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FOLLOW UP OF PREGNANT WOMEN WITH SHORT CERVIX RECEIVING PROGESTERONE

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List of abbreviations

17-OHPC	17α-hydroxyprogesterone caproate
ACOG	American College of Obstetricians and Gynecologists
ART	Assistant Reproductive Technology
BMI	Body Mass Index
CCI	Cervical Consistency Index
CI	Confidential Interval
CIN	Cervical intraepithelial neoplasia
CKC	Cold-knife conisation
CL	Cervical Length
CRL	Crown Rump Length
C-Section	Cesarean Section
fFN	Fetal Fibronectin
FGR	Fetal growth restriction
FIGO	International Federation of Gynecology and Obstetrics
FMF	Fetal Medicine Foundation
GDM	Gestational Diabetes Mellitus
HPV	Human papillomavirus
ISUOG	International Society of Ultrasound in Obstetrics and Gynecology
LEEP	Loop electrosurgical excision procedure
LLETZ	Large loop excision of the transformation zone
MMP	Matrix Metalloproteinases
NICE	National Institute for Health and Care Excellence)
NICU	Neonatal Intensive Care Unit
OR	Odds Ratio
PAPP-A	Pregnancy Associated Plasma Protein A
PE	Preeclampsia
PLGF	Placental growth factor
PPAQ	Pregnancy Physical Activity Questionnaire

pPORM	Preterm Premature Rupture of Membrane
PROM	Premature Rupture of Membranes
PTB	Preterm Birth
RCOG	Royal College of Obstetricians and Gynaecologists
RDS	Respiratory Distress Syndrome
sFLT-1	Serum soluble fms-like tyrosine kinase-1
SOGC	Society of Obstetricians and Gynaecologists of Canada
TNF-a	Tumor Necrosis Factor-a
TPL	Threatened Preterm Labour
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

Definitions and Prevalence of Preterm Delivery

Preterm Birth is defined as delivery before 37 weeks of gestation and can be either spontaneous or iatrogenic (1). The lower gestational age for considering a preterm neonate viable varies among different countries, but in most of the cases, including Greece, the lowest gestational age when resuscitation of a newborn should be commenced is 22 weeks or birthweight of 500gr. However, during the gray zone period of 22 to 24 weeks of gestation, an appropriate counseling with the parents about the prognosis is indicated and the final decision for resuscitation should be made on parental preferences when possible (2).

The latest estimates showed that in 2020, almost 10% of all live birth globally were preterm. About 13.4 million children every year are born preterm worldwide, with the vast majority in southern Asia, where the rate of preterm births is 13.3% (3). Neonatal and infant mortality associated with preterm birth and subsequent low birth weight is estimated at 104.6 infant deaths per 100,000 in 2014 in the USA alone (4). Based on the World Health Organization, Greece is among the group of high-income countries with rates preterm birth higher that the average, namely 11.6%, with steady upward trend (3).

There are four categories of preterm birth based on the gestational age at the time of delivery; late preterm birth when it occurs between 34 and 37 weeks of gestation, moderately preterm for 32 to 34 weeks, very preterm birth for 28 to 32 weeks and fourthly extremely preterm birth for deliveries before 28 weeks. About 7% of all deliveries are late and moderate preterm births, meaning 32 to 37 weeks of gestation (5) (6). In terms of preterm deliveries, 84% of them happen after 32 weeks, 10% between 28 and 32 weeks and 6% before 28 weeks (7).

Preterm delivery is further distinguished into spontaneous or iatrogenic. When the delivery happens because of spontaneous contractions or after preterm rupture of membrane (with or without contractions) then is considered spontaneous preterm birth. On the contrary, cases of delivery after induction of labour or elective cesarean section because of maternal or fetal

indications are considered iatrogenic preterm delivery. Examples of indications for iatrogenic preterm birth are preeclampsia, intrauterine growth restriction, placenta abruption and others. Based on the NICE (National Institute for Health and Care Excellence) statistics, about 75% of all preterm birth are spontaneous, number which however varies between different countries and clinical practices. Among those women who have spontaneous preterm deliveries, only half of them are multiparous and from them only 30% have a history of preterm delivery (8).

