a randomized control preliminary (RCT) contrasting both vaginal and intramuscular progesterone administration in pregnant women with a past history of PTB. Altogether less preterm deliveries were seen among women on vaginal progesterone [24].

Geographical contrasts exist overall as indicated by the types, dosage and routes of administration of progesterone. In an enormous multi-institutional review directed in the National Institute of Child Health and Human Development (NICHD) Maternal-Foetal Medicine Units Network, Meis et al., showed that 17-OHP-C given intramuscularly diminished recurrent the PTB rate by 30% (RR 0.66, CI, 0.54–0.81) [25]. Adoption of prophylactic progestin treatment was related with a diminished OR of recurrent PTB before 35 and 37 weeks of gestation after adoption of program dependent on early progestin treatment [26]. Thus, current practices in the US is to offer 17-OHP-C, when a pregnant patient presents with a background marked by a past unconstrained PTB. Furthermore, 17-OHP-C is the main endorsed progesterone treatment by the Food and Drug Administration (FDA) for the avoidance of PTL in the US. Notwithstanding, it very well might be sensible to think about the utilization of vaginal progesterone, which albeit not FDA supported for this sign, was observed by a several studies to be effective in PTB prevention [22].

3.1 Oral Administration

Oral organization is related with better persistent consistence, yet has a several disadvantages, for example, the outrageous changeability in plasma of concentrations because of individual variety in gastric filling and enterobiliary circulation. Besides, food intake might impact the rate of medication absorption by diminishing gastric emptying, diminishing gastrointestinal (GI) motility, expanding GI secretions and splanchnic blood stream. Oral progesterone intake is additionally affected by passage through the liver and hepatic metabolism. The metabolites created by the liver are not progestogenically dynamic as shown by the discrepancy between the measured progesterone levels and endometrial histology [27].

A few manufactured oral progestogens have been developed to overcome progesterone's low oral bioavailability. Their pharmacological impacts, however has uncovered many incidental effects, like androgenic impacts, fluid retention tendency, changes in lipoprotein profile, migraine, mood disturbances, nausea, sleepiness, GI discomfort. Micronization of progesterone into molecule sizes of <10 microns builds the accessible surface region and upgrades the aqueous dissolution rate consequently improving intestinal absorption. Suspension in oil and packaging in gelatine containers has additionally improved digestive absorption [28].

3.2 Intramuscular Administration

Historically, the most well-known route of administration was intramuscular [28]. IM administration brings about ideal blood progesterone levels. Subsequently, the IM route can be utilized in patients with vaginal bleeding and doesn't require in excess of a daily or weekly doses [29]. In any case, IM use is related with local discomfort and pain, and periodic nearby non-septic abscesses at the site of infusion. Additionally, side effects have been described, like tiredness, dizziness migraine, bloating, abdominal pain, constipation, diarrhoea, nausea, vomiting, joint pain, depression, sleepiness, breast tenderness, flu-like symptoms, infection predisposition and hypersensitivity reactions. Recent studies, have additionally related the intramuscular utilization of 17-OHP-C with an expanded rate of gestational diabetes (GD) because of its diabetogenic impacts by promoting pancreatic beta-cell hyperplasia and in this way expanding insulin production [30]. Rebarber et al. concentrated on GD in patients who got 17-OHP-C

infusions to prevent recurrent PTB: The GD occurrence in the 17-OHP-C treated group was 12.9% contrasted with 4.9% in the control group ($p < 0.001$) without medication [31]. In any case, 17-OHP-C is the main agent approved to date by the US FDA for avoidance of recurrent PTB [30].

