Progesterone as therapy or prophylaxis in pregnancy

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ABBREVIATIONS

FSH - follicle-stimulating hormone

LH - luteinizing hormone

hCG - Human chorionic gonadotropin

LPD - Luteal phase deficiency

ART - assisted reproductive technology

IVF - in vitro fertilization

17-OHPC - 17-alpha hydroxyprogesterone caproate

IM - intramuscular

PTL - preterm labor

PTB - preterm birth

PPROM - premature rupture of membranes

RDS - respiratory distress syndrome

NICU - neonatal intensive care unit

RPL - recurrent pregnancy loss

IVH - intraventricular hemorrhage

NEC - necrotizing enterocolitis

aCL - anticardiolipin

LAC - lupus anticoagulant

NFKB - nuclear factor-kappa B

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SUMMARY

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Background and aims: fecundability of humans is quite low compared to the majority of other species and further impairment of fertility has been noticed in recent decades. An estimated twenty percent of pregnancies miscarry. Early and late pregnancy loss leaves great emotional stress and burdens both partners with a lot of unanswered questions. Preterm birth (PTB), defined as a delivery of a live born infant before 37 weeks or 259 days of pregnancy complicates a bit over 12% of all US deliveries and it is one of main causes of neonatal morbidity and mortality. Therefore it is clear that there is a need for further research to discover a successful treatment to these conditions. Since progesterone is the essential pregnancy hormone, various randomized controlled studies have been made with the aim to bring clarity to wether or not the supplementation of progesterone really is effective in improving the pregnancy outcome when used as a treatment for threatened miscarriage and/or preterm delivery. The aim of this paper is to present a comprehensive review of literature on the effects of progesterone supplementation in pregnancy. With ambiguous results of research so far, a better understanding of progesterone's role in pregnancy is being sought for.

Methods: PubMed, Cochrane Library and Google scholar were primary sources for finding relevant material. Search was limited to English articles and terms included were: progesterone in pregnancy; recurrent miscarriage; recurrent pregnancy loss; preterm delivery; habitual abortions and therapy. The main criteria in the selection process was to find a good selection of published evidence-based research as well as avoiding outdated articles.

Findings: There is still inconsistency of results regarding progesterone's role as therapy or prophylaxis in pregnancy with results from two of the newest and largest studies contradicting each other. It is therefore still questionable whether or not progesterone should still be recommended as therapy or prophylaxis in pregnancy and which of the factors are of the greatest value when estimating the possible outcome of its use. Further research with larger groups is needed.

Key words: progesterone; miscarriage; preterm delivery; habitual abortions.

SAŽETAK

Naslov: Terapijsko ili zaštitno djelovanje progesterona u trudnoći
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Pozadina i ciljevi: Dvadeset posto trudnoća završi pobačajem. Gubitak trudnoće ima negativne posljedice za emotivno stanje žene a također ostavlja brojna neodgovorena pitanja o njihovom fizičkom oporavku. U razvijenim zemljama prijevremeni porođaj komplicira oko 12% porođaja i definira se kao rođenje djeteta prije 37. tjedna ili 259 dana trudnoće. Prijevremeni porođaj predstavlja značajan rizik za neonatalni morbiditet i mortalitet. Još uvijek ne postoji jasno definiran terapijski pristup za liječenje ili sprječavanje prijevremenog porođaja. Obzirom da je progesteron esencijalni hormon trudnoće, brojna istraživanja i meta-analize su učinjene kako bi se definiralo je li nadomjesno liječenje ovim hormonom zbilja učinkovito u poboljšanju ishoda prijetećeg pobačaja i/ili prijevremenog porođaja. Obzirom na oprečne rezultate dosadašnjih istraživanja traži se bolje razumijevanje uloge progesterona u trudnoći. Cilj ovog rada je sveobuhvatni pregled literature o učincima progesterona u trudnoći i učincima nadomjesne progesteronske terapije.

Metode: Analizirani članci nađeni su pretraživanjem baza PubMed, Cochrane Library i Google scholar. Svi članci koji su uzeti u obzir bili su na engleskom jeziku. Pojmovi koji su korišteni kod pretraživanja su: progesteron u trudnoći, rani gubitak trudnoće, ponavljajući spontani pobačaj, prijevremeni porođaj, habitualni pobačaj i terapija. Glavni kriteriji pri odabiru radova koji su uključeni u analizu bilo je pronalaženje članaka temeljenih na znanstvenim istraživanjima i dokazima, kao i izbjegavanje zastarjelih članaka**.**

Zaključak: Još uvijek postoje nedosljednosti u pogledu uloge progesterona kao terapije ili profilakse u trudnoći. Rezultati najnovijih i najvećih studija su proturječni. Stoga, još uvijek nije jasno definirana terapijska ili profilaktična uloga progesterona u trudnoći, te koji čimbenici imaju najveću vrijednost kod procjene mogućeg ishoda njegove uporabe. Potrebna su daljnja istraživanja s većim skupinama.

Ključne riječi: progesteron; spontani pobačaj; habitualni pobačaji, prijevremeni porođaj

1. INTRODUCTION

Progesterone as a key hormone in human reproduction is synthesized and secreted by ovaries and adrenal glands. It has an important role in both follicular and secretory phases of the menstrual cycle and is crucial for embryo implantation and development of a successful pregnancy. The effects of progesterone are mediated by nuclear progesterone receptors, PR-A and PR-B. These receptors are expressed in the ovary, the uterine endometrium and myometrium, preovulatory granulosa cells, other reproductive tissues, endocrine organs such as the hypothalamus-pituitary complex as well as other tissues where its' role is less clear.[1]

During the follicular phase progesterone is mainly produced in the pathway of estrogen production. A high concentration of estrogen during a sustained period of time provokes ovulation as well as an increase in progesterone production as a response to a pituitary LH surge. After ovulation the corpus luteum is formed from theca and granulosa cells together with blood resorbed from the surrounding ruptured vessels caused by the follicle rupture.[1]