Neonatal outcomes

Preterm birth is the leading cause of both neonatal and child mortality, in children less than 5 years old, accounting for around 16% of all deaths, and 35% of deaths among newborn babies (up to 28 days old) (9). Neonates born preterm are at increased risk of both short-term complications, attributed to immaturity of multiple organ systems, namely bronchopulmonary dysplasia, respiratory distress syndrome, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, retinopathy and sepsis. They are at further risk of long-term adverse health outcomes, such as neurodevelopmental disabilities, behavioral problems, childhood asthma, cardiovascular disease, diabetes and depression, in adult life. In addition, preterm birth is associated with a substantial economic cost and adverse psychosocial and emotional effects on families (10) (11) (12) (13) (14) (15) (16).

Delivery before 32 weeks of gestation is associated with higher mortality and morbidity, with the most serious complications been seen in neonates born before 28 weeks. Many studies suggest that even moderate and late preterm neonates have significant morbidity rates, mainly neurodevelopmental delay and learning disabilities compared to full term neonates. However, the complications of this latter group are overall less severe than in cases of preterm delivery before 32 weeks (6).

More specifically, the chance of neonatal death is about 40% if born at 24 weeks, 10% at 28 weeks, 1-5% at 31 weeks, while after 34 weeks the risk is similar to full term neonates. Manuck et al. demonstrated that the risk of severe complications including pulmonary hypertension, intraventricular hemorrhage III/ IV degree, hypoxic encephalopathy, necrotizing enterocolitis

stage II/III and bronchopulmonary dysplasia was seen in 50% of neonates born at 24 weeks, 40% for 27 weeks, 22% for 28 weeks, percentage that drops to 7% for neonates born at 31 weeks. Similarly, the chance of less severe complications such as respiratory distress syndrome, hyperbilirubinemia and hypotension requiring medical treatment was 16% if born at 24 weeks, 48% at 27 weeks, 73% at 28 weeks and 81% at 31 weeks (17). Overall, early and extremely early preterm neonates are facing more severe complications while moderate and late preterm neonates are more likely to face mild complications.

A similar study by Boyle et al. examined the long-term health outcomes at 3 and 5 years old of children born prematurely, based on the gestational age at the time of delivery. They demonstrated that infants who were born before 32 weeks of gestation, had lower body mass index, higher incidence of asthma under medications and more admissions to the hospital due to infections or other respiratory and gastrointestinal complications (6).

Although preterm birth is the main problem in obstetrics and there is a plethora of studies aiming in establishing preventative measurements, the incidence of preterm babies remains significant. The main reason for that is probably the multifactorial nature of preterm delivery rather than a specific causal relationship.

Causes of Preterm Birth

Causes of Spontaneous Preterm Birth

Delivery, either prematurely or at term, includes a “common pathway” of labour. This pathway involves uterine contractility, cervical dilatation, and rupture of the chorioamniotic membranes (18). This pathway is activated by natural processes which happen throughout pregnancy. In the beginning, there is abundance of anti-inflammatory markers to maintain the pregnancy and the semi-allograft fetus. The physiological shift during the third trimester, from the anti-inflammatory to pro-inflammatory markers; chemokines, cytokines and contraction-associated proteins, activates the membranes and uterine contractions (19). Cervical remodeling and ripening which facilitate the cervical dilatation during labor, also occurs throughout pregnancy by changes in the

extracellular matrix proteins and minerals. The texture and consistency of a cervix is thereby altered, becoming softer, irrespective of its length (20).

Preterm birth is a syndrome attributable to multiple pathological processes, which activate any of the three elements in the common pathway of labour, before 37 weeks. Examples of those processes are infection, vascular disorders, uterine overdistension, a decline in progesterone action, cervical disease, stress, uterine abnormalities, reduction in feto-maternal tolerance and short cervical length (21). In many cases, no specific cause is actually identified and in others multiple causes may co-exist.

Some of the known risk factors which present isolated or as a combination are: history of preterm birth or second trimester miscarriage in previous pregnancy, maternal infection such as urinary infection, chorioamnionitis, previous cervical surgery or cervical trauma (e.g. cervical tear during vaginal labour or emergency cesarean section at full dilatation), congenital uterine malformations (e.g. bicurnate uterus), polyhydramnios, preterm rupture of membranes, placental abruption or abnormal placental location, smoking, alcohol or substance abuse, short inter-pregnancy internal (<18 months), extreme maternal age (<18 or >40 years old), weigh disorders (22) (23) (24) (25) (26).

