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Premature Labor Management Protocol

Introduction and pathophysiology of preterm labor/cervical insufficiency continuum

The cause of premature labor for the most part remains unknown. Several factors have been implicated in the onset of premature labor such as, bleeding, placental ischemia, infection, premature rupture of membranes, stress of any kind (emotional, financial, health related), and a large number of patients go into premature labor for yet undefined reasons and considered as idiopathic cases. Over the last ten years, however, a significant body of literature has been accumulated that points towards one common denominator, pro-inflammatory cytokines. Pro-inflammatory cytokines seem to be in the center of action in most of the patients, if not all, who suffer from premature labor. Although genital infection has been traditionally considered a strong cause of premature labor, if one analyzes critically the recent data, it becomes evident that inflammation is the main problem and not infection. Most of the reports in the past that considered infection as the cause of premature delivery were based on the presence of pro-inflammatory Cytokines in the vaginal fluid or in the amniotic fluid in patients with premature labor. However, as it is well known, pro-inflammatory cytokines are significantly elevated in patients who have tissue degradation (damage) regardless of etiology. The most common reason for tissue degradation in human pregnancy is placental thrombosis, either from accidental vascular breakdown that might cause a small degree of placenta abruptio or repetitive small incidences of vessel breakdowns at the periphery of the placenta. Even more commonly, it may be caused from intraplacental and fetal vascular thrombosis secondary to maternal and/or fetal thrombophilia.

Thrombosis of the placental vascular bed (maternal and/or fetal) leads to necrosis (death of tissues) and apoptosis. Thrombin anti-thrombin complex (TAT), a marker of activated coagulation system increases the risk for premature delivery by a factor of 6 (*J Matern Fetal Med. 2001 Oct;10(5):297-300, Am J Obstet Gynecol 2004;191:1996-2001, Am J Obstet Gynecol 2001; 185:1059-63*).

Cell necrosis provokes an inflammatory reaction by mobilization of macrophages, which consume necrotic or semi-necrotic cells that have been opsonized by CRP. In many patients with signs of premature labor CRP is significantly elevated as well as a host of other pro-inflammatory cytokines.

At Kofinas Perinatal, with our extensive (over 20 years) experience relating to placental thrombosis and management of patients with placental thrombosis regardless of etiology, we have come to realize that most of the complications of the pregnancy and premature labor are very closely related to placental thrombosis and placental degeneration. Therefore, we have instituted the protocol as described below for the management of premature labor. This protocol has given us the ability to reduce premature delivery to less than 5 percent in comparison to the national average of 13 percent. The rate of prematurity

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is rising every year over the last ten to fifteen years. Premature delivery, defined as delivery prior to thirty-seven completed weeks of gestation, was eight percent in 1980 and currently is at 13 percent with a continuous and relentless rise.

At Kofinas Perinatal, most of the premature deliveries are intended and indicated due to fetal or maternal indications other than premature labor.

Patients with cervical shortening prior to twenty-eight weeks were found to be at significantly elevated risk for premature delivery prior to thirty-four weeks. It is well known that delivery prior to thirty-four weeks is not only costly due to expensive neonatal care, but also detrimental to the long term and life-long well being of the neonate. Therefore, it is of importance to eliminate such deliveries by all means. Cervical length is inversely proportional to the timing of delivery and the rate of prematurity increases as much as eighty-five percent in patients whose cervix prior to twenty-eight weeks is less than 22 mm in length (normal range 35-45 mm) { *N Engl J Med 1996;334:567-7* }.

At Kofinas Perinatal, all patients who are seen for any high-risk indication prior to 24 weeks undergo a transvaginal sonography also to identify and document cervical length. In addition, patients are educated about the symptoms and signs of premature labor and encouraged to report them to their obstetrician whenever the symptoms arise. We understand that the only way that premature cervical changes can be identified is by extensive education of the patient so that they report symptoms that otherwise might have been thought of as normal. Such symptoms are usually attributed to intestinal gas pain, round ligament stretching, etc. (**Appendix A**). At Kofinas Perinatal, no pelvic pain is normal unless the cervix has been proven to be of normal size and there is no evidence of contractility of the lower uterine segment. A vaginal examination entails detailed assessment of the cervical length, and the quality of the cervical stroma (presence or absence of Nabothian cysts or inclusion cysts). The presence of cervical shortening or the presence of Nabothian (inclusion) cysts that may affect the integrity of the cervical stroma prompt timely follow-up of the cervical condition in order to identify early cervical changes and prevent pregnancy loss or premature delivery.