3.3 Vaginal Administration

The vaginal route is the favoured route of administration in clinical practice in various centres around the world. The scientific literature upholds vaginal progesterone application as an effective strategy for PTB prevention. The vaginal route of administration brings about higher concentrations of progesterone inside the uterus because of the so called first uterine pass effect [29]. Three distinct hypotheses have been accounted for to clarify the primary uterine pass effect: (1) high immediate concentration inside the vaginal and uterine cells; (2) presence of portal like lymphatic vessels which connect the upper vagina to the uterus; (3) presence of a reverse circulation system, similar as the portal system, with vein to artery diffusion between the upper vagina and the uterus. Bulletti et al., exhibited that a first uterine pass impact occurred when progesterone was regulated vaginally, affirming that the vaginal route allows designated drug delivery to the uterus, augmenting the desired effect while limiting the potential adverse systemic side effects identified with different routes of administration [32]. After vaginal application the uterine progesterone tissue concentration was found to surpass more than ten times the levels seen after systemic administration. An opportunity to arrive at top concentration was for the most part somewhat not exactly that after oral administration of micronized progesterone. Plasma concentrations with a plateau like profile and more consistent progesterone concentrations over the long run are different benefits getting from the vaginal route of administration. Furthermore, the vaginal application doesn't appear to interfere with glucose metabolism or the induction of GD [33].

3.4 Rectal Administration

Recently, Afridi et al., thought about the viability of oral dydrogesterone and a micronized progesterone rectal suppository (Cyclogest) in the avoidance of PTB among patients at risk for PTL. Group A was given oral dydrogesterone (10 mg twice per day) while group B was given a cyclogest pessary (400 mg per day) per rectum at sleep time. The authors noticed a good profile with rectal administration of progesterone: prophylactic micronized progesterone per rectum was more powerful in diminishing the incidence of PTBs in high risk cases of prematurity compared with dydrogesterone and was additionally related with less maternal and neonatal complications [34]. Furthermore, Elder et al., saw that rectal progesterone diminished uterine contractions and decreased PTBs, which led to significant perinatal mortality decrease ($p < 0.05$) [35].

Abdali et al., additionally noticed the impact of rectal progesterone on the latent phase and maternal and neonatal results in females with preterm premature rupture of membranes (PPROM). Rectal progesterone (400 mg each night) was directed until delivery or completion of the 34th gestational week in a group of patients with PPROM somewhere in the range of 26 and 32 weeks. The preliminary was placebo controlled. The median latent phase was 8.5 days in the intervention group versus 5 days in the control group in the 28th–30th weeks of gestation, which was significantly higher ($p = 0.001$). Also, in the neonates, the birth-weight was essentially higher in the intervention group ($p = 0.03$) [36]. In any case, a new methodical audit and met analysis on progestogens in PPROM in singleton gestations showed that there were no distinctions in the latency period for women who got rectal progesterone (one preliminary surveyed rectal progestogen, and one preliminary had three arms that looked at 17-α hydroxyprogesterone caproate, rectal progestogen, and placebo treatment) [37].

The little example sizes and single source of information and still limit the overall acceptance of these studies, albeit the everyday utilization of rectal progesterone could address another possible therapeutic option.

Table 1 summarises the main different routes of progesterone administration.

Table 1. Progesterone routes of administration

Route	Pharmacokinetic and dynamic features
Oral	• Rapid increase and gradual decrease in plasma circulation • First liver pass impact with biological active metabolites • Specific target organs: uterus, brain • Metabolism in the gut (bacteria with 5b-reductase activity), in the intestinal wall (5a-reductase activity) and in the liver (5b-reductase, 3a- and 20a-hydroxylase activities)
Intramuscular	• Supra physiological plasma concentrations • 17-OHP-C seems to interfere with glucose metabolism (diabetogenic effect?)
Vaginal	• Stable plasma concentrations and consistent tissue levels • First uterine pass impact with targeted delivery into the endometrium • Minimal systemic effects • Metabolism: normal vaginal bacteria and mucosa seem devoid of 5a- and5b-reductases. After vaginal absorption, only a small increase in 5a-pregnanolone levels were observed and 5b- pregnanolone levels were not affected • No evidence of effects on glucose metabolism profile
Rectal	• Good profile on clinical efficacy (PTB reduction in higher risk patients, neonatal outcomes) • Lower maternal side effects