The corpus luteum is responsible for progesterone secretion and is reliant on pulsations of the LH. Progesterone inhibits new folliculogenesis as well as diminishes the frequency and amplitude of GnRH and LH peaks. Concentration of progesterone peaks in the middle of the luteal phase and helps the endometrium to prepare for implantation as well as nourish the fertilized ovum by inducing endometrial protein secretion. By the end of the menstrual cycle, the LH sensitivity is decreased and is not sufficient to maintain the corpus luteum. This gives an explanation of why the corpus luteum regresses after 12-16 days if fertilization fails to occur, and as a consequence of the demised corpus luteum, progesterone levels drop. Since estrogen and progesterone are main influencers of the proliferative and secretory changes of the uterine endometrium, the decreased levels resulting from the demised corpus luteum will also cause changes great enough to cause interruption of endometrial blood supply and a subsequent shredding of its superficial, proliferative layer, also called the *decidua functionalis.*[2] This marks the end to the luteal phase as well as the beginning of a new menstrual cycle by the onset of menstruation.[3]

When fertilization occurs, the blastocyst implants into the uterine endometrium approximately nine days post ovulation. Human chorionic gonadotropin (hCG) produced by the embryo disrupts the menstrual cycle by stimulating the corpus luteum to continue

the production of estrogen and progesterone. The surge in estrogen and progesterone prevents the endometrial shedding that would otherwise occur. The corpus luteum production of progesterone is critical for the maintenance of pregnancy in the first trimester until the placenta takes over this function at approximately 7 to 8 weeks of gestation. Even though placentation is initiated shortly after fertilization, the placenta is not mature enough to produce sufficient levels of progesterone on its own during these early weeks of gestation. The LH action is mimicked by the hCG which acts on the corpus luteum and ensures adequate progesterone levels in order to avoid pregnancy loss.

Progesterone is not only contributing to the thickening of the endometrium as preparation for implantation of the embryo but also supports pregnancy maintenance by providing endometrial secretory transformation, ensures uterine quiescence, and inhibits contractions of the uterine myometrium. These mechanisms of action of progesterone are indeed complex. Progesterone endometrial effects are dependent on estrogen that causes an increase in endometrial progesterone receptors during the proliferative phase of the menstrual cycle. By various actions, progesterone opposes the effect of estrogen causing diverse stromal and epithelial effects, leading to improved endometrial receptivity for possible implantation of an embryo. Regardless of the complex mechanism, insufficient progesterone action causes alteration in the hormonal balance between progesterone and estrogen, effecting critical steps in the acquisition of an ideal uterine receptivity for embryonal implantation.[4]

It is indisputable that proinflammatory cytokines play a critical part in delivery, regardless of if there is an associated infection present or not and whether or not the delivery is at term or preterm. Proinflammatory cytokines cause activation of the myometrium and prostaglandin synthesis.[5] An increased prostaglandin synthesis causes cervical ripening and stimulation of uterine contractions which triggers the initiation of labour by increasing myometrial gap junctional communication as well as the receptors for oxytocin and arginine vasopressin.[5,6] Progesterone is proposed to ensure uterine quiescence by inhibiting the prostaglandin synthesis.[7] The presence of progesterone also contributes to the prevention of ovulation during pregnancy, reassures the growth of mammary glands essential for upcoming breastfeeding and have various actions on the immunomodulatory and anti-inflammatory elements essential for a successful pregnancy. It is therefore essential that progesterone levels remain elevated throughout pregnancy in order to ensure pregnancy maintenance. Indeed, removal of the source of progesterone by

removing the corpus luteum (luteectomy), as well as administration of progesterone receptor antagonists such as mifepristone (RU-486) readily induce abortions.[8,9,10] This hypothesis was further improved when exogenous progesterone administration was shown to prevent abortion after luteectomy. It is therefore understandable that any change in production, metabolism and concentration of progesterone can have various impacts to pregnancy maintenance, i.e. increase a risk of early pregnancy loss as well as compromise the later pregnancy physiology.

Not only are fertilization and implantation extremely complicated fields in medicine, there is also a variety of possible pregnancy complications. Preterm birth, defined as a delivery of a live born infant before 37 weeks or 259 days of gestation is currently one of the most common pregnancy related complication in developed countries, complicating one in eight deliveries in the US and accounts for a considerably increased risk of neonatal morbidity and mortality.[11]

As mentioned above, progesterone has an essential role in early pregnancy.[12] Progesterone stimulates vascularization in the growing endometrium that aids the development of fetal circulation and provides myometrial quieting by opposing actions of myometrial contraction. The importance of progesterone in myometrial quieting throughout the pregnancy is proven by the parturition induction as the outcome of anti-progestin administration.[13,14] Administration of progesterone receptor antagonists such as mifepristone (RU-486) affect endometrial function and implantation and causes abortion in over 95% of early pregnancies.

By the variety of actions mentioned above, progesterone is able to impede cervical ripening and maintain uterine quiescence by suppressing chemokine synthesis, thereby hindering parturition.[15]

In 2011 the US Food and Drugs Administration (FDA) approved a medication for preterm birth prevention in the form of progesterone.[11] Progesterone's roles as therapy or prophylaxis in pregnancy have been presumed many. Different randomized trials have been designed to establish its reliability in *in vitro* fertilization (IVF) outcome, for prevention of preterm birth, including women with a short cervix, as well as in the management of recurrent pregnancy loss (RPL).

Most authorities recommend progesterone supplementation in assisted reproductive technology (ART) in order to increase the success rate.[12]

However, progesterone's efficacy in the prevention of preterm birth has not been as successful as it was first anticipated. Despite numerous published studies about it's role in pregnancy, there is still no consensus about it's efficacy in the prevention of spontaneous preterm birth. Some studies suggest a reduced risk, while others do not. A significant number of researches has been done in recent years with the aim to bring clarity to these questions. However, there are still notable gaps to be filled. The latest published meta-analysis regarding progesterone's role in preventing preterm birth is a Reuters Health meta-analysis, published in December 2017. The data from 974 women provides us with convincing evidence that vaginal progesterone does reduce the risk of preterm birth, as well as perinatal morbidity and mortality in singleton gestations where the woman had a short cervical length, defined as 25 mm or less.[17] This contradicts the result of the OPPTIMUM study from May 2016, a slightly larger study with data from 1228 women and the largest randomized trial when it comes to identifying the efficacy of vaginal progesterone in preventing preterm birth in high risk women. The OPPTIMUM study strongly suggests that the efficacy of progesterone is non-existent or weak in this field of application.[18]

The aim of this review is to gain a better understanding of why previous data show such a diversity in results when it comes to progesterone therapy and prophylaxis in pregnancy. What differed in the approach and patient selection that made the results so ambiguous?
Progesterone supplementation is indeed suggested to be efficient in the PTB prevention in some women at high risk, however new research has given us a good reason not to consider progesterone as ‘'a cure-all'' but to raise questions about which patients might benefit from the treatment. This thesis will review the controversy related to progesterone supplementation in habitual abortions, threatened miscarriage and PTB in singleton versus multiple gestation pregnancies, as well as the difference in progesterone preparation and dosing. The aim is to answer if there is enough systematic reviews on this topic to assure whether or not progesterone should continue to be used in these circumstances or considered obsolete.