The following groups of patients are followed on a regular basis for cervical assessment every two weeks, or more frequently when indicated based on cervical length change:

Patients with a history of infertility that conceived with assisted reproductive technologies (IVF, ovulation induction and intrauterine insemination). These patients are more likely to have multiple gestations, which by definition are a risk factor for prematurity. However, what is of importance is that singleton gestations that are the product of ART have a substantially higher risk for preterm delivery than the general population. In fact, the risk of preterm delivery in such patients is as high as 35% according to the latest studies here and abroad and that is 2-3 times the rate of the average normal population in the United States. Since we know that prematurity is of the highest risk for fetal well-being and neonatal outcomes, it is very important that this risk is mitigated. *{N Engl J Med. 2002*

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Mar 7;346(10):731-7, BMJ. 2004 Jan 31;328(7434):261. Epub 2004 Jan 23, Obstet Gynecol. 2004 Mar;103(3):551-63}

- 1) Patients with previous preterm birth who have a risk as high as 30-60% for a subsequent preterm delivery. {*N Engl J Med 2003;348:2379-85*}
- 2) Patients with placental Thrombosis, which is known to cause placental ischemia and subsequent preterm delivery and growth failure. {*Kofinas A et al. Ultrasound Obstet Gynecol, in Press*}
- 3) Patients who experience one or all of the following symptoms: low back pain, pelvic pressure, and contractility such as pains similar to menstrual cramping, vaginal wetness, or other nonspecific pelvic symptoms.

In any of the above patients, if the cervix is less than 35 mm and greater than 25 mm, we recommend one week of complete bed rest and a follow-up visit in one week to reassess the cervix. If the cervix normalizes and continues to remain normal in the subsequent one to two visits then the patient goes back to the regular follow-up. If the cervix is between 25 mm and 30 mm, but the rate of decline based on previous assessment is acute, then we treat the patient according to the protocol noted below with medication in addition to bed rest.

On any patient whose cervix is less than 25 mm on any occasion, with or without prior measurements, the patient would be treated with complete bed rest and medication as noted below in the protocol.

Any patient with a cervical length less than 15 mm will undergo cerclage placement in addition to the subsequent treatment with complete bed rest and tocolysis.

Out-patient Treatment Protocol

Our treatment protocol consists of complete bed rest at home, the use of Indomethacin, the use of Nifedipine (Procardia) and the use of 17-alpha-hydroxyprogesterone-caproate as indicated.

Approximately 17% of the patients improve with bed rest only and then continue their regular pregnancy follow-up. Most of the patients deteriorate with bed rest and require subsequent medical treatment. (**Appendix B**)

The following modalities are employed in the management of patients with signs and/or symptoms of preterm labor:

1. If the **cervix is normal** in length and appearance the patient is advised to continue her life as usual and watch for any deterioration in the symptoms. A follow up evaluation of the cervix is scheduled in 1-2 weeks according to the symptoms.
2. If the **cervix is short** with or without funneling (the internal opening of the cervical canal assumes the shape of a funnel), the patient will be treated with bed rest and/or oral tocolysis according to the cervical condition as noted below:

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- a. If the **cervix is between 25-35 mm** we prescribe complete bed rest only and re-evaluation in one week.
- b. If the **cervix is between 15-25 mm** the patient is treated with complete bed rest and tocolysis as follows:
 - i. One week of **Indomethacin 50 mg orally every 6 hours** followed by **Procardia XL 60 mg twice a day** for as long as the cervix remains above 30 mm.. Usually if the treatment is successful the cervix regains its normal length after one week of treatment with Indomethacin.
 - ii. Fetal ductus arteriosus flow pattern and amniotic fluid are assessed before the start of treatment and one week after. This allows us to use this potentially hazardous medication in the safest possible way. We have never identified any fetal complication as a result of the use of such medications in the past 16 years that we use it for the management of preterm labor.
 - iii. If the cervical length does not improve with the above treatment then the diagnosis of **cervical insufficiency along with preterm labor** is made. In such patients we continue the tocolytics as noted above but we also place a cervical cerclage for added mechanical support.
 - iv. If the cervix declines below 30 mm while the patient is on Procardia 60 mg BID, we continue the procardia treatment but the patient is also instructed to take Indomethacin 50 mg q6h for 48 hours during the weekend. In such cases the patient is seen weekly for fetal assessment with BPP, fetal Doppler (including Ductus arteriosus and tricuspid valve assessment) and amniotic fluid assessment. This scheme is continued until 32 weeks if needed.
 - v. We never use Indomethacin after 32 weeks since patients do well with Procardia only.

The above treatment schemes may be adjusted according to the individual patient's needs and responses to treatment. There will be instances where the cervix will remain stable after one week of Indomethacin. The use of cerclage vs. tocolysis will depend on other factors such as gestational age, previous OB history, cervical pathology etc.. We believe strongly based on our long experience in treating such patients that every patient is unique and requires customized management within the scope of the guidelines mentioned above. One size does not fit all.

We use 17-alpha-hydroxy-progesterone-caproate as an adjunct to the above treatments and not alone. We mostly use it in patients that have evidence of ongoing inflammation as indicated by the presence of elevated CRP or other inflammatory markers and patients that require frequent use of Indomethacin. The use of 17-alpha-hydroxy-progesterone-caproate helps us reduce the total amount of Indomethacin used. (*N Engl J Med.* 2003 Jun 12;348(24):2379-85. *Erratum in: N Engl J Med.* 2003 Sep 25;349 (13): 1299).

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The above protocol is executed on an outpatient basis and patients may be admitted only for concomitant indications that may require hospitalization.

Kofinas Perinatal does not perform home uterine monitoring (HUM) since it has never shown to be of any benefit. In fact, we believe that home uterine monitoring may be desensitizing the patient and her obstetrician due to frequent false alarms and when real labor comes, the patient does not comply. Likewise, we do not use fibronectin. Fibronectin is an indirect test of tissue degradation due to chorionic (fetal) tissue apoptosis, necrosis and consequent inflammatory process (production of pro-inflammatory cytokines). Such inflammatory process causes increased uterine contractility, premature cervical ripening and finally cervical shortening. Cervical length is the gold standard for pregnancy failure and we only use that. Our protocol helps us achieve term pregnancy in 90% of patients with preterm labor, and 96% of such patients reach 35 weeks. We believe that such a performance has never been achieved before regardless of protocol.

We do not use MgSO₄ because it:

1. Requires lengthy and costly hospitalization
2. Can be lethal to the mother
3. Has only been proven to stop labor for up to 24 hours (enough to give steroids for lung maturation and then deliver the patient prematurely). (*The Cochrane Library Review, 2006 Issue 4, Obstet Gynecol, 2006; 105:986- 9*)
4. Neonates born after intrauterine exposure to MgSO₄ for preterm labor have higher rates of **neonatal death** in proportion to MgSO₄ levels in umbilical cord blood in a dose-dependent effect. At Kofinas Perinatal, the only reason we might use MgSO₄ is in patients that cannot take any of our protocol medications due to concomitant maternal indications or allergies and we make every effort to stop it for at least 24h prior to delivery. (*The Cochrane Library Review, 2006 Issue 4, Obstet Gynecol, 2006; 105:986- 9*)

We also do not use beta₂- receptor agonists (Terbutaline) for the following reasons:

1. Usage of beta₂-agonists (Terbutaline and related drugs) leads to an immediate uterine relaxing effect that is very short lived. Always, this first response is followed by lack of effect due to the down-regulation of beta-receptors, which renders the treatment ineffective. (*Acta Obstet Gynecol Scand Suppl. 1982;108:47-51*). Most randomized trials failed to identify any clinical benefit beyond a delay sufficient to administer steroids. There is no benefit in delaying delivery for more than 7 days in comparison to placebo effect. Randomized trials comparing beta-mimetics with calcium channel blockers revealed the superiority on the later in terms of delivery delay as well as superior neonatal outcomes. (*Cochrane Database of Systematic Reviews 2006 Issue 4*) Further more, beta₂-agonists have been associated with a 3-fold increase in the incidence of IVH and with an increase in the incidence of neuropsychiatric, cognitive, cardiovascular, and metabolic abnormalities in the offspring. (*Brain Res Bull 2003 Jan 15;59(4):319-29*), (*Br J Obstet Gynaecol 1998 Aug; 105(8): 865-71*)

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2. Prolonged use of beta agonists leads to stimulation of the **cyclic-AMP phosphodiesterase enzyme system**, which causes degradation, and depletion of intracellular cyclic-AMP. This in turn leads to increased uterine muscle contractility and preterm labor. *{Gynecol Obstet Invest. 1982;14(1):56-64.}*
3. Tolerance of medication is very low due to intense cardiovascular effects (positive chronotropic effect with tachycardia) and significant increase in the pulse pressure that causes an intense feeling of palpitations, which the patients cannot tolerate and this brings compliance to the lowest with as many as 70% of the patients discontinuing the medication or under-dosing within one week. *{Cochrane Database of Systematic Reviews 2006 Issue 4}*

Appendices C, D and E depict cervical measurements in various treatment modalities and Appendix F depicts the intracellular molecular interactions that are associated with uterine cell contractility and relaxation.

APPENDIX A

Patient symptoms and signs:

Many of the patients that develop premature cervical changes experience vague symptoms that may last for weeks and go unnoticed. Very few patients experience cervical changes without any symptoms. The latter group is most likely to experience incompetent cervix. However, even in this group most of the patients have some warning symptoms and signs that if noted may help prevent loss of pregnancy or premature birth.

The following symptoms have been described by patients who either lost their pregnancies in the early second trimester (between 13 and 24 weeks gestation) or delivered prematurely (between 24 weeks and 37 weeks gestation):

- 1. Pelvic pressure**
- 2. A feeling of stretching and pulling in the pelvis**
- 3. Low back pain (in the region of the tail-bone).**
- 4. Pressure in the vagina**
- 5. Excessive discharge (feeling wet in the vagina)**
- 6. Having pelvic discomfort that they cannot define clearly**
- 7. A feeling of menstrual cramping**
- 8. Intermittent deep pelvic discomfort**
- 9. Gas pains**
- 10. Rectal pressure and constipation**