IV. Progesterone and PTB: "Which, When and How"

Only 50% of all PTBs occur in women with recognizable risk factors, making screening and observation troublesome. The central point having the best predictive worth at present, is a past history of preterm delivery, which is related with a 1.5-to 2.0-fold risk increased risk [7]. Attempts to treat premature labour once settled, have been generally inefficient bringing about just 2–7 days of pregnancy prolongation. The best mediation in the intervention of PTL is the utilization of progestogens, which add to the decrease of PTB and the attendant long-life unfavourable outcomes [22, 26].

The systems of human parturition incorporate complex biochemical, physiological, physical and clinical events that develop both mother and foetus in both term and pre-term pregnancies. This pathway, likely including a multifactorial basis, contains: decidual/foetal membrane activation, increased uterine contractility and cervical maturing (dilatation and effacement). The vital role of progesterone in PTB prevention is identified with the progesterone receptor (PR) isoform expression, its anti-inflammatory and immunomodulatory function.

Prior to undertaking any therapeutic strategy, cautious distinguishing proof of high risk patients is required. In this way, past obstetrical history (past spontaneous PTB), current clinical signs and side effects (abdominal pain, uterine contractility, cervical

modifications on vaginal assessments) and instrumental/lab assessments by transvaginal ultrasound cervical length (CL) estimation, biochemical identification of PTB risk factors, for example, foetal fibronectin (fFn), placental alpha microglobulin-1(PAMG-1) test, phosphorylated insulin-like growth factor binding protein (phIGFBP-1) tests are fundamental in any subsequent decision making process.

Once a threatened PTL diagnosis is made, tocolysis and administration of corticosteroids to initiate foetal lung maturation are the first therapeutic tools. Furthermore, bed rest and hydration are frequently prescribed albeit none has demonstrated to be clearly effective. Progesterone, 17-OHP-C just as different progestogens have been tried in a several clinical preliminaries for the prevention of PTB [38]. The most applicable logical proof depended on information of progesterone (P4) and 17-OHP-C utilized as a prophylactically in patients with threatened PTB. The outcomes are controversial. All in all, progesterone and progestogens seemed, to be advantageous, particularly considering cost, availability and biological safety [39, 40].

In women with prior history of PTB, the incidence of recurrent PTL was significantly reduced weekly intramuscular administration of 17-OHP-C. A new meta-examination, notwithstanding, proposed that daily vaginal progesterone began at around 16 gw is a sensible option in compared weekly 17-OHP-C for PTB prevention in singleton pregnancies with a past history of PTB [41].

Recent guidelines recommended offering prophylactic vaginal P4 to women with no history of spontaneous preterm delivery or mid-trimester pregnancy loss in whom transvaginal sonography somewhere in the range of 16 and 24 gw revealed a CL <25 mm [41]. Nonetheless, 17-OHP-C has been found to increase the incidence of GD three fold [30, 31]. Also, the latest scientific opinions on 17-OHP-C use, have not viewed 17-OHP-C to be useful in preventing preterm birth. The PROLONG study, a large multicentre, international, randomized double- blind preliminary, found that 17-OHP-C didn't diminish recurrent PTB: there were no significant differences in the frequency of PTB < 35 weeks between the 17-OHP-C group and a placebo group (17-OHP-C 11% versus placebo 11.5%) [42].

Vaginal micronized progesterone (in soft capsule of 200 mg or 90 mg gel) administration is usually the preferred route and the optimal biochemical regimen in current clinical practice [41]. Jarde et al. in an updated systematic review and network meta-analysis affirmed that vaginal progesterone was the only intervention with predictable proof of viability for preventing preterm birth in singleton at risk pregnancies generally and in those with previous PTB [43]. Table 2 summarises the types, route of administration, dosage and intervals to prevent PTBs dependent on the most relevant significant scientific studies and guidelines [44].