Infection and intrauterine inflammation are among the first causes described in the literature as in many cases of preterm delivery, pathogenic microorganisms are found in the amniotic cavity. It is therefore, the only parameter that has been causally linked to spontaneous preterm birth (22). Early evidence derived by animal studies showed that intra-amniotic infection can lead to preterm birth. More specifically, Takeda et al., showed that administering Escherichia coli endotoxin into mice and rabbits could cause abortion (27). Romero et al. showed that 51.5% of patients with second trimester cervical insufficiency and dilatation of at least 2cm but intact membranes, have a positive amniotic fluid culture for micro-organisms (28). One third of preterm births are associated with intra-amniotic infection (29).

Although a positive culture of amniotic fluid is pathognomonic for intrauterine infection, the diagnosis is often challenging due to the fact that the vast majority of cases remain subclinical. Romero et al. demonstrated that only 12.5% of women in preterm labour with intact membranes and a positive culture of amniotic fluid, actually have clinical chorioamnionitis (30).

There are two techniques in acquiring amniotic fluid for culture. Either by transabdominal amniocentesis or by transvaginal aspiration. The latter, however, entails the risk of contamination by the vaginal flora. Studies examining the amniotic fluid and chorioamniotic space in the same patient, isolated double concentrations of micro-organisms from the chorioamniotic space, which indicates that microbial invasion intrauterine advances from the extra-amniotic to the intra-amniotic space (31).

Different routes of transmission have been described in cases of intrauterine infection. The most common pathway is the ascending infection from the vagina and cervix. Additionally, studies demonstrating that bacteria associated with periodontal disease are often found in positive amniotic fluid cultures, indicate that hematogenous dissemination through the placenta can also occur. Alternatively, retrograde transmission from the peritoneal cavity through the fallopian tubes and lastly accidental introduction at the time of invasive procedures have been accused (29).

Whatever the route of transmission is, the final outcome is the same; stimulation of por-inflammatory markers and activation of either of the three components of the common pathway of labour (uterine contractility, cervical dilatation, rupture of membranes) and eventually preterm delivery. Often, intrauterine infection can also affect the fetus with congenital infection which can evolve as congenital pneumonia, otitis, conjunctivitis and omphalitis. In 30% of cases of intra-amniotic infection, bacteria are found in fetal circulation and those neonates are at risk for long-term complications, such as lung disease, neurological impairment and cerebral palsy (32; 33). The estimate mortality rate of neonates with congenital neonatal sepsis varies from 25% to 90% and this wide range depicts the effect of gestational age on mortality rate, besides sepsis. A study by Carroll et al. who examined neonates born before 33 weeks, showed that the mortality rate was double in infected fetuses (33% vs 17% for non-infected fetuses) (34).

Organisms commonly cultured from the amniotic cavity following preterm delivery include Ureaplasma urealyticum, Mycoplasma hominis, Bacteroides spp., Gardnerella vaginalis, Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis, and Group B Hemolytic Streptococci (35).

Studies using a combination of cultivation and molecular techniques introduced the fact that intra-amniotic inflammation associated with spontaneous preterm labor occurs also in the absence of microorganisms, suggesting a role for **sterile intra-amniotic inflammation** (36).

Bacterial vaginosis, which is attributed to an instability between the microbial ecosystem and the usual Lactobacillus-dominant microbiota, allowing the overgrowth of predominantly anaerobic bacteria, is associated with ascending intra-amniotic infection and spontaneous preterm birth. Asymptomatic pregnant women with bacterial vaginosis have a 2-fold increased risk of preterm delivery in comparison to those without vaginosis. Interestingly, the risk increases further the earlier the diagnosis is made (5-fold increase for diagnosis before 20 weeks and 7-fold increase for diagnosis before 16 weeks) (37). However, which women are more susceptible in developing bacterial vaginosis is yet to be established.

Periodontal disease during pregnancy has also been accused of increasing the risk of preterm delivery. An older meta-analysis in 2007 showed an increased probability of preterm birth in women with periodontal disease (overall odds ratio 2.83; 95% CI: 1.95-4.10, $P < .0001$), warning however about the low quality of the included studies (38). Indeed, a more recent umbrella review failed to support a causal relationship between periodontal disease and adverse pregnancy outcomes (39).