2. TYPES OF PROGESTERONE

Progesterone is a natural progestogen, a sex steroid secreted by the corpus luteum and subsequently the placenta, as well as the cortex of the adrenal gland.[19,20] Most commonly used preparations of progesterone in pregnant women in clinical practice today are natural micronized progesterone, 17-alpha hydroxyprogesterone caproate (17-OHPC) and dydrogesterone.

2.1 Natural micronized progesterone

The bioidentical micronized progesterone is as the name suggests a natural form of progesterone and is composed of fine dispersed particles made in the lab in order to provide the best possible uptake in the body. This type of progesterone is self-administered and the route of administration is either oral or vaginal. Natural micronized progesterone is widely used in obstetrics and gynecology by showing efficient results with minimum side effects.[21] Side effects most commonly seen in women taking the natural micronized progesterone include depression, breast tenderness, dizziness, nausea and vomiting, as well as bloating. These side effects can be minimized by taking the supplementation before bedtime. According to a study by Marinov et al., natural micronized progesterone shows equal effectiveness when administered through the oral or the vaginal route when prescribed for threatened miscarriage during the first trimester or as a prophylaxis for preterm delivery in women with either a short cervix or a previous history of preterm delivery.[21,22] This result contradicts many other studies, where the majority are showing a significantly higher serum progesterone concentration and a higher number of term deliveries when micronized progesterone is administered through the vaginal route.[23,24,108,109] The oral form provides greater and durable patient compliance by offering continuous effectiveness by a more or less effortless route or administration. However, the oral form is susceptible to a first-pass hepatic effect and thereby causes a decrease in potency as well as unfavorable side effects.[23] The vaginal route, usually in the form of a gel or suppository is not exposed to the first-pass hepatic effect and has less side effects than the oral route. It achieves greater uterine concentrations by it's instant absorption from the vagina to the endometrium where is causes secretory changes.[23,24] Even though the vaginal route might not be as convenient for the patient as the oral route, it is still self-administrable by the patient and the benefits of the vaginal route have made this form the main route of administration. For preterm delivery prevention, natural micronized progesterone together with 17-OHPC are the forms of progesterone that are

most commonly used.[23] In general, the therapy tends to be well tolerated with most reported side effects being mild and transient.

2.2 17-alpha hydroxyprogesterone caproate (17-OHPC)

The counterpart of the natural progesterone is a synthetic form of progestogen 17-alpha hydroxyprogesterone caproate.[25] It should not be confused with the endogenous derivative of progesterone, 17-alpha hydroxyprogesterone. Since it is ineffective by the oral route, the main route of 17-OHPC administration is intramuscular.[23] When administered by the intramuscular route it has been shown to reduce the incidence of preterm delivery extensively.[26] It also decreased a risk of pregnancy complications in women with a previous preterm delivery when administered in a dose of 250 mg as weekly injections.[26,27] A trial by Meis et al. showed that weekly intramuscular injections of 17-OHPC significantly decreased a risk of a preterm delivery before week 37 of gestation in women with a previous spontaneous preterm delivery, and there was also a lower incidence of neonatal complications such as a necrotizing enterocolitis and supplemental oxygen need.[28] Due to promising results, this trial provided clinical indications for 17-OHPC use in preterm birth prevention. Since 17-OHPC is administered through the IM route, pain and swelling at the injection site is one of the most commonly reported side effects. Other side effects include hives, pruritus, nausea and vomiting.

2.3 Dydrogesterone

Dydrogesterone is a synthetic derivative of progesterone used in various gynecological conditions such as infertility and threatened or habitual abortions due to its good oral bioavailability, tolerability and potency as well as safety.[29] Dydrogesterone is readily absorbed in the GI tract with a bioavailability of 28% even at low doses. Dydrogesterone's oral form gives a high compliance and just like the micronized progesterone, it has the benefit of acting directly on the uterus, exhibiting anti-estrogen activity able to cause secretory changes of the endometrium.[30] Despite its structural and pharmacological similarity to endogenous progesterone, dydrogesterone is efficient in much lower oral doses and does not possess as high of a risk of unsatisfactory hormonal side effects such as menstrual irregularities like spotting, breast tenderness, weight gain, edema, acne and libido changes and is therefore beneficial over most endogenous progesterones as well as the majority of other synthetic progestogens. The most frequent side effects from dydrogesterone is bloating, vertigo, nausea, and vomiting. Prescribing information also

mention infrequent side effects including liver function alternations and therefore caution has to be taken in patients with acute or chronic liver diseases with abnormal liver function tests.

A 2016 systematic literature review analyzed 9 randomized trials totally including 913 pregnant women and showed a lowering of threatened abortions in the women receiving oral dydrogesterone or vaginal progesterone in comparison to the placebo group.[31] However, there was no clear difference between these two administration routes of progesterone.[31] Another review published in 2012 analyzed data from five randomized trials with 660 pregnant women with threatened miscarriage, 335 of them receiving dydrogesterone.[29] The dose somewhat differed from one trial to another with a standard dose of 10 mg BID.[29] Result showed a 47 percent decrease in the risk for miscarriage as well as minimal side effects.

Other small sample size studies also showed promising results of dydrogesterone treatment over placebo in maintaining pregnancy until 20 weeks of gestation.[32-34] These studies did indeed show a lower incidence in spontaneous miscarriage in women receiving dydrogesterone in comparison to the group not receiving therapy and did not show any convincing discrepancy in congenital malformations. However, due to the small sample size and poor study quality larger sample size studies should be more trustworthy. Dydrogesterone indeed appears to be beneficial in miscarriage prevention in threatened abortions and does not show an increased risk for any congenital abnormalities.