Table 2. Types, routes of administration, dose and intervals of progesterone use [34, 42]

Type	Route of administration	Dose (mg)	Interval
17-OHP-C	Intramuscular injection	250	Weekly
Micronized progesterone	Vaginal soft capsule	100, 200, 400	Daily
Micronized progesterone	Vaginal gel	90	Daily
Micronized progesterone	Oral (capsule)	200, 400	Daily
Micronized progesterone	Rectal (pessary)	400	Daily

Adapted from Koun et al.

V. Progesterone and Twin-Pregnancy

The accessible data on progesterone use in twin-pregnancy is controversial. Many studies didn't track down any advantageous impact of progesterone use in twin pregnancy, while just few studies reported a likely benefit in terms of gestational length and neonatal outcomes. In both twin and triplet pregnancies, neither micronized progesterone nor 17-OHP-C had been shown to

prevent preterm delivery [38]. Recently, a meta-investigation dependent on information from 13 RCTs showed that treatment with progestogens, either intramuscular 17-OHP-C or vaginal micronised progesterone, didn't prevent PTBs, or improve perinatal result in unselected women with uncomplicated twin pregnancy [45].

A new Cochrane examination from 2017 included 17 investigations (n = 4773) on vaginal progesterone or 17-OHC-P use versus placebo use or no treatment in multiple pregnancies without additional selection standards at a risk for PTB [46]. There was impressive heterogeneity among studies and predominantly poor review quality. Notwithstanding, no significant differences were seen as far as the PTB rate neither with 17-OHP-C use at <37 gw (RR 1.05; 95% CI 0.98–1.13) nor use at <28 gw (RR 1.08; 95% CI 075–1.55) compared with the placebo/no treatment group. Similar outcomes were seen with vaginal progesterone used to diminish the PTB rate at <37 gw: RR 0.97; 95% CI 0.89–1.06) and at <28 gw: RR 1.22; 95% CI 0.68–2.21.

Individual patient data meta-analysis by Romero et al., from 2017 on the organization of vaginal progesterone versus placebo or no treatment in 303 asymptomatic twin pregnancies with a CL of ≤25 mm in the second trimester of pregnancy did in any case, exhibit a significant reduction in the PTB rate at <33 gw as an primary outcome (31.4 versus 43.1%; RR 0.69; 95% CI 0.51–0.93) and an improvement in neonatal outcome as an secondary outcome, for example decrease in respiratory distress syndrome (RR 0.70; 95% CI 0.56–0.89), neonatal mortality (RR 0.53; 95% CI 0.35–0.81) and a decrease in babies with birth weight of <1500 g (RR 0.53; 95% CI 0.35–0.80) [47].

VI. Progesterone as a Tocolytic Agent and additionally for Maintenance Therapy?

Progesterone has been evaluated as a tocolytic agent, however different studies have shown a weak and slow ability to inhibit uterine contractions, where 17-OHP-C appeared to have definitely no impact [38]. Consequently, the utilization of progesterone for acute tocolysis is irrational or may assume a part just in conjunction with other tocolytic agents with synergistic impacts (atosiban, beta-agonists, indomethacin, nifedipine, etc.) As of late, Ashraf examined the adequacy of joined treatment of utilizing nifedipine with vaginal progesterone in the administration of acute successful in most of patients. The extra daily utilization of vaginal progesterone suppositories brought about significant prolongation of pregnancy just as decrease not just in the rate of neonatal low birth weight yet in addition in neonatal intensive care unit admissions. Mean pregnancy prolongation was 11.13 ± 5.08 days in group A (just on nifedipine), while it was 29.73 ± 3.10 days in group B (on a combined treatment with nifedipine and vaginal progesterone of 200 mg/every day, $p \leq 0.001$ [48]. Nonetheless, there was insufficient evidence to suggested progesterone/progestogens utilize alone for primary tocolysis. There was likewise no evidence that progesterone or 17-OHP-C combined with other commonly utilized tocolytics prompted effective prolongation of pregnancy or a significant diminishing in the rate of PTBs.