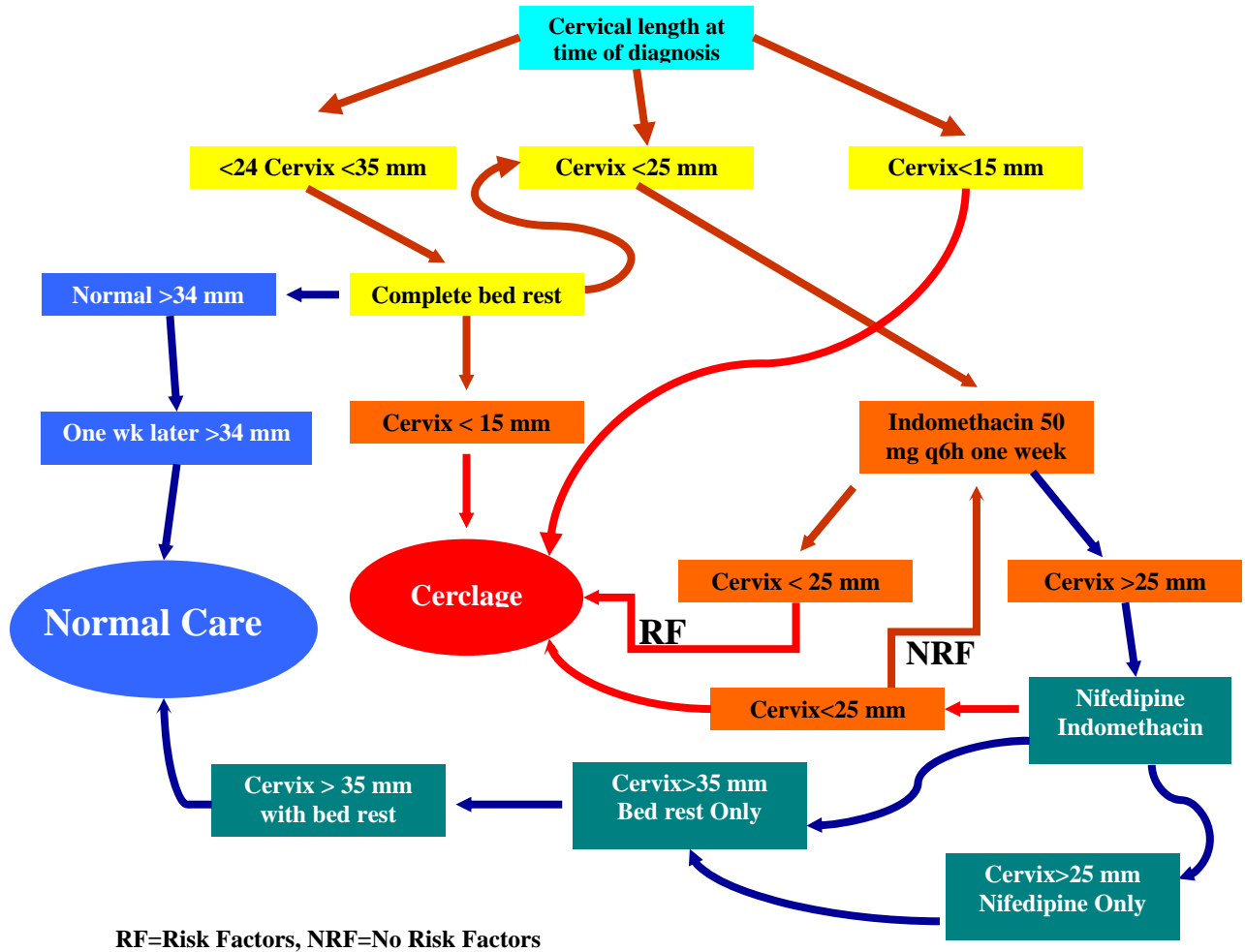
The above mentioned symptoms are usually ignored by most patients and their obstetricians. This is detrimental and leads to pregnancy loss and /or premature delivery.

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APPENDIX B

Stepwise approach to the treatment of ultrasonically assessed short cervix: When the cervix is >25 mm the patient is treated with bed rest only. When the cervix is between 15 and 25 mm we treat patients with bed rest and Indomethacin as per protocol. If the cervix is <15 mm we treat with cerclage (emergency) and Indomethacin as per protocol. (Kofinas et al. in press).