3. ROUTE OF PROGESTERONE ADMINISTRATION

Three main routes of progesterone administration are oral, vaginal and intramuscular (IM) and are all effecting the pharmacokinetics. The initial administration of progesterone back in 1997 was by the vaginal route in a form of a gel, followed by an oral capsule in 1998, an intramuscular injection in 2001, and a vaginal suppository in 2007.[35,36,37]

3.1 Oral progesterone

Even though the oral route of progesterone administration is likely a route with the highest compliance, it is seldom the preferred route. The absorption and clearance of orally administered progesterone has been proven to be less beneficial compared to other forms. [16] This is due to the high first-pass metabolism of progesterone by the liver, leading to nonuniform blood levels, less potency, as well as an increased risk of side effects. Due to

the low bioavailability (only 10 percent of the IM type) and the major absorption differences depending on food intake, the oral route is seldom preferred as the main route of progesterone delivery. However, the use of synthetic progestogens over natural progesterone is less effected by the liver metabolism and therefore has a higher bioavailability.[38,39,40] Due to the poor GI absorption of oral progesterone, the oral preparations should not be prescribed in assisted reproductive technology due to the lower success rate in comparison to the other formulations.[16]

Since the half-life of micronized progesterone taken by the oral route is approximately 17 hours, with peaking concentrations seen after 2-4 hours, the typical dose interval is two to three times a day.[17,41] The serum concentration will remain elevated for approximately 12 hours but the reestablishment of the baseline level value will occur first after 24 hours.[17]

Neurosteroids are metabolites of progesterone potentiating $GABA_A$ receptors and are the cause of unwanted sedative side effects of progesterone. Other side effects include everything from nonspecific flu-like symptoms, breast tenderness, dysmenorrhea, irregular bleedings, to systemic and sedative side effects such as fatigue, nausea and vomiting.[42] Since the oral dose of progesterone tends to be higher compared to the IM and vaginal route, side-effects of oral progesterone are more frequent.

3.2 Intramuscular progesterone

The IM route shows good absorption with high blood concentration peaking 8 hours after a 10 mg injection as well as a possible progesterone depot with accumulation in adipose tissue.[43] In that case, IM progesterone would give a more constant concentration in comparison to the other routes of administration. Serum progesterone reaches luteal phase levels when doubling the initial dose of 10 mg IM progesterone and reaches mid-pregnancy levels if the dose is increased tenfold.[44] This causes exalted levels of serum progesterone for a minimum of 48 hours. Although fairly efficient, intramuscular administration is not too convenient and reduces the likelihood of compliance since it is an uncomfortable way of administration. It possesses a risk of tissue irritation such as discomfort, pain, inflammation and bruising.[45] Even though oral progesterone has considerably more sedative side-effects, IM progesterone is capable of causing similar side-effects if administered in adequately high dose, thus demonstrating that the liver metabolism of progesterone into neurosteroids like allopregnanolone is not necessarily

crucial for these sedative effects to ensue. Since IM progesterone has the capacity to reach high serum levels, it it capable to coerce anterior pituitary secretion of gonadotropins, showing antigonadotropic efficacy and thereby decreased production of sex hormones.[16] IM preparations are connected with greater serum levels while greater uterine concentrations are seen with vaginal preparations.[16] Both vaginal and IM progesterone preparations are the formulations with documented beneficial effects on assisted reproductive technology outcome.[16]

3.3 Vaginal progesterone

The benefit of vaginal progesterone is that this route of administration bypasses the first-pass metabolism by the liver and intestines that the oral route is exposed to, as well as avoiding the uncomfortable and troublesome administration that the IM route requires.[24] The relatively uncomplicated way of application together with the absence of systemic side effects and the favorable pharmacokinetic characteristics has made the vaginal route the preferred route of progesterone delivery.[46] Since the vaginal route is less of a burden for the patient in comparison to the IM route, it increases the likelihood of compliance. Also, the bioavailability is greater, showing increased uterine concentrations suggestive of sufficient delivery of progesterone from the vagina to the uterine endometrium. This is contributing to uterine quiescence by regulating the expression of the uterine progesterone receptor genes responsible for myometrial contractility regulation.[11,24] Research showed that the vagina could function as a progesterone reservoir but is also capable of causing unwanted side-effects such as discharge and irritability.[43] Peak plasma concentrations are reached 3-8 hours post-admission of vaginal progesterone. The usual daily dose of vaginal progesterone is 300-600 mg, divided in 2-3 dosages. The vaginal route requires a higher dose and the plasma concentration drops faster in comparison to the IM route.[43]

Growing trial evidences propose that the vaginal route of progesterone administration could be the superior route due to its hypothesized uterine first-pass effect, providing a superior uterine bioavailability in comparison to the oral and IM route. Nonetheless, continuous randomized trials are needed to properly confirm the supremacy of the vaginal administration route in comparison to the other routes as well as the ideal dosing of the formulations.

In general, the vaginal or IM form is superior to the oral form as the route of choice. By avoiding the oral dose, it is possible to bypass progesterone’s exposure to the metabolic

first-pass effect by the liver as well as the large doses needed in the oral form, thereby being more efficient.[38-40] This further reduces undesirable side effects of progesterone like drowsiness and irritability.[42]

4. COMBINING INTERACTIONS

Combining interactions are seen in circumstances where progesterone therapy is used in combination with another intervention. Adjunctive use of progesterone and cerclage can be seen in cases with cervical insufficiency. A cerclage is a prophylactic procedure where sutures are put around and into the cervix in order to support the cervix during pregnancy and prevent the risk of ascending infections and decrease the risk of pregnancy loss or premature delivery. Progesterone on the other hand is contributing to uterine quiescence and the combining interaction of progesterone and cerclage was therefore anticipated to bring greater effectiveness in reducing the risk of miscarriage and PTB.

