Section A-Research paper

Roles of Cervical Cerclage and Progesterone in Prevention of Preterm Labour

Anwar Ezat Ismael[1], Walid Abdullah Mohamed Abdel salam[1], Hudi Alshareef Thabit [2]*, Wafaa Mohamed Ibrahim Diab[1]

1 Department of Obstetrics and Gynecology, Faculty of Medicine, Zagazig University, Egypt.
2 MBCCH, Faculty of Medicine, Benghazi- University -Libya
Email: hudathabit67@gmail.com, hudialshareef@gmail.com

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Abstract

Background: Cervical cerclage, an encircling suture placed around the cervix before or during pregnancy, has been used to help structural defects or cervical weakening in high-risk women with a shortened cervix. Studies have shown that cerclage is associated with a decrease in preterm labor and in perinatal death when used in women with a prior preterm labor and a cervical length of 25 mm or less. Cervical cerclage is performed as an attempt to prolong pregnancy in certain women who are at higher risk of preterm labor. The McDonald and Shirodkar techniques, or modifications thereof, are the most commonly used methods for placing a cerclage. The most recent Cochrane review on progesterone for the prevention of Preterm labor examined evidence on the use of any progestogen for women at risk of Preterm labor either because of a previous Preterm labor or because of a short cervix. Although the two risk categories were examined separately, all progestogens were considered together. For women with a previous Preterm labor, the review suggested that progestogens reduce the risk of Preterm labor before 34 gestational weeks, reduce perinatal mortality, reduce the incidence of low birthweight and reduce neonatal death.

Keywords: Cervical Cerclage, Progesterone, Preterm Labor

Introduction

Cervical cerclage, an encircling suture placed around the cervix before or during pregnancy, has been used to help structural defects or cervical weakening in high-risk women with a shortened cervix. Studies have shown that cerclage is associated with a decrease in preterm labor and in perinatal death when used in women with a prior preterm labor and a cervical length of 25 mm or less. Cervical cerclage is performed as an attempt to prolong pregnancy in certain women who are at higher risk of preterm labor. The McDonald and Shirodkar techniques, or modifications thereof, are the most commonly used methods for placing a cerclage **(1).**

Introduction

Throughout the natural course of pregnancy, the cervix remains long, thick and firm until the late third trimester when it slowly begins to soften, dilate and efface to eventually allow the passage of a fetus. The inability of a cervix to maintain its integrity prior to that time can result in miscarriage or Preterm labor. When this occurs in the absence of clinical signs or symptoms of labor, it is referred to as cervical insufficiency or incompetence. In the past, nonsurgical approaches such as activity restriction and pelvic rest have been suggested, though their use has not proven effective and should be discouraged **(2)**.

Indication for cerclage:

According to Royal College of Obstetricians and Gynecologists (RCOG) cerclage is indicated in :

1. History-indicated: performed in women with ≥ 2 midtrimester miscarriage.
2. Ultrasound-indicated: performed on asymptomatic women with cervical shortening or length < 2.5 cm at 22 weeks gestation.
3. Rescue cerclage, where the cervix is already open and the fetal membranes exposed. **(3)**

Vaginal cerclage insertion, either ultrasound- or history-indicated, is not associated with an increased risk of preterm prelabour rupture of membranes, chorioamnionitis, or cesarean section **(4).**

Anatomy and Physiology

The pathophysiology behind cervical insufficiency is still not well understood but is thought to arise from a structural or functional defect of the cervix. Risk factors include any prior cervical procedures or trauma, including loop electrode excisional procedure, cone biopsy, prior cervical lacerations, and repetitive cervical dilation and/or pregnancy terminations. Other possible etiologies include maternal connective tissue diseases or abnormalities, congenital Mullerian anomalies, or maternal exposure in utero to diethylstilbestrol **(1).**

Contraindications

While American College of Obstetricians and Gynecologists (ACOG) does not list any absolute contraindications, special attention should be given to the considerations listed above. Additionally, cerclage is not recommended in pregnancies of multiple gestations **(5).**

Technique

The most common technique for performing transvaginal cervical cerclage is:

A- The McDonald method. First applied in 1951, this procedure involves a simple purse-string suture at the cervicovaginal junction. Under regional anesthesia, the patient is placed in the dorsal lithotomy position and prepped with a vaginal betadine solution. A speculum or right-angle retractors are used to adequately visualize the cervix. The anterior lip of the cervix may be gently grasped using ring polyp forceps, and the vesicocervical junction should be identified. Just anterior to this junction, a nonabsorbable suture is inserted into the cervix in a purse-string manner, taking caution to avoid the paracervical vessels. The suture is then tied down with a surgeon knot, either anterior or posterior **(6)**.