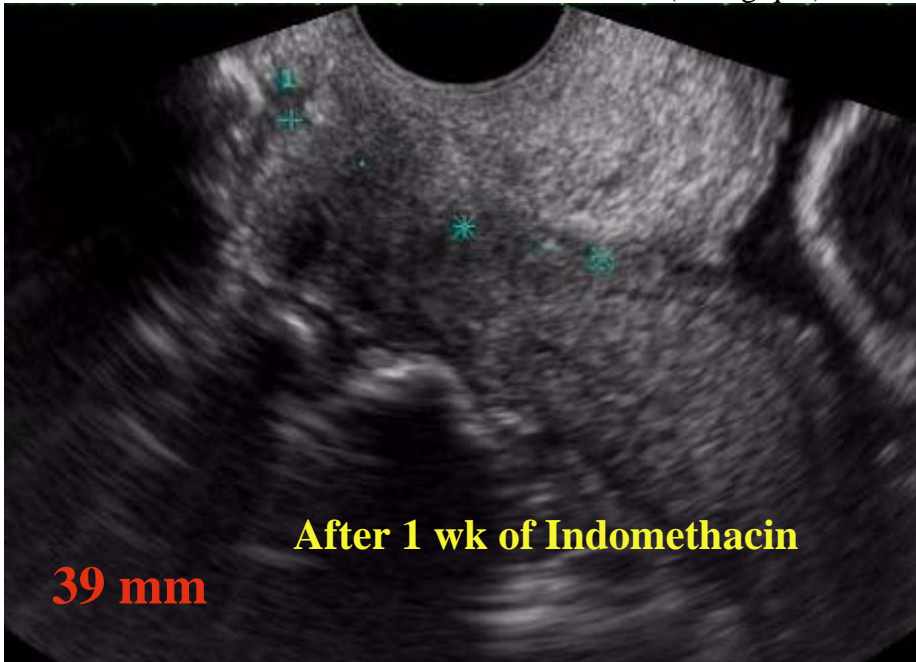
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APPENDIX C

Short Cervix before treatment



Cervix normalized after one week of Indomethacin (50 mg q6h)



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APPENDIX D

Poorly placed (too close to the external cervical os) cerclage. If this patient has incompetent cervix or minor labor will eventually lose the baby since the amniotic sac will descent into the cervical canal and lead to PROM. In fact this patient lost her baby two weeks later.