Ultrasound measurement of a cervical length of 20 mm or less has been proposed for induction of prophylactic progesterone treatment with or without cerclage.[47] Collected data show an equal efficiency of cerclage and vaginal or IM progesterone in women with a sonographic short cervical length and a history of PTB during the mid trimester.[48,49,50] However, no randomized controlled trial has directly compared progestogen administration to cervical cerclage for the prevention of PTB in women with a sonographic short cervix in the midtrimester, singleton gestation, and previous PTB.[48,51] The result of a 2012 study showed equal effectiveness of vaginal progesterone and cerclage in lowering the risk of preterm delivery and negative perinatal outcomes before week 32 of gestation.[48] However, when used as separate interactions, studies have shown greater efficacy of cervical cerclage than vaginal progesterone.[52] The results of a very recent prospective cohort study by Sinkey et al. did not show any benefit in combining vaginal progesterone with cervical cerclage over cerclage alone in decreasing PTB.[49]

5. SINGLETON VS MULTIPLE-GESTATION PREGNANCIES

5.1 Singleton gestations

A previous spontaneous preterm birth possess a greater risk of another PTB in consecutive gestations.[28] Vaginal progesterone in women with a singleton gestation and a sonographic short cervix is shown to prevent preterm delivery.[53,54] Even though some studies are lacking convincing evidence that IM injections with 17-OHPC would reduce the risk of PTB, numerous trials still suggest that it 17-OHPC may reduce the risk of PTB.[55]
A double-blinded trial by Meis et al included women between week 16 to 20 of gestation until week 36 of gestation or the onset of a spontaneous preterm delivery.[28] One group received weekly IM injections of 250 mg 17-OHPC and the other group received a placebo. Results of this study showed a 30 percent decrease of recurrent PTB in singleton gestations as well as a reduced risk of neonatal complications such as IVH and NEC when given 17-OHPC. The risk reduction was the greatest in pregnancies less than 37 weeks of gestation, followed by <35 weeks and <32 weeks of gestation compared to the placebo group. Due to promising results of this singleton gestation study, further studies were performed in order to estimate wether or not 17-OHPC therapy could also be useful in multiple gestations.[56-62] Another randomized trial by Saghafi et al also evaluating the effect of weekly 17-OHPC injections was likewise correlating with a decreased risk of subsequent PTB in women with a previous PTB as well as an enhancement in birth weight.[27]

Da Fonseca et al. as well as O'Brien et al. both evaluated the efficiency of micronized vaginal progesterone as PTB prevention in singleton gestations of women at risk of a PTB.[63,64] It is important to highlight that these two studies included only women with a history of previous spontaneous PTB's and not by any diagnostic tools like a transvaginal measurement of the cervical length. Even though the trials had great similarities, the results contradict each other. The Da Fonseca trial did not only include women with a history of prior PTB but also included women with malformations of the uterus and those already receiving a cerclage.[63] However, these included only a fraction of the trial group and should not be able to explain the great difference between the results from the two trials. This trial showed a reduction of PTB by reducing myometrial contractility and the amount of PTB in women at risk when receiving a daily dose of 100 mg of micronized

progesterone suppositories. The O'Brien trial from 2007 on the other hand did not include women with uterine malformations or cerclage and did not show any benefits of 90 mg micronized vaginal progesterone daily in reducing the rate of subsequent PTB's prior to week 32 of gestation in women with a previous PTB.[64] The O'Brien trial is larger than the Da Fonseca trial with 659 patients versus 149 patients.[63,64] Since the trials were so similar in all other aspects; type of progesterone used, the route of application and the patients participating in the trials, it is difficult to anticipate what caused the ambiguous results.

When evaluating the effect of oral micronized progesterone on the rate of PTB, a randomized trial by Rai et al. in 2009 indeed showed a reduction in subsequent PTB less than week 37 of gestation in women receiving a two times daily dose of 100 mg oral progesterone.[65] Opposite results were however shown by Glover et al. who were unable to show any benefits of 400 mg oral micronized progesterone daily in comparison to placebo in reducing the rate of PTB.[66] However, these trials 2have a greater variability in dosing as well as a smaller test group. It is therefore uncertain how reliable the contraindicating results are.

5.2 Multiple gestations

Just as in singleton gestations, multiple gestations are at risk of preterm delivery in women with a short cervix. However, a shorter cervical length is tolerated in a singleton gestation versus a multiple gestation in the same week of gestation. A cervical length of less than 15 mm carry a 50 percent risk of a preterm delivery before week 32 of gestation in a singleton gestation.[67] This can be compared to the equally high risk with a cervical length of less than 25 mm in a twin gestation.[68] So the higher the number of gestations, the less tolerated is a short cervical length. A systematic review and meta-analysis published in 2010 showed convincing results that sonographic cervical length measurement in weeks 20 to 24 of gestation is a strong risk factor for spontaneous PTB in multiple gestations.[69] Conde-Agudelo et al gave the strongest evidence to date that transvaginal sonographic measurement of cervical length at 20-24 weeks of gestation is a good predictor of spontaneous preterm birth in asymptomatic women with twin pregnancies, stating that a cervical length ≤20 mm predicts spontaneous PTB at <32 and <34 weeks of gestation, whereas a cervical length ≤25 mm predicts PTB at <28 weeks of gestation.[69]

After a publication by the National Institute of Child Health and Human Development-Maternal Fetal Medicine Unit in 2003 showed a 30 percent decrease of recurrent PTB in

singleton gestations, weekly 250 mg 17-OHPC IM injections have also been encouraged for PTB prevention in women with short cervical length in multiple gestations as well as for nulliparous women.[28] Different trials have been made in order to determine whether or not 17-OHPC is efficient in preventing preterm delivery in multiple pregnancies.[56-62] The hypothesis that a higher dose of progesterone is necessary to prevent preterm delivery in multiple gestations have failed to be proven correct.[15] Regardless of the dose (90-200 mg) of progesterone administered and wether or not the trials have been made on twin or triplet pregnancies, the trials have failed to show any benefits or progesterone administration in preventing PTB in multiple pregnancies. Consequently there is no data proving that progesterone therapy would reduce the risk of preterm delivery in multiple gestations. 17-OHPC have failed to show any benefit in these circumstances.[56-57]

Invasive procedures such as a rescue cerclage have also failed to show a significant reduction in PTB in women with multiple gestations and a short cervix and rather show an increased rate of detrimental outcomes.[70,71] The difference in PTB between cerclage and no cerclage in twin pregnancies with a short cervical length is just marginal and actually shows an average of 0.4 weeks increase in gestational age at delivery in favor of no cerclage (P=.77) versus cerclage. However, there is a slight favor for cerclage over no cerclage seen in triplet pregnancies (P=.21).[71]

From all the trials performed so far, it can be concluded that neither 17-OHPC or cerclage is prolonging pregnancy significantly enough to be recommended as a treatment in multiple gestations. The cervix shortens earlier in multiple versus singleton gestations and new research is trying to find the answer to wether or not cervical length shortening in multiple gestations can have an inflammatory element sensible to 17-OHPC.[72,73] Regardless of the reason why cerclage as well as progesterone therapy has failed to prove efficacy in multiple gestations, further trials are highly recommended in order to estimate which effective treatments could be offered to women with multiple gestations diagnosed with a sonographic short cervical length in order to prevent PTB.