B- The Shirodkar technique begins with the patient positioned and prepared in the same manner. Once the vesicocervical reflection has been identified, the mucosa of the anterior cervix is incised at this junction, similar to a vaginal hysterectomy. An Allis clamp can be used to elevate the bladder flap while the bladder is then mobilized cephalad using blunt or sharp dissection. This is continued until reaching the level of the internal cervical os. A similar incision is then made in the posterior cervical mucosa. Again, an Allis clamp can be used for traction on the posterior mucosa, while the reflection of the Pouch of Douglas is created using blunt dissection. An Allis clamp can then be applied at the 9 o'clock position to retract and isolate the paracervical vessels. A nonabsorbable suture can then be passed from anterior to posterior just beneath the Allis clamp so as not to enter the cervical os. The Allis should then be removed and placed in a similar fashion at the 3 o'clock position. The suture can then be passed from posterior to anterior, with special attention to lay the suture flat against the posterior aspect of the cervix. The suture can then be securely tied anteriorly. The anterior and posterior mucosa can then each be reapproximated in order to bury the cerclage stitch. This may be done in the running or interrupted fashion using an absorbable suture. The free ends of the cerclage stitch may be left exposed to facilitate subsequent removal **(6)**.

Both ultrasound-indicated and physical examination-indicated cerclages should be placed prior to 24 weeks gestation. Women undergoing a history-indicated cerclage procedure should have placement between 12-14 weeks gestation. There have been no proven clinical benefits to routine post-cerclage cervical length surveillance. Studies have demonstrated the comparative efficacy of McDonald and Shirodkar techniques. Thus, due to relative ease of placement and removal of the McDonald cerclage,

that technique tends to be used more frequently. There is also a consideration for abdominal cerclage placement for women who have failed a previous transvaginal cerclage **(7).**

Cervical cerclages should be removed between 36-38 weeks of gestation, prior to the onset of labour. Removal can safely be performed in the office setting. If preterm labour is suspected or diagnosed, cerclage should be removed at that time to minimize potential trauma to the cervix. If a cesarean is planned, removal may be delayed until the time of surgery **(5)**.

Complications

This procedure is not without risk, but the ultrasound-indicated and physical examination-indicated cerclages have more risk than history-indicated cerclages. Risks include infection, inadvertent rupture of membranes, lacerations at the surgical site, and anesthesia-related complications. Recent reviews suggest that initial dilation greater than 4cm is associated with a poor prognosis. These risks must be weighed against the benefit of the structural support of the cervix **(8).**

Clinical Significance

Cervical cerclages have been used to prevent Preterm labour since the 1950s, yet their efficacy continues to be questioned and studied. A 2017 Cochrane review supports that "pregnant women with cerclage were less likely to have Preterm labours compared to controls before 37, 34, and 28 completed weeks of gestation." However, outcomes may vary based on indication for cerclage **(9)**.

A meta-analysis showed that patients undergoing elective cerclage delivered at a significantly higher gestational age and had significantly higher birth weights compared to those undergoing emergency cerclage. Additionally, there was a higher incidence of premature rupture of membranes in the emergency cerclage group **(10)**.

Progesterone

Progesterone allows the endometrial transition from a proliferative to the secretory stage, facilitates blastocyst nesting and is essential to the maintenance of pregnancy. These characteristics explain the ethymology of the hormone's name, which comes from the Latin pro gestationem. Progesterone also plays an important role in several tissues not belonging to the reproductive system, such as the mammary gland in preparation for breastfeeding, the cardiovascular system, central nervous system and bones **(11)**.

Progesterone is a key physiological component of the menstrual cycle, reproduction, and steroid hormone biosynthesis. Other physiological actions of progesterone in the central nervous system and immune system also support the concept that progesterone is key to life, and a better understanding of this important hormone helps its extensive clinical implication for human health. Progesterone also plays an important role in mammary gland development and affects the function of the central nervous system and cardiovascular system **(12)**.

The Role of Progesterone in the Menstrual Cycle, Pregnancy, and Lactation

Preovulatory and Ovulatory Functions

The preovulatory follicles synthesize progesterone and also convert progesterone to estrogens **(11)**. Follicle-stimulating hormone (FSH) and Luteinizing hormone (LH) act one after the other on ovaries enhancing steroid production; however, other factors can also be important in this "switch over" of steroid production. Acetylcholine and serotonin induce progesterone release from granulosa cells, while noradrenaline and nicotine significantly inhibit progesterone production. Progesterone acts directly on granulosa cells by promoting follicular growth and inhibiting apoptotic genes via progesterone receptormembrane component-1 (PGRMC1). This non-genomic progesterone receptor is localized in the cell membrane. The modest increase in progesterone level appears to be a trigger of LH surge and the consequent ovulation. Progesterone increases GnRH release and enhanced gonadotropin pituitary sensitivity to GnRH **(12)**.