Data on the utilization of progesterone for maintenance treatment was questionable. While RCTs of low quality showed promising outcomes, high quality studies didn't reveal any significant differences with respect to the rate of PTBs <37 gw, the latency period until delivery and the neonatal result between the progesterone/17-OHP-C group of patients and the placebo or no treatment group [49]. Significant differences in the strategy, the inclusion and result standards, the method of utilization and the dosage of substances, the inadequate statistical power because of the low number of cases, make the interpretation and comparability of studies difficult. In this way, all around planned randomized, placebo controlled, double-blinded studies with uniform primary outcome criteria are important to explain whether progesterone is of clinical advantage for patients with showed preterm contractions as well as maintenance treatment after arrest of PTL is achieved. The optimal route of administration and the ideal dosage additionally require explanation.

VII. Future Strategies on PTB Prevention

The latest clinical data proposes a beneficial outcome of combined treatment dependent on progesterone use and different strategies to prevent preterm delivery in high risk patients. In particular, ongoing studies have detailed advantageous outcomes derived from the combined utilization of vaginal progesterone and Arabin's pessary or cerclage. Melcer et al. seen that for women with singleton pregnancies with a short CL, the combined treatment of Arabin's cervical pessary and vaginal progesterone led to a lower rate of preterm delivery <34 gw and prolonged gestation compared with those women who were just on vaginal progesterone [50].Shor et al. analysed the result of pregnancy in women with a short CL dealt with four distinct treatment protocols: vaginal progesterone, cervical cerclage and Arabin's cervical pessary (group A), Arabin's cervical pessary and vaginal progesterone (group B), cervical cerclage and vaginal progesterone (group C), or vaginal progesterone alone (group D). These

combined methodologies brought about promising methodologies in pregnant women who had a short CL and a high background risk for preterm delivery [51].

Comparative methodologies appear to be encouraging likewise in twin pregnancies. Zimerman et al., compared twin pregnancies and a short ≤25 mm cervix in the second trimester of pregnancy somewhere in the range of 16 and 28 gw on combined treatment for PTB with Arabin's cervical pessary and intravaginal micronised progesterone of 200 mg/every day with a control group on a conservative regimen. The treatment group had a lower incidence rate of PTL before 28 gw. Notwithstanding, further prospective studies are required the efficiency and the utilization of Arabin's cervical pessary in twin pregnancies [52].

VIII. Conclusions

Recent years have seen the publications of various clinical preliminaries utilizing progestogens for the prevention of a several obstetrical complications, including RPL, threatened miscarriage and PTB. Because of various incorporation measures and the utilization of various progestogens and their route of administration, it is hard to draw a comparison from these studies and to propose an absolute regimen of treatment for clinical practice. Considering the recent and relevant RCTs, geographical differences and differences in management, the following evidence-based proposals affirm to be sensible:

- Progesterone and progestogens show an interesting medical profile with regards to all pregnancy phases.
- Early PTB risk evaluation is required (prevention, prediction, education).
- Prophylactic progestogen treatment comprises of the utilization of micronized progesterone form (P4) administered daily as a vaginal suppository (sometimes orally) or the utilization of 17-alpha hydroxyl progesterone caproate (17-OHP-C) in oil suspension administered weekly as an intramuscular injection.
- In asymptomatic women with singleton pregnancies and a short CL on ultrasound of ≤25 mm the daily administration of vaginal progesterone (in capsules of 200 mg or 90 mg gel) until 34 gw leads to a significant decrease in the PTB rate and an improvement in neonatal outcome.
- 17-OHP-C is administered weekly from 16 to 36 gw as an intramuscular injection. Notwithstanding, the most recent shows a preference for vaginal micronized progesterone.
- The most recent data additionally recommends a constructive outcome of progesterone treatment in cases of twin pregnancies with a short CL on ultrasound of ≤25 mm [44].
- Progesterone ought not be utilized as an agent for primary tocolysis. Be that as it may, it very well may be utilized in conjunction with tocolytic agents (in the acute phase) and for maintenance therapy (after the acute phase).
- Promising future pathways for PTB prevention (including twin pregnancies) could be combined treatment containing progesterone and Arabin's pessary or cerclage [50].