Maternal systematic infection, like pneumonia and pyelonephritis, is also associated with spontaneous preterm birth. The exact mechanism is not clear, but it is probably attributed to the general activation of maternal immune system as a response to a systematic infection, which involves an increase in pro-inflammatory medians like chemokines, cytokines and prostaglandins. All the latter are also responsible for activating the delivery pathway as mentioned earlier in this chapter.

Another cause of spontaneous preterm birth is thought to be the **disruption of maternal-fetal tolerance**. The placenta and the fetus express equally maternal and paternal antigens and are therefore semi-allografts (40). Immune tolerance is required for a successful pregnancy, which is evident by the increase anti-inflammatory medians mainly during first and second trimesters. The inability of a woman to maintain this tolerance can lead to several complications, with features of allograft rejection, such as miscarriage and preterm birth. The most frequent placental lesion found in late preterm births is chronic chorioamnionitis, which is characterized by maternal T-cell infiltration of the chorion and trophoblast apoptosis, which resembles allograft rejection (41).

Decline in progesterone action is another contributor to preterm birth. Progesterone plays a crucial role in maintaining a healthy pregnancy, affecting each element of the ‘common pathway’

of labour. This is evident from the fact that administration of progesterone receptor antagonists, like mifepristone, initiates cervical ripening, spontaneous abortion and labour. Furthermore, progesterone reduces the contraction-associated proteins and inflammatory markers, promoting myometrial relaxation (42) (43). Lastly, progesterone inhibits basal- and TNFa-induced apoptosis and reduces cytokine-induced MMP expression and activity which have a positive effect of the decidua and chorioamniotic membranes (44).

Uterine overdistension, like in cases of multiple gestations or polyhydramnios is also associated with spontaneous preterm birth. In non-human primates, inflation of intra-amniotic balloons can stimulate uterine contractility, preterm labor, and an "inflammatory pulse," which is characterized by increased maternal plasma concentrations of IL-β, TNFα, IL-8 and IL-6 (45).

Maternal stress is also a risk factor for PTB. Stress increases maternal and fetal cortisol which stimulate placental production of corticotrophin-releasing hormone (CRH) and its release into the maternal and fetal circulations (46). Depression is one of the most common complications during pregnancy and the childbearing years. The prevalence of major depressive disorder defined by diagnostic criteria during pregnancy is 12.7%, while up to 37% of women report experiencing depressive symptoms at some point during their pregnancy (47). Anxiety has even higher prevalence, while these conditions often co-exist. A systematic review by Staneva et al., summarized that indeed women with depression, anxiety, or perceived stress have higher risk for spontaneous preterm birth (48).

Congenital uterine anomalies include bicornuate, arcuate, unicornuate, septated and didelphys uterus. A very recent cross-sectional study of 50,180 with congenital uterine anomalies revealed that the risk for preterm birth in this group of women is 26.8% and the risk for abortion or stillbirth is 2.1%. Among preterm deliveries 61.8% occurred between 33 and 36 weeks, 16.9% between 30 and 32 weeks, and 21.3% at <30 weeks. Finally, they highlighted that the preterm and periviable birth rates were highest in the uterine didelphys group (34.5% and 6.9% respectively) (49).

Cervical surgical procedures are used for excision of cervical intraepithelial neoplasia (CIN) and include laser conisation, the cold-knife conisation (CKC) and the loop electrosurgical excision procedure (LEEP), also known as large loop excision of the transformation zone (LLETZ). In a meta-analysis by Zhuang et al. which included 27 studies, it was shown that both CKC and LLETZ are associated with preterm birth and lower birth weight (50).

The **history of prior preterm birth** is a major risk factor for preterm delivery in subsequent pregnancy. Specifically, women with a previous preterm birth have a 2-fold higher risk of recurrence (51). In addition, an **inter-pregnancy interval of less than six months** is another risk factor for preterm delivery. Smith et al. showed with an observational cohort study of 89,414 women that an inter-pregnancy interval of less than 6 month conferred an odds ratio of 2.2, 1.6 and 3.6 for extremely preterm birth, moderately preterm birth and neonatal death, respectively (52).