Progesterone prophylaxis is initiated the earliest in week 18 and latest in week 32 of gestation and is usually only given in singleton gestations due to the failing of showing benefits in multiple gestations. Usually a daily dose of 90-200 mg of vaginal progesterone is used until spontaneous rupture of the membranes or when reaching week 34 of gestation.

6. POSSIBLE INDICATIONS FOR PROGESTERONE SUPPLEMENTATION

6.1 Short cervical length

The cervical length is measured through a transvaginal ultrasound examination. The mean cervical length in a non-pregnant woman is between 40 and 50 mm. During pregnancy, the cervix shortens to an average length of 35 mm during week 24 of pregnancy.[74] The definition of a short cervix is a cervical length of 25 mm or less during week 18-32 in pregnancy.[47] These women possess a greater risk of having a preterm delivery. In the case of a cervical length of 20 mm or less, prophylactic progesterone treatment is recommended with or without other options like cerclage.[47] There are different mechanism in which progesterone is believed to affect cervical ripening. Progesterone antagonist administration promote cervical ripening and the administration of mifepristone, a selective progesterone receptor modulator induced cervical ripening when tested on guinea pigs.[75] There is an increased cervical response to progesterone antagonists with progressive gestational age but this is not necessarily followed by alterations in the activity of the myometrium, suggesting that the cervix is the dominant location of progesterone action and not necessarily the myometrium as previously emphasized.[76] The exact mechanism by which progesterone action blockage induces these cervical changes leading to cervical ripening is complex but is believed to be influenced by inflammatory processes like infiltration of leukocytes, chemokine and prostaglandin production as well as nuclear factor-kappa B which arbitrate the effect of interleukin-1B and tumor necrosis factor-α.[77] Since NF-KB is able to counter the effect of progesterone, it has a key role in providing cervical ripening.[77,78] Since progesterone antagonists are proven to induce cervical ripening, it is understandable why progesterone became a promising pharmaceutical therapy in possible preterm birth prevention in women with a short cervical length.

The OPPTIMUM study publication in 2016 included a total of 1228 women, with 618 women receiving 200 mg vaginal progesterone prophylaxis.[18] Even though the findings did not show any teratogenic or other harmful effects on outcomes during the first two postnatal years of children, it did not show any benefits and neither any reduction in the preterm delivery risk.[18] It is therefore understandable that the OPPTIMUM publication lead to increased questioning wether or not progesterone is as efficient as previously stated when it comes to PTB prevention.[17]

However, various studies still show that progesterone prophylaxis is useful in prolonging pregnancy in women at increased risk of premature delivery, as well as results that progesterone does not possess any risk for the fetus, and improve the neonatal outcome. Romero R et al study included 775 women and 827 newborns and showed a significant decrease in PTB risk as well as perinatal complications in asymptomatic women with a short cervical length when administered vaginal progesterone.[79] Women with a short cervix of 10-20 mm proven by sonography before week 24 of a singleton gestation given 90 mg prophylactic vaginal progesterone showed a 45% reduction in preterm delivery before week 33 of gestation according to a 2011 published research involving 458 asymptomatic women at risk of preterm delivery.[53]

Also a new study from 2017 contradicts the results of the OPPTIMUM study.[17] The study collected data from 974 women with singleton gestations and a cervical length of 25 mm or less during the mid-trimester, all receiving vaginal progesterone prophylaxis.[17] The outcome opposed the results from the OPPTIMUM study by showing a convincing decrease in preterm delivery risk in women receiving progesterone prophylaxis over placebo as well as a reduction in RDS, neonatal morbidity and mortality and lower NICU admissions.[17]

6.2 Threatened miscarriage

Approximately 20% of all pregnancies miscarry, the majority prior to week 12 of gestation. A miscarriage before gestation week 13 is most commonly due genetic factors such as aneuploidy: an abnormal chromosome number, the most common being trisomy 16.[80] The risk for aneuploidy is the highest at both extremes of maternal age. Somewhat 50% of miscarriages prior to week 13 are believed to be due to chromosomal abnormalities. Other factors contributing to the risk of miscarriage are infections throughout pregnancy. These could be both viral or bacterial, abdominal trauma, maternal age > 35 years, obesity and unregulated diabetes mellitus. Definition of a threatened miscarriage is presentation of signs and symptoms suggestive of a possible miscarriage when the pregnancy is less than 20 weeks of gestation or a fetal weight is less than 500 grams.[81] The most common single complaint in threatened abortion is early pregnancy bleeding. Vaginal bleeding, abdominal cramps with or without vaginal bleeding, together with a closed cervix are all signs and symptoms of a threatened miscarriage and must be taken seriously. In order to be labeled a threatened miscarriage, the fetus must still be viable within the uterus.[82] Unfortunately,

pregnancy loss is unavoidable once cervical dilatation starts.[80] Sonography is a useful tool in the diagnosis and management of threatened miscarriage since it is able to tell us wether the pregnancy is viable or non-viable, molar, or an unavoidable abortion.[80,83]

Since progesterone has an essential role in both pregnancy establishment and maintenance, insufficient levels of this hormone have historically been associated with threatened miscarriage and vaginal bleeding. The hypothesis is therefore that it is the insufficient level of progesterone that is inevitably leading to miscarriage rather than progesterone lack as a secondary effect of an already failing pregnancy.[84]

A publication from Everett et al back in 1987 showed that progesterone was prescribed as a treatment of threatened miscarriage in 13-40% of women.[83,85] However there is limited newly published data about the frequency of progesterone administration in women with threatened miscarriage in recent years. Various meta-analyses had been made with the aim to bring clarity to whether or not progesterone really is effective in improving the pregnancy outcome when used as a treatment for threatened miscarriage.