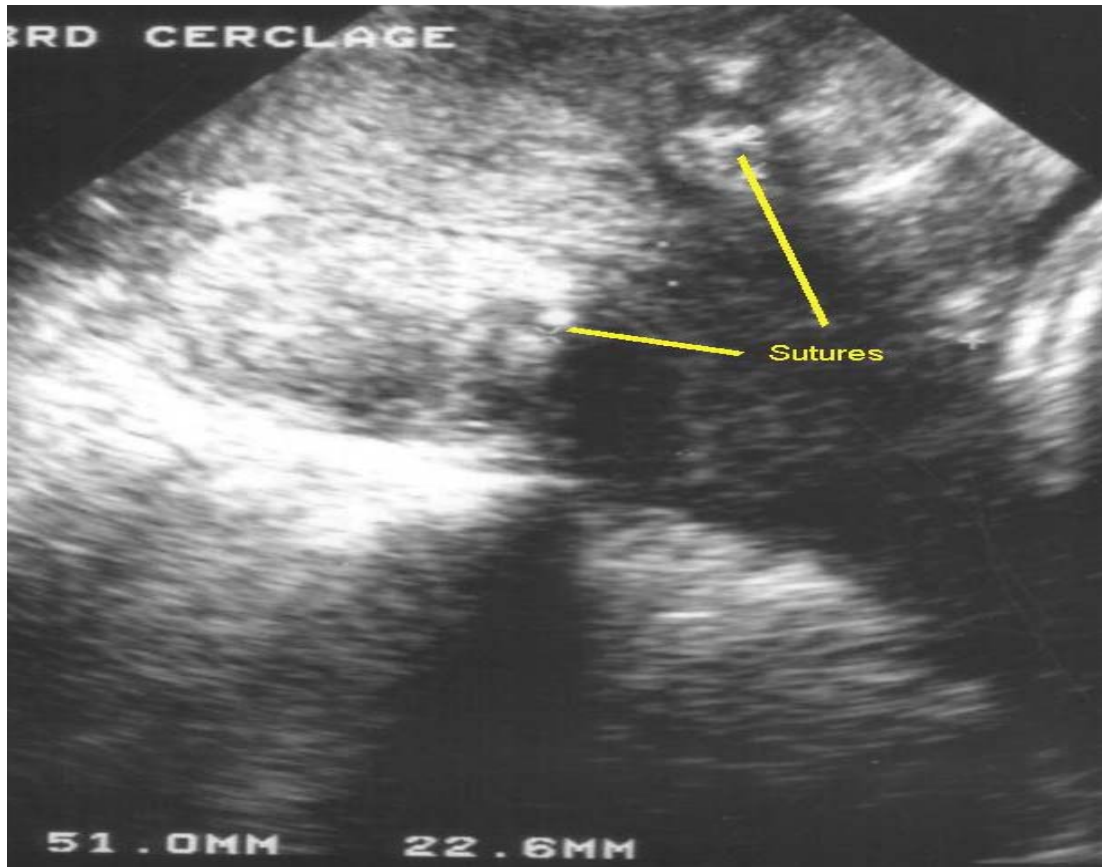


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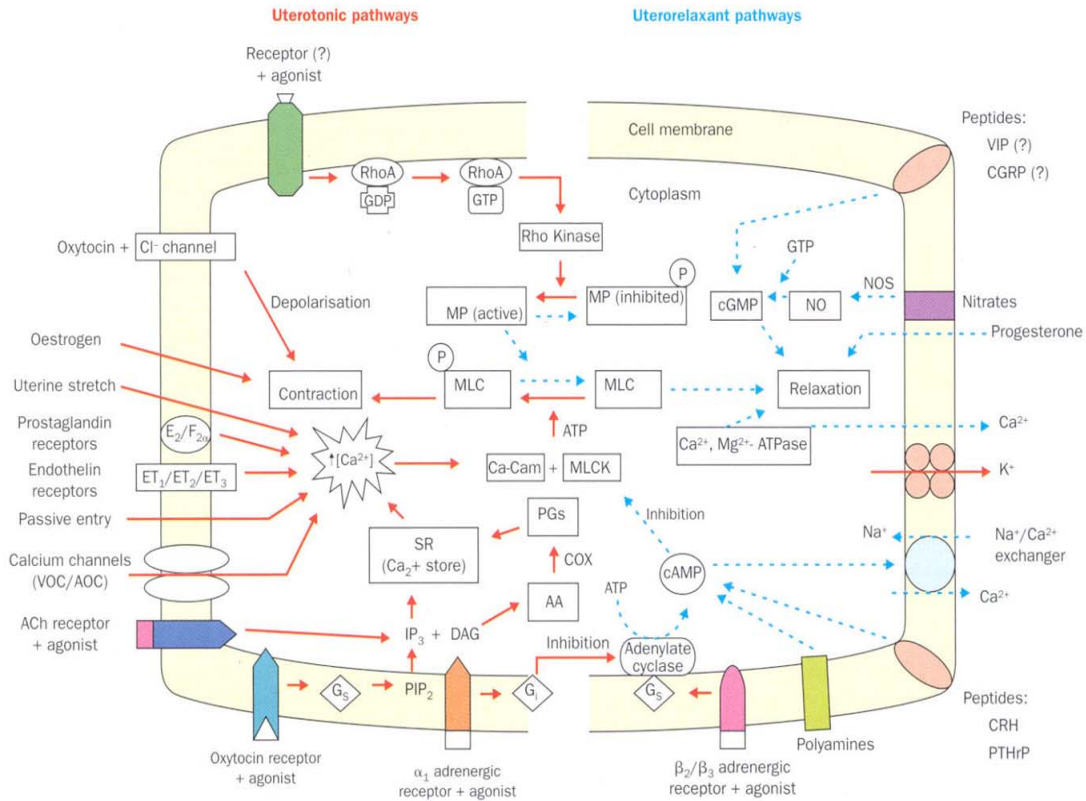
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APPENDIX E

This cerclage is placed at approximately 30 mm from the external os and the entire cervical length has been restored to 51 mm. Suture diameter is 22 mm.



APPENDIX F



Some of the potential mechanisms of uterine contractility and relaxation: Note that Ca^{++} is at the center of most mechanisms and that is the reason Ca calcium channel blockers make sense and work in contrast to Mg and β_2 -agonists. In addition, note the important role of prostaglandins since most of the reasons of preterm labor have to do with some form of an inflammatory reaction that increases the production of all kinds of cytokines. **{Lancet 2002; 360:1489-97}**