Finally, **short cervical length** during mid-gestation is strongly associated with spontaneous preterm birth. A cervical length less than 25mm identify 40% of women who will deliver before 34 weeks (53). A separate chapter is dedicated to cervical length.

In view of the multifactorial nature of preterm birth, we recently published an umbrella review examining 170 risk factors for preterm birth found in published meta-analyses of observational studies. Eighty-six eligible meta-analyses were identified, which included 1511 primary studies providing data on 170 associations, covering a wide range of comorbid diseases, obstetric and medical history, drugs, exposure to environmental agents, infections and vaccines. From all 170 risk factors, only seven were found to be statistically significant with reproducibility among the literature due to high heterogeneity among the studies. Those risk factors are single umbilical artery, sleep-disordered breathing, exposure to amphetamine, maternal personality disorder, prior induced termination of pregnancy with vacuum aspiration, inter-pregnancy interval following miscarriage < 6 months and low gestational weight gain. Other risk factors but with less robust evidence are intimate partner violence, unmarried women, cancer survivors, African/Black race, placental previa, hemorrhagic and hepatic disorders, endometriosis, chronic kidney disease, and treatments for CIN (54).

Causes of Iatrogenic Preterm Birth

The aforementioned causes are associated with spontaneous preterm birth. Yet, almost 40% of deliveries before 34 weeks have iatrogenic etiology. In terms of iatrogenic preterm births, the indications include but not restricted to preeclampsia, intrauterine growth restriction, intrahepatic

cholestasis, uncontrolled diabetes mellitus, hemorrhage due to placental abruption or due to other maternal comorbidities unrelated to pregnancy, like cardiovascular or respiratory disease.

Preeclampsia is characterized by new-onset hypertension after 20 weeks of pregnancy with at least one organ dysfunction; renal, hepatic, neurologic, hematological, or uteroplacental (55). Pre-eclampsia is a major cause of maternal and perinatal mortality and morbidity worldwide causing 15% of all direct maternal deaths in the UK and a fivefold increase in perinatal mortality due to iatrogenic preterm birth. This disease encompasses 2% to 8% of pregnancy-related complications, more than 50,000 maternal deaths, and over 500,000 fetal deaths worldwide (56).

Screening for preeclampsia during the first trimester of pregnancy (11-13 weeks) is accomplished using maternal factors, mean arterial pressure, uterine-artery pulsatility index, and maternal serum pregnancy-associated plasma protein A and placental growth factor. A randomized double-blind, placebo-controlled trial in 2017, which included 1620 women, demonstrated that the administration of 150mg of aspirin daily until 36 weeks, to women deemed to be high risk for preeclampsia (PE) is associated with a 62% reduction in the incidence of preterm PE < 37 weeks and 82% reduction in the incidence of PE <34 weeks' gestation (57).

Recent studies have focused on two additional biomarkers for the improvement of the preeclampsia prediction model, namely placental growth factor (PLGF) and serum soluble fms-like tyrosine kinase-1 (sFLT-1). PLGF is produced by the placenta and has strong a angiogenic role. In women who develop preeclampsia (PE), serum PLGF is decreased. The deviation from normal values is greater in cases of preterm PE and therefore the performance of screening using PLGF in greater in preterm PE than term PE (58).

sFLT-1 on the other hand, is an anti-angiogenic factor. In a study by Maynard et al., exogenous administration of sFLT-1 to pregnant rats induced hypertension, proteinuria and glomerular endotheliosis, indicating that sFLT-1 probably has a crucial role in the pathogenesis of PE (59). In women with PE, sFLT-1 in elevated, and this increase is noted about 5 weeks before the establishment of the disease. Therefore, sFLT-1 is useful if measured closer to the development of PE. Measuring sFLT-1 at 11-13 weeks of pregnancy does not improve the prediction of PE with the traditional model, mentioned previously. However, measurement at 22 weeks is useful in the prediction of PE before 32 weeks, measurement at 32 weeks is useful for the prediction of PE

before 37 weeks and finally measurement at 36 weeks is useful for the prediction of late preeclampsia, after 37 weeks (60).