Before ovulation, the granulosa cells of the dominant follicle begin their transformation into large luteal cells by becoming vacuolated and taking up the yellow pigment lutein. Progesterone production of luteal cells depends on the availability of circulating cholesterol substrate and is facilitated by a low-level LH stimulation. Large luteal cells have a greater steroidogenic capacity but lack the LH and

human chorionic gonadotropin (hCG) receptors. The small luteal cells, likely to be derived from the theca cells, contain LH and hCG receptors and are linked to large cells by gap junctions. With the help of rapid transport of signals between the cells, large luteal cells respond to LH stimulation and synthesize progesterone **(12)**.

Progesterone in the Luteal Phase

Progesterone is produced by the corpus luteum, and it is the dominant hormone after ovulation in the luteal phase. In the early luteal phase, progesterone secretion is stable and does not correlate to LH pulses, while in the mid- and late luteal phase, progesterone secretion is episodic and correlates with the pulsatile release of LH. During this period, a progressive reduction in LH pulse frequency and amplitude occurs. Compared to low levels (1–2 nmol/L) during the follicular phase, progesterone levels increase to 15–20 nmol/L in the early luteal phase and then peak in the middle of the luteal phase (35–50 nmol/L). If conception does not occur, the corpus luteum starts to break down 9 to 10 days after ovulation, causing progesterone levels to fall (20–40 nmol/L). Lowered plasma steady-state levels of progesterone combined with declining progesterone levels during the luteal phase may predict premenstrual syndrome (PMS); however, some clinical trials did not show that progesterone is an effective treatment for PMS **(13)**.

The Endometrial Effect of Progesterone

Rising progesterone levels in the early luteal phase play an important role in the transition of the endometrium from the proliferative to the secretory phase. Because of the suppressive action of progesterone during the ovulatory phase, estrogen receptors of stromal and myometrial epithelial cells drop rapidly. At the same time, due to estradiol action, the expression of progesterone receptors (PR) exponentially increases in endometrial endothelial cells and then dramatically decreases in the late luteal phase **(11)**. Endometrial progesterone and its metabolite 17-hydroxyprogesterone are significantly associated with endometrial receptivity. A higher proportion of receptive endometria was observed when endometrial progesterone levels were higher than 40.07g/mL, and a lower proportion of receptive endometria was associated with endometrial 17-hydroxyprogesterone lower than 0.35 ng/mL **(14)**.

Progesterone during Pregnancy

Progesterone is recognized as a key physiological component of implantation and maintenance of pregnancy. Removal of corpus luteum or treatment with progesterone antagonist, e.g., mifepristone, terminates the pregnancy. Progesterone is crucial for preparing the endometrium for implantation and for regulating trophoblast invasion and migration. Progesterone establishes uterine receptivity by blocking the proliferative effect of estrogen, by inducing genes that allow the endometrium to permit embryo attachment, and also acts as a negative regulator of trophoblast invasion by controlling matrix metalloproteinase (MMP) activity **(12)**.

Progesterone and Tryptophan Catabolism

Progesterone has also been claimed to play a prominent role in the control of tryptophan catabolism that provides essential compounds to achieve successful pregnancy. The essential amino acid tryptophan acts as a precursor to various metabolic pathways, including protein synthesis and production of serotonin and kynurenine. The kynurenine pathway represents the major non-protein route for tryptophan metabolism (>95%). Along this pathway, bioactive intermediates are generated that are involved in pregnancy-related immune tolerance, inflammation, oxidative stress, neuroprotection/toxicity. Two enzymes initiate tryptophan catabolism; the hepatic tryptophan–2, 3-dioxygenase (TDO) that is induced by glucocorticoids and tryptophan and inhibited by progesterone and oestrogens, as well as the extrahepatic indoleamine-2, 3-dioxygenase (IDO) that is up-regulated by inflammatory cytokines, in particular, by interferon gamma **(12)**.