Different studies have been made to find an answer to whether a threatened miscarriage is associated with an increased risk of further pregnancy and perinatal complications. There is ambiguous data regarding the exact cause of a threatened miscarriage. Older studies found normal development despite threatened abortions, while a high number of recent research showed increased pregnancy and perinatal complications such as PTB and a low birth rate in these pregnancies which should be considered as high risk pregnancies.[86-90]

A 2014 study by Ahmed et al. showed a link between threatened miscarriage and later pregnancy complications. Early gestational bleeding possesses a woman to an increased risk of a complete abortion, preterm birth, and a low birth weight of a baby. Hypertension and/or preeclampsia in pregnancy, placenta praevia, intrauterine growth restriction, premature rupture of membranes and cesarian section are slightly more common in these circumstances, leading to a higher rate of admissions to neonatal ICU.[90]

A study by Omar et al. came to the conclusion that the risk of pregnancy loss and pregnancy complications in threatened miscarriage can be diminished by corpus luteum support by progesterone administration if the woman did not have a history of recurrent pregnancy loss.[33] The women receiving an initial dose of 40 mg dydrogesterone, followed by 20 mg of dydrogesterone daily during one week had almost ten percentage point greater pregnancy success rate in comparison to the women who did not receive

dydrogesterone.[33] The systematic analyses by Lee at al. supports these results, showing that progesterone therapy and dydrogesterone in particular is capable of significantly decrease the risk of pregnancy loss in the case of threatened miscarriage.[31] Thereby progesterone indeed seems to be able to decrease the risk of later pregnancy complications in the case of threatened miscarriage.

6.3 Habitual abortions

When a woman miscarries three or more consecutive times with the same partner, she is said to have habitual abortions or recurrent miscarriage.[82] It is estimated that incidence of habitual abortions is somewhere between 1-2%. Unfortunately, almost 50% of these cases are idiopathic even after comprehensive analyses and it is therefore complicated to find a successful treatment option. The majority of detectable explanations are found to be in luteal phase deficiency, aneuploidy with trisomies being the most frequent cause, derangement of immune responses as well as endocrinological abnormalities like diabetes and polycystic ovary syndrome (PCOS). In other words, a variety of factors like genetical, anatomical, or hormonal abnormalities, dietary deficiencies, endocrinological abnormalities as well as autoimmunity can be associated with habitual abortions.[91] Endocrinological investigations of the thyroid, ovaries, as well as the pituitary should be performed. Reznikoff-Etievant et al. found an occurrence of autoantibodies in 33,9% of 678 otherwise healthy women with habitual abortions, with anticardiolipin being the most frequent autoantibody present.[91] All women later received aspirin and/or prednisone. Women with a high concentration of aCL had a 27 percentage point lower success rate of live birth compared to the women with a negative autoantibody test.[91] In habitual abortions, antiphospholipid antibody syndrome has been found positive in 10-20% where the most frequent antibodies were found to be aCL, LAC, and anti-beta2 glycoprotein I.[92]

Since it is proven that progesterone is essential in pregnancy and that the removal of its main producer corpus luteum by luteectomy in early pregnancy frequently causes abortion before the 7th week of gestation, it is justifiable that progesterone has become the main treatment for women with habitual abortions.[93,94]

The PROMISE trial published in 2016 was unable to show any evidence that progesterone supplementation in early pregnancy in women with unexplained habitual abortions would be beneficial for the pregnancy outcome.[95] It is understandable that this is causing dispirit for the physicians as well as the patients eager to find a therapy to bring an end to a

couple's recurrent pregnancy loss. Undeniably, all physicians caring for women with habitual abortions want to decrease this incidence by finding the right treatment. Sadly, progesterone has not been proven as beneficial as first anticipated in this patient group. To bring some positives to this, there are no detrimental effects on the mother or the fetus from progesterone therapy. This is crucial for ongoing trial like the PRISM (progesterone in threatened miscarriage) trial for other progesterone indications like fertility treatments (ISRCTN Number: 14163439). Also, nearly 70 percent of women with habitual abortions will become pregnant, regardless if they were prescribed progesterone or not. Other studies do however show beneficial effects of progesterone administration in women with habitual abortions.[96,97] A cohort study showed that micronized progesterone starting during the luteal phase reduces the risk for habitual abortions.[96] Evaluation of other trials including women with habitual abortions also concluded the efficacy of progesterone in reducing the risk of consecutive miscarriages when administered 17-OHPC IM injections weekly.[97] This systematic review by Saccone et al. analyzed the effect of all types of progesterone administration in women with a history of unexplained habitual abortions. Women with habitual abortions benefit from synthetic progestogen administration like weekly intramuscular injections with 17-OHPC by showing a decreased incidence of habitual abortions in these circumstances.[97] However, the review failed to show any benefit of natural progesterone administration.[97] Study limitations made it challenging to adequately justify the dosage and route of its administration. Further trials are needed to further analyze the types of progesterone as well as dosing in order to properly recommend an optimal treatment regime.

In the previously mentioned cohort study, Klinman and colleagues at Yale School of Medicine together with the University of Illinois have shown promising results in progesterone's possible effect in reducing the risk of continuous pregnancy losses in women with habitual abortions if administered in the early weeks of pregnancy.[96] They found an association between an anomalous endometrial function test and habitual abortions. The endometrial marker, nuclear cyclin E undergoes changes throughout the menstrual cycle and an abnormal expression has been shown to be associated with infertility due to deficient development of the endometrium. In other words, the pregnancy loss seems to be correlated with the inability of the woman's uterine endometrium to preserve the embryo and therefore a pregnancy. During the greater part of the first trimester, the uteroplacental blood circulation is not adequately developed to support the pregnancy by itself. The endometrium is therefore needed to provide enough nutrients for

pregnancy maintenance during these initial eight weeks of pregnancy. By providing progesterone to these women, the risk of a lost pregnancy can be reduced by giving the endometrium a better chance to provide efficient nutrients for pregnancy maintenance. A 17 percentage points higher pregnancy success rates were seen in women with habitual abortions when administered 100-200 mg of vaginal micronized progesterone twice daily, beginning three days after the LH surge.[96]