Both factors are dependent to maternal characteristics and therefore should be standardized into MoM (multiple of median) values. Screening for preeclampsia at 11-13 weeks, using maternal factors, mean arterial pressure, uterine-artery pulsatility index and PLGF predicts about 90% of early PE (<34 weeks), 75% of preterm PE (<37 weeks) and 45% of term PE (≥37 weeks), at screen positive rate of 10% (61). Those women, would subsequently benefit from aspirin administration.

Fetal growth restriction (FGR) is the condition when a fetus does not achieve the expected in utero growth potential due to maternal, fetal, and/or placental factors. FGR is distinguished into early FGR if diagnosed before 32 weeks and late FGR if diagnosed after 32 weeks. The criteria for the diagnosis were established in 2016 with a Delphi consensus and are shown in table 1 (62).

Table 1: Consensus-based definitions for early and late fetal growth restriction (FGR) in absence of congenital anomalies

Early FGR: GA <32 weeks, absence of congenital anomalies	**Late FGR:** GA ≥ 32 weeks, absence of congenital anomalies
AC/EFW < 3rd centile or UA-AEDF Or 1. AC/EFW < 10th centile combined with 2. UtA-PI > 95th centile and/or 3. UA-PI > 95th centile	AC/EFW < 3rd centile Or at least two out of three of the following 1. AC/EFW < 10th centile 2. AC/EFW crossing centiles >2 quartiles on growth centiles * 3. CPR < 5th centile or UA-PI > 95th centile

*Growth centiles are non-customized centiles. AC, fetal abdominal circumference; AEDF, absent end-diastolic flow; CPR, cerebroplacentalratio; EFW, estimated fetal weight; GA, gestational age; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery

Those fetuses are at high risk of stillbirth antenatally and the only available treatment is delivery, with all the concomitant complications of prematurity. The Fetal Medicine Foundation has developed a prediction model for FGR, similar to that for preeclampsia, based on maternal factors,

mean arterial pressure, uterine-artery pulsatility index, pregnancy associated plasma protein A (PAPP-A) and PLGF (63). Unlike preeclampsia and aspirin, there is no preventative measurement known to reduce the risk of FGR. However, women at high risk for FGR using the aforementioned prediction model, should be offered closer monitoring, serial growth scans and potentially lifestyle advice.

Screening for Preterm Birth

Screening is 'a preliminary procedure, such as a test or examination, to detect the most characteristic sign or signs of a disorder that may require further investigation' (64). In other words, screening interventions are designed in a way to identify markers which may at some point turn into disease. In case of preterm birth, screening methods are designed to identify asymptomatic women at high risk of delivering prematurely, before labour starts, in order to apply preventative interventions.

There is still no efficient screening method to identify and thereby treat all women who will deliver prematurely. This is likely due to the multifactorial aetiology of preterm birth as mentioned in the previous section. Therefore, many women with risk factors for preterm delivery will eventually deliver after 37 weeks and on the contrary, women without any risk factors will deliver prematurely.

The most established screening method up to date is the cervical length measurement with or without the fetal fibronectin test. Other methods such as screening based on previous obstetric history and maternal characteristics have been proposed, with less encouraging results.

Obstetric History

History of preterm birth (PTB) in previous pregnancy is considered as the strongest risk factor for spontaneous PTB in subsequent pregnancies. However, among those women who have

spontaneous preterm deliveries, only 50% are multiparous and from them only 30% have a history of preterm delivery. In other words, history detects only 15% of preterm births (65).

The reported risk of recurrent PTB varies among the literature, from 1.5-fold to 4-fold increase, depending on the population. Overall, the risk of recurrent preterm birth is about 30% and is higher the earliest the previous delivery occurred, while additionally increases if more than one preterm deliveries have taken place (66).

Second trimester loss occurs in the previable period, between 16 and 22 weeks of gestation. Although it is typically considered a miscarriage, the pathophysiology, to a significant extend, is similar with that of preterm labour. It includes activation of at least one component of the 'common pathway' of labor, as mentioned in previous chapter, which are uterine contractility, cervical dilatation, and rupture of the chorioamniotic membranes.

Elbow et al. demonstrated through a retrospective cohort study that patients with a prior second-trimester loss were nearly 11 times more likely to have a recurrent second-trimester loss or PTB, compared with those with a prior full-term delivery (odds ratio [OR] 10.8, confidence interval [CI] 3.6 to 32.1, P< 0.0001). In terms of spontaneous preterm birth only, women with history of second trimester loss had about 32% risk of PTB in subsequent pregnancy and for women with history of spontaneous preterm birth, the risk of recurrence was about 40% (67).