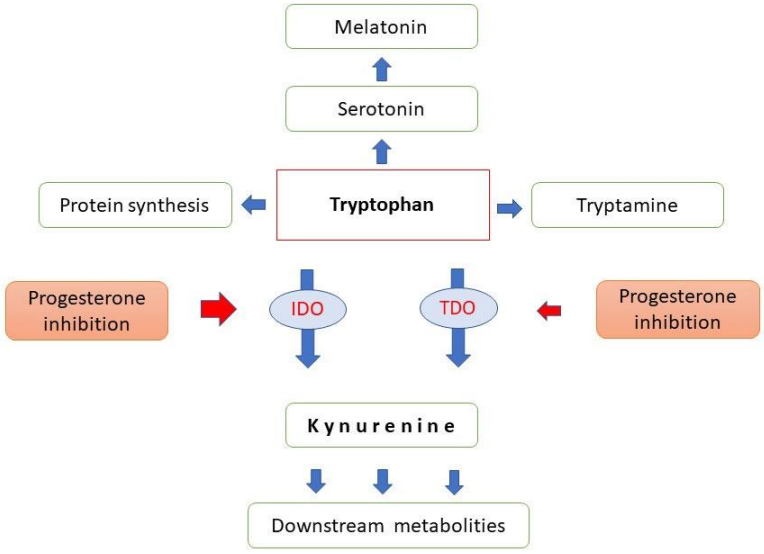


Figure 1. Major pathways of tryptophan metabolism. IDO: indoleamine-2,-3- dioxygenase, TDO: tryptophan-2,-3-dioxygenase, red arrows indicate progesterone inhibition (12).

The mRNA and protein expression for both TDO and IDO has been documented in the placenta, decidua, and early embryonic/fetal tissues. Importantly, progesterone proved to inhibit IDO mRNA expression and enzyme activity. Reduced conversion of tryptophan to kynurenine, therefore, results in an increase in the bioavailability of tryptophan for protein and serotonin synthesis **(15).**

Progesterone and Lactation

Progesterone and progesterone receptor B have primary importance in mammary gland development by enhancing epithelial cell proliferation and differentiation. These effects are achieved through acting in concert with insulin-like growth factor-1 (IGF-1). As a result of their synergistic action, ductal length increases, and an extensive network of branching develops. Furthermore, progesterone increases the anti-apoptotic effects of IGF-1 and induces alveolar development when IGF-1 and oestrogens are present. Progesterone also serves as an inhibitor of lactogenesis during gestation, and the postpartum decrease in progesterone levels is required to ensure full lactation. If plasma progesterone remains elevated or progesterone is sequestered into the adipose tissue of the mammary glands, lactogenesis is delayed, and lactation failure may occur **(16)**.

3. Clinical Implications of Progesterone

Progesterone and other progestational agents have several clinical applications, and extensive research has been conducted to evaluate the physiological effects and also the side effects of exogenous progesterone administration. Progesterone is the only native ligand, while progestogens comprise all substances that activate PR and result in progesterone-like effects, and progestins are synthetic PR agonists **(17).**

After oral administration, more than 90% of progesterone is metabolized during the first hepatic pass, leading to decreased efficacy and also high levels of metabolites that may be responsible for dizziness and drowsiness. Because of the poor oral absorption and rapid first-pass metabolism of oral progesterone, a variety of oral, injectable, and implantable synthetic analogs have been developed. Progestins, e.g., medroxyprogesterone acetate and norethindrone acetate, were designed to resist enzymatic degradation and remain active after oral administration. However, synthetic progestins may exert significant side effects, such as dysphoria, depression, anxiety, fatigue, as well as headaches, hypercoagulant states, increased androgenicity, reduction in HDL cholesterol levels, and fluid retention. Transdermal administration of norethindrone acetate can also exert undesirable effects on the liver. In the case of transvaginal administration of progesterone with the help of suppositories or with polycarbophil-based gel, the plasma progesterone concentration remains low, resulting in minimal side effects. However, the local vagina to uterus transport of progesterone results in uterine uptake of

progesterone and allows secretory transformation of the endometrium and maintenance of pregnancy despite the low plasma progesterone levels **(12)**.

Subcutaneous administration of progesterone is effective and safe. No statistically significant or clinically significant differences exist between subcutaneous and vaginal progesterone administration for luteal phase support **(18)**.

Natural progesterone is obtained primarily from plants such as soybeans and Mexican yam roots. Micronization decreases the particle size and enhances the dissolution, resulting in an increased half-life and decreased destruction in the gastrointestinal tract. An oral micronized progesterone has improved bioavailability and fewer side effects compared with synthetic progestins. Micronized progesterone has been shown not to affect mood or decrease HDL cholesterol levels; however, fatigue and somnolence have still been reported as side effects. Therefore oral administration of micronized natural progesterone appears to be a safe and effective alternative to synthetic progestins **(12)**.