6.4 Previous preterm delivery

Multiple factors contribute to the risk of a preterm labor syndrome. Preterm labor syndrome is caused by a variety of pathological processes and is believed to be the cause of the majority of preterm births. The syndrome activates components of the common pathway of parturition just as a term labor does, however in the preterm labor syndrome, this activation is pathologic.[98,99] Factors such as cervical insufficiency, stress, uterine overdistention, infection and/or inflammation, vascular disorders, uterine ischemia, breakdown of maternal-fetal tolerance, and hormonal disorders are some of the pathological processes associated with this syndrome.[99] Intrauterine infections are estimated to cause 25-40 percent of all premature deliveries worldwide, most commonly due to bacterial chorioamnionitis - an inflammation of the fetal membranes. The earlier in pregnancy the preterm labor occurs, the greater the chance that there is an infectious etiology. There are several different bacteria associated with PTB. These include Mycoplasma hominis, Escherichia coli, Ureaplasma urealyticum, Klebsiella, Gardnerela vaginalis, Bacteroides, Peptostreptococcus, and group B streptococcus as well as Helicobacter pylori infections.[100] Some extra-uterine infections such as malaria, can lead to the onset of inflammatory processes that activate the partition pathway via chemokine, cytokine and prostaglandin production.[98] Placental thrombosis as a consequence of vascular disorders such as the increased generation of thrombin also contributes to an increased risk, as well as senescence of the decidua; failure of immune tolerance; a short cervix and cervical insufficiency; hormonal imbalance such as insufficient progesterone action; uterine overdistention or ischemia; and the effects of stress and anxiety during pregnancy.[98,101,102]

The incidence of PTB is about 12 percent in the general population. In the situation of a previous PTB however, the risk increases to as much as 20 to 50 percent in consecutive pregnancies.[103,104] The earlier the PTB occurred in preceding pregnancies, the greater the risk of a recurrent PTB. Additional contributing factors to a rise in frequency of PTB

includes a larger number of preceding preterm pregnancies which is almost twice as common in African American women.[103] One of the main indications in trials evaluating the effect of progesterone therapy in women with recurrent PTB is hence the history of PTB in the past.[23]

A transvaginal ultrasound is recommended in the week 18-20 of pregnancy if the woman had a previous spontaneous premature delivery before week 32 of pregnancy without further complications, alternatively a premature delivery before week 34 of pregnancy in combination with complications. As previously mentioned, FDA approved progesterone as a treatment for preterm delivery in 2011.[11] In a case of a preceding singleton PTB and/or a sonographic short cervical length, progesterone supplementation has shown promising results in reducing the likelihood of a subsequent PTB.[93] A 2013 meta-analysis evaluated 36 trials from the Cochrane Pregnancy register and showed a symbolic decreased risk for PTB as well as perinatal mortality in women with a preceding spontaneous singleton PTB and/or a sonographic short cervical length.[105] Results are unfortunately less bright in regards to multiple gestations where no effect of progesterone administration could be demonstrated.[105] Due to the absence of data showing any efficacy of its administration, progesterone is not routinely used as a therapy in multiple gestations. In spite of this fact, 17-OHPC is sometimes prescribed in the case of a history of PTB in the past. Since a preceding PTB of a singleton is a risk factor for an additional PTB in a multiple gestation and trials with 17-OHPC did not display any harm to the mother or fetus, it has been considered safe to prescribe in these circumstances.[73,106] However, this can be questionable since available data on the efficacy is very limited.[73] It is therefore justifiable not to prescribe progesterone in these circumstances.

7. CONCLUSION

The pathophysiology of pregnancy is very complex, making research related to pregnancy complications such as habitual abortions, threatened miscarriages and preterm birth extremely challenging. Since the majority of women with a previous pregnancy complication such as spontaneous abortion or preterm delivery will not have the same issue in subsequent pregnancies, it is difficult to recognize the natural history of this condition and presume the effect of a treatment prescribed. Published data has given a lot of ambiguous results with the OPPTIMUM study being one of the largest studies most dubious to the effect of progesterone supplementation.[18] The weakness of this study was a low compliance of 69%. Even though a newly published meta-analysis shows promising results with a 38% reduction of PTB with vaginal progesterone supplementation, there is still a lot of unanswered questions related to the efficacy of progesterone in pregnancy.[11,17] All of the data do have the same conclusion when it comes to multiple gestations regarding PTB prevention where all of the trials have failed to show efficacy of progesterone supplementation. Whether the ambiguity of previous published date in all other cases is due to poor study design or not is hard to tell. Furthermore, there is a wide variety of aetiology correlated to miscarriage and the heterogeneity of published trial data has not always been accounted for. However, there is no evidence that progesterone would put a mother or a child at any risk of harmful effects, giving a good reason why progesterone should still safely be administered until proven otherwise. Administration of progesterone to a pregnant woman at risk might not always show a statistical significant improvement in pregnancy outcome but can still bring some reassuring placebo effect to a woman who might feel abandoned if not given any treatment options at all. Larger randomized controlled trials are needed to continue investigating effects of progesterone as prophylaxis or treatment in pregnancy and which factors help estimate the possible positive outcome of its use, as well as exploring other treatment options.

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10. BIOGRAPHY

Ann Sofia Sundin is a medical student enrolled in the sixth year at the University of Zagreb, Medical Studies in English. She was born in a small town of Örnsköldsvik in the northern part of Sweden where she attended Nolaskolan High School. She is fluent in Swedish and English, and has adequate knowledge of the Croatian language. During her summer holidays she has been working in the field of Internal medicine at the county district hospital, Örnsköldsvik Hospital. Initially as a nursing assistant and later as a junior doctor. She is the vice-chairman for Sveriges läkarförbund Student Utland (SLFSU) Zagreb which is a part of the Swedish Medical Association for students abroad. As a part of a trade union, SLFSU Zagreb's aim is to keep their members updated regarding their rights, important changes in the Swedish Medical System, as well as keeping a close contact with other local sections of the Swedish Medical Association all around Europe. She has also been a part of the female University soccer team during the last five years and has been representing the University at Humanijada on three occasions. She performed her Internal Medicine rotations in Örnsköldsvik, Sweden and her Surgical rotations at the Department of Gynecology and Obstetrics in Zagreb, Croatia. On her free time, she enjoys soccer, skiing, reading and travel. In the future she plans to specialize in the field of Gynecology and Obstetrics.