A meta-analysis of 37 studies by Shah et al., showed that **induced terminations** during first and second trimester are associated with increased risk for low birth weight (OR 1.35, 95% CI 1.20-1.52) and preterm labour (OR 1.36, 95% CI 1.24-1.50) (68).

Short interpregnancy interval less than 6 months is also considered to increase the risk of prematurity in the following pregnancy. More specifically, Elbow et al. demonstrated 10.1 times greater odds of a second-trimester loss or spontaneous PTB in their subsequent pregnancy (CI, 1.9 to 52.9, P = 0.006) (67). Smith et al. showed with an observational cohort study of 89,414 women that an inter-pregnancy interval of less than 6 month conferred an odds ratio of 2.2, 1.6 and 3.6 for extremely preterm birth, moderately preterm birth and neonatal death, respectively (52).

Finally, **method of conception** also seems to be relevant. In vitro fertilization and all medications for ovulation promotion (clomiphene) and stimulation (gonado-tropins), have been associated with a 2-fold increased risk of PTB (69).

Maternal History and Characteristics

The general **gynecological history** should be examined with caution when assessing the risks in current pregnancy. **Cervical surgery** was associated with a higher risk of preterm delivery (RR: 1.643, 95% CI: 1.127–2.396, p: 0.01) in a meta-analysis of 27 studies (50).

Congenital uterine anomalies are known to increase the risk of delivery before 37 weeks. It seems that women with such anomalies are 3 times more likely to experience preterm birth, with didelphys uterus carrying the highest risk for pregnancy complications (49).

Other risk factors that have been linked with preterm birth in different studies with various statistical associations are black race, low socio-economic status, maternal smoking, cocaine abuse, opioid abuse, vaginal bleeding in the first and second trimester and carriage of male fetus (70).

Despite several studies examining such relationships, none of these can actually be used in an independent prediction model and identify at least the majority of women who will delivery prematurely, due to low sensitivity and specificity. Therefore, over the last decades the focus has turned to cervical length assessment and fetal fibronectin measurement.

Cervical Length Assessment

The cervix is the lower part of the uterus and form its' narrow end, connecting the uterus to the vagina. During labour the cervix shortens and then widens (effacement) to allow the birth of the fetus. Cervical remodeling occurs throughout pregnancy and is explained by changes happening in the water and collagen consecration starting even from the first trimester. This rearrangement of the cervical extracellular matrix is physiologically more evident during the third trimester and is followed by labour onset (71).

Measuring the cervical length by ultrasound during pregnancy is the most established method of identifying women at risk for preterm delivery. Andersen et al. in 1990 were the first to report that the measurement of cervical length by vaginal ultrasound could be used to predict the risk of

spontaneous preterm delivery (72). Women found to have short cervix are subsequently offered treatment based on the length such as progesterone, cervical cerclage or pessary, as a measure of reducing the risk of preterm delivery. In addition, cervical length measurement is useful in symptomatic women who are for example experiencing lower abdominal pain. Demonstrating a short cervix is this group of women raise the diagnosis of threatened preterm labour and should initiate further management, for example hospitalization and steroids for fetal lung maturation.

Although the strongest risk factor is the history of previous preterm delivery, only 15% of women who will deliver prematurely have such a history (53). A short cervix on the other hand, which is traditionally defined as a transvaginal sonographic cervical length (CL) ≤25 mm in the mid-trimester of pregnancy, is an important risk factor for preterm birth and has emerged as one of the strongest and most consistent predictors of preterm birth in asymptomatic women with a singleton or twin gestation (73) (74). It is therefore recommended that all women should have a routine cervical length assessment between 18 and 24 weeks of gestation (75). Furthermore, women with history of second trimester miscarriage or preterm birth in previous pregnancy, in subsequent pregnancies should have their cervical length measured earlier, around 14 to 16 weeks (76).

The cervical length at 20 to 24 weeks of gestation is 34 mm on average and gradually shortens throughout pregnancy, as previously mentioned, due to the physiological remodeling. Cervical length of 25 mm corresponds to the 10th percentile for this gestational age and based on this observation, the cutoff for short cervix has been defined as ≤25 mm (77).