Regardless of whether progesterone use shows a general good profile of safety as far as possible short-and long term outcomes, exposure should be avoided ought to be kept away from if not indicated. careful patient selection is crucial for treatment success.

Conflict Of Interest

All authors declare no conflicts of interest.

Authors Contribution

Authors have equally participated and shared every item of the work.

References

[1] Steer, Philip. "The epidemiology of preterm labour." BJOG: An International Journal of Obstetrics & Gynaecology 112 (2005): 1-3.

[2] Wen, Shi Wu, et al. "Epidemiology of preterm birth and neonatal outcome." Seminars in Fetal and Neonatal Medicine. Vol. 9. No. 6. WB Saunders, 2004.

[3] Kuehn, Bridget M. "Groups take aim at US preterm birth rate." Jama 296.24 (2006): 2907-2908.

[4] Tracy, S. K., et al. "Spontaneous preterm birth of liveborn infants in women at low risk in Australia over 10 years: a population-based study." BJOG: An International Journal of Obstetrics & Gynaecology 114.6 (2007): 731-735.

[5] Blondel, B., et al. "General obstetrics: Preterm birth and multiple pregnancy in European countries participating in the PERISTAT project." BJOG: An International Journal of Obstetrics & Gynaecology 113.5 (2006): 528-535.

[6] McCormick, Marie C., and Douglas K. Richardson. "Premature infants grow up." (2002): 197-198.

[7] Saigal, Saroj, and Lex W. Doyle. "An overview of mortality and sequelae of preterm birth from infancy to adulthood." The Lancet 371.9608 (2008): 261-269.

[8] Hamilton, B. E., J. A. Martin, and S. J. Ventura. "Births: preliminary data for Natl Vital Stat Rep. 2007." (2006).

[9] Druckmann, René, and Marc-Alexandre Druckmann. "Progesterone and the immunology of pregnancy." The Journal of steroid biochemistry and molecular biology 97.5 (2005): 389-396.

[10] Szekeres-Bartho, Julia, et al. "Progesterone as an immunomodulatory molecule." International immunopharmacology 1.6 (2001): 1037-1048.

[11] Di Renzo, Gian Carlo, et al. "Progesterone in normal and pathological pregnancy." Hormone Molecular Biology and Clinical Investigation 27.1 (2016): 35-48.

[12] 12- Schwartz, Nadav, et al. "Progesterone suppresses the fetal inflammatory response ex vivo." American journal of obstetrics and gynecology 201.2 (2009): 211-e1.

[13] Fanchin, Renato, et al. "Hormonal influence on the uterine contractility during ovarian stimulation." Human Reproduction 15. suppl_1 (2000): 90-100.

[14] Perusquía, Mercedes, and Jaime Jasso-Kamel. "Influence of 5α-and 5β-reduced progestin's on the contractility of isolated human myometrium at term." Life sciences 68.26 (2001): 2933-2944.

[15] Chanrachakul, Boonsri, et al. "Progesterone enhances the tocolytic effect of ritodrine in isolated pregnant human myometrium." American journal of obstetrics and gynecology 192.2 (2005): 458-463.

[16] Liu, Jin, et al. "The effects of progesterone on apoptosis in the human trophoblast-derived HTR-8/SV neo cells." Molecular human reproduction 13.12 (2007): 869-874.

[17] Czajkowski, Krzysztof, et al. "Uteroplacental circulation in early pregnancy complicated by threatened abortion supplemented with vaginal micronized progesterone or oral dydrogesterone." Fertility and sterility 87.3 (2007): 613-618.