Progesterone in Recurrent Miscarriage

Women with a history of miscarriage who present with bleeding in early pregnancy may benefit from the use of vaginal progesterone. Treatment with vaginal micronized progesterone 400 mg twice daily was associated with increased live birth rates **(19)**.

Maintenance of Uterine Quiescence in Late Pregnancy

Progesterone administration maintains uterine quiescence in late pregnancy and delays labour, particularly in patients with short uterine cervixes. Recent meta analysis proved that vaginal progesterone decreases the risk of Preterm labour and improves perinatal outcomes in singleton gestations with a mid-trimester sonographic cervical length ≤25 mm **(20).**

Role of pr ogesterone in pregnancy maintenance

Progesterone clearly plays a role in the maintenance of pregnancy. Circulating levels of progesterone rise during pregnancy: the major source (in humans) is the corpus luteum until approximately week 8 of pregnancy, and the placenta thereafter. One of the major mechanisms of progesterone action in maintaining pregnancy is inhibition of the contractions of the myometrium: research has demonstrated the relaxant effect of progesterone on myometrial strips in vitro. The importance of progesterone in maintaining human pregnancy in vivo has been demonstrated by studies administering receptor antagonists such as mifepristone (RU486). If administered in early pregnancy, mifepristone increases uterine contractility in vivo,3 sensitizes the uterus to the pro-contractile effects of prostaglandins, and acts as an effective abortifacient (although it is much more effective when combined with prostaglandin). In late pregnancy, mifepristone can be used to induce labour, although its safety in the absence of intrauterine fetal death is unclear. Lastly, the withdrawal of progesterone is probably involved in the spontaneous initiation of labour at term. In many animal species, progesterone withdrawal is caused by a decrease in circulating levels of progesterone. In humans, progesterone levels are maintained until the end of pregnancy and in labour, but complex alterations in progesterone receptor activity result in a decline in progesterone receptor signaling at the time of labour onset **(21).**

Efficacy of progesterone for Preterm labour prevention

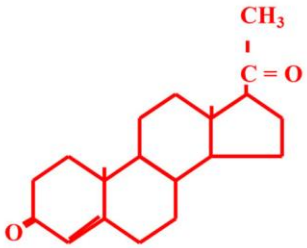
The most recent Cochrane review on progesterone for the prevention of Preterm labour examined evidence on the use of any progestogen for women at risk of Preterm labour either because of a previous Preterm labour or because of a short cervix. Although the two risk categories were examined separately, all progestogens were considered together. For women with a previous Preterm labour, the review suggested that progestogens reduce the risk of Preterm labour before 34 gestational weeks, reduce perinatal mortality, reduce the incidence of low birthweight and reduce neonatal death **(22)**.

Long-term risks and harms of progesterone prophylaxis

Clinicians and pregnant women wishing to use progesterone to prevent Preterm labour need to be aware of the long-term risks and benefits. The primary rationale for preventing Preterm labour is to avert adverse consequences for the newborn. Worldwide, 15 million Preterm labours per annum result in around 2000 neonatal deaths, and neurodevelopmental disability in nearly 1 million survivors **(23).**

In conclusion Progesterone is necessary for successful embryo implantation and pregnancy

maintenance. Vaginal progesterone treatment minimizes the risk of recurrent miscarriage and decreases the risk of Preterm labour, saving many fetal lives. However, progesterone is far more than a gestational agent. Progesterone is an essential steroidogenetic precursor of other gonadal and non-gonadal hormones such as aldosterone, cortisol, estradiol and testosterone. These hormones are responsible for innumerable functions such as sodium conservation in the kidney, regulation of blood pressure, response to stress and low blood-glucose concentration, development of female and male secondary sexual characteristics. Progesterone also plays an important role in the nervous system. Its neurogenic effect is essential for normal brain development in fetuses, while the neuroprotective effect of progesterone improves the patient's survival after traumatic brain injury. Progesterone and novel progestins have many important functions, including contraception, luteal phase support, treatment of dysfunctional uterine bleeding, and endometriosis. Progesterone has an important role in immune response and also in the prevention and treatment of various cancers **(12)**.



Progesterone

Progesterone is a key to:
Reproduction
Birth control
Female and male secondary sexual characteristics
Salt and water balance, regulation of blood pressure
Stress adaptation
Thermoregulation
Protection against tumors
Neurogenesis and neuroprotection

Figure (2): progesterone really a key to life

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