[18] Raghupathy, Raj, et al. "Modulation of cytokine production by dydrogesterone in lymphocytes from women with recurrent miscarriage." BJOG: An International Journal of Obstetrics & Gynaecology 112.8 (2005): 1096-1101.

[19] Hudić, Igor, et al. "Dydrogesterone supplementation in women with threatened preterm delivery—the impact on cytokine profile, hormone profile, and progesterone-induced blocking factor." Journal of reproductive immunology 92.1-2 (2011): 103-107.

[20] Hung, Tai-Ho, et al. "Micronized progesterone pre-treatment affects the inflammatory response of human gestational tissues and the cervix to lipopolysaccharide stimulation." Placenta 57 (2017): 1-8.

[21] Ruddock, Nicole K., et al. "Progesterone, but not 17-alpha-hydroxyprogesterone caproate, inhibits human myometrial contractions." American journal of obstetrics and gynecology 199.4 (2008): 391-e1.

[22] KEIRSE, MARC JNC. "Progestogen administration in pregnancy may prevent preterm delivery." BJOG: An International Journal of Obstetrics & Gynaecology 97.2 (1990): 149-154.

[23] Nold, Christopher, et al. "Prevention of preterm birth by progestational agents: what are the molecular mechanisms?" American journal of obstetrics and gynecology 208.3 (2013): 223-e1.

[24] Maher, Mohammad Ahmed, et al. "Prevention of preterm birth: a randomized trial of vaginal compared with intramuscular progesterone." Acta obstetricia et gynecologica Scandinavica 92.2 (2013): 215-222.

[25] Meis, Paul J., et al. "Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate." New England Journal of Medicine 348.24 (2003): 2379-2385.

[26] Markham, Kara B., et al. "Preterm birth rates in a prematurity prevention clinic after adoption of progestin prophylaxis." Obstetrics & Gynecology 123.1 (2014): 34-39.

[27] Nahoul, K., L. Dehennin, and R. Scholler. "Radioimmunoassay of plasma progesterone after oral administration of micronized progesterone." Journal of steroid biochemistry 26.2 (1987): 241-249.

[28] Fitzpatrick, Lorraine A., and Andrew Good. "Micronized progesterone: clinical indications and comparison with current treatments." Fertility and sterility 72.3 (1999): 389-397.

[29] Di Renzo, G. C., et al. "The changing role of progesterone in preterm labour." BJOG: An International Journal of Obstetrics & Gynaecology 112 (2005): 57-60.

[30] Nelson, David B., et al. "17-alpha Hydroxyprogesterone caproate did not reduce the rate of recurrent preterm birth in a prospective cohort study." American journal of obstetrics and gynecology 216.6 (2017): 600-e1.

[31] Rebarber, Andrei, et al. "Increased incidence of gestational diabetes in women receiving prophylactic 17α-hydroxyprogesterone caproate for prevention of recurrent preterm delivery." Diabetes care 30.9 (2007): 2277-2280.

[32] Bulletti, Carlo, et al. "Targeted drug delivery in gynaecology: the first uterine pass effect." Human Reproduction (Oxford, England) 12.5 (1997): 1073-1079.

[33] Zipori, Yaniv, et al. "Vaginal progesterone for the prevention of preterm birth and the risk of gestational diabetes." European Journal of Obstetrics & Gynecology and Reproductive Biology 230 (2018): 6-9.

[34] Afridi, Nighat, et al. "Comparison of efficacy of oral progesterone and micronized progesterone pessary in reduction of incidence of spontaneous preterm births." Journal of Ayub Medical College Abbottabad 31.2 (2019): 248-251.

[35] Elder, D. E., et al. "Hospital admissions in the first year of life in very preterm infants." Journal of paediatrics and child health 35.2 (1999): 145-150.

[36] Abdali, Fatemeh, et al. "Effect of progesterone on latent phase prolongation in patients with preterm premature rupture of membranes." Acta Medica Iranica (2017): 772-778.

[37] Quist-Nelson, Johanna, et al. "Progestogens in singleton gestations with preterm prelabor rupture of membranes: a systematic review and metaanalysis of randomized controlled trials." American journal of obstetrics and gynecology 219.4 (2018): 346-355.

[38] Kamat, S., P. Veena, and R. Rani. "Comparison of nifedipine and progesterone for maintenance tocolysis after arrested preterm labour." Journal of Obstetrics and Gynaecology 34.4 (2014): 322-325.

[39] Di Renzo, Gian Carlo, et al. "Guidelines for the management of spontaneous preterm labor: identification of spontaneous preterm labor, diagnosis of preterm premature rupture of membranes, and preventive tools for preterm birth." The Journal of Maternal-Fetal & Neonatal Medicine 24.5 (2011): 659-667.

[40] GOLDSTEIN, PETER, et al. "A meta-analysis of randomized control trials of progestational agents in pregnancy." BJOG: An International Journal of Obstetrics & Gynaecology 96.3 (1989): 265-274.

[41] Di Renzo, Giancarlo C., et al. "Preterm labor and birth management: recommendations from the European Association of Perinatal Medicine." The Journal of Maternal-Fetal & Neonatal Medicine 30.17 (2017): 2011-2030.

[42] Blackwell, Sean C., et al. "17-OHPC to prevent recurrent preterm birth in singleton gestations (PROLONG study): a multicenter, international, randomized double-blind trial." American journal of perinatology 37.02 (2020): 127-136.

[43] Jarde, Alexander, et al. "Vaginal progesterone, oral progesterone, 17-OHPC, cerclage, and pessary for preventing preterm birth in at-risk singleton pregnancies: an updated systematic review and network meta-analysis." BJOG: An International Journal of Obstetrics & Gynaecology 126.5 (2019): 556-567.

[44] Kuon, Ruben-J., Pauline Voß, and Werner Rath. "Progesterone for the prevention of preterm birth–an update of evidence-based indications." Geburtshilfe und Frauenheilkunde 79.08 (2019): 844-853.

[45] Schuit, E., et al. "Effectiveness of progestogens to improve perinatal outcome in twin pregnancies: an individual participant data meta-analysis." BJOG: An International Journal of Obstetrics & Gynaecology 122.1 (2015): 27-37.

[46] Dodd, Jodie M., et al. "Prenatal administration of progestogens for preventing spontaneous preterm birth in women with a multiple pregnancy." Cochrane Database of Systematic Reviews 10 (2017).

[47] Romero, Roberto, et al. "Vaginal progesterone decreases preterm birth and neonatal morbidity and mortality in women with a twin gestation and a short cervix: an updated meta-analysis of individual patient data." Ultrasound in Obstetrics & Gynecology 49.3 (2017): 303-314.

[48] Ashraf, Bushra. "Efficacy and safety of oral nifedipine with or without vaginal progesterone in the management of threatened preterm labor." International Journal of Reproductive BioMedicine 17.9 (2019): 629.

[49] Rath, Werner, and Ruben-J. Kuon. "Progesterone–Effective for Tocolysis and Maintenance Treatment After Arrested Preterm Labour?" Geburtshilfe und Frauenheilkunde 79.08 (2019): 834-843.

[50] Melcer, Yaakov, et al. "Arabin cervical pessary with vaginal progesterone versus vaginal progesterone for preventing preterm delivery." The Journal of Maternal-Fetal & Neonatal Medicine 33.20 (2020): 3439-3444.

[51] Shor, Shimrit, et al. "Combined therapy with vaginal progesterone, Arabin cervical pessary and cervical cerclage to prevent preterm delivery in high-risk women." The Journal of Maternal-Fetal & Neonatal Medicine 34.13 (2021): 2154-2158.

[52] Zimerman, Ariel, et al. "Prevention of preterm birth in twins with short mid-trimester cervical length less than 25mm-combined treatment with arabin's cerclage pessary and intravaginal micronized progesterone compared with conservative treatment." Harefuah 157.5 (2018): 301-304.