There are several risk factors in having a short cervix during pregnancy, including prior preterm birth, prior cervical surgery, being underweight, at least 1 prior uterine evacuation, African-American race and others (78) (79) (80) (81).

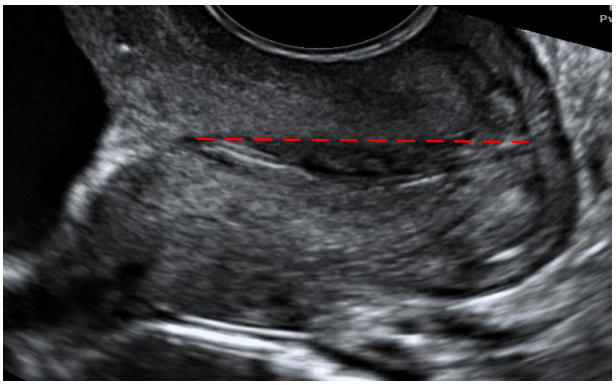
In singleton pregnancies, screening with cervical length and demographic factors in the mid trimester can identify two thirds of the cases that will deliver before 32 weeks of gestation for a false positive rate of 10%. Cervical length of less than 15 mm (around 1% of pregnant women) predicts 58% of the cases who will deliver before 32 weeks. The group of women with CL<25 mm contains 40% of deliveries before 34 weeks. (53). Yet, the ultimate risk of spontaneous PTB in the case of a short cervical length depends on the a-priori risk of spontaneous PTB. The risk is therefore highest among those with a prior spontaneous PTB and a short cervix and this combination confers a relative risk for spontaneous PTB of 3.3 (82).

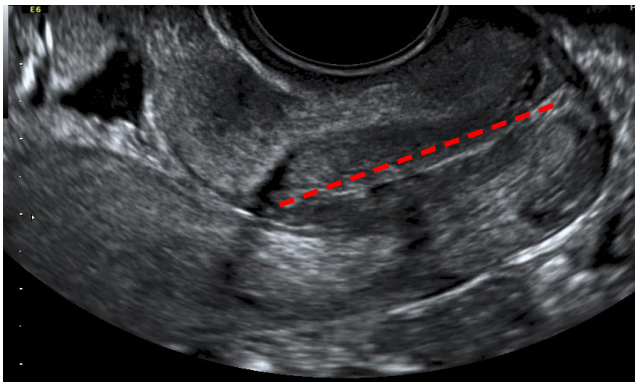
The incidence of short cervix (≤25 mm) in the 2nd trimester varies from 0.45% up to 10%. This can be attributed to the numerous other factors affecting the cervical length, depending on the study population, like maternal characteristics, lifestyle, racial and socioeconomic factors as well as technical aspects such as different cutoffs and the operator assessing the cervical length per se (53) (81) (83).

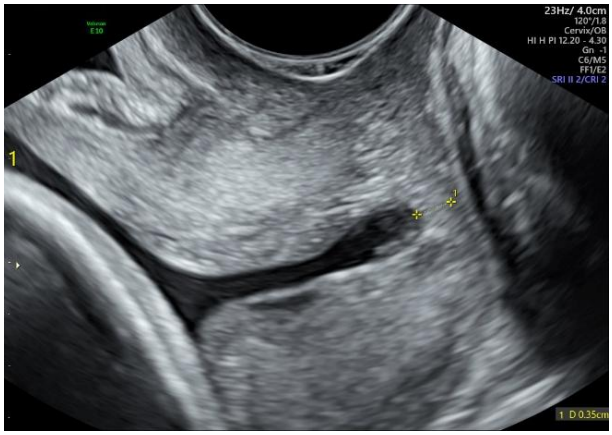
Measurement of the cervical length during pregnancy can be achieved by transabdominal, transvaginal or transperineal ultrasound. The gold standard technique is the transvaginal approach, because it provides higher resolution and therefore higher accuracy as the ultrasound transducer is closer to the cervix. On the contrary, with the transabdominal approach the distance between the cervix and the ultrasound transducer is larger and frequently pressure must be applied to better visualize the cervix which can falsely increase the cervical length (72). Additionally, in women with increased body mass index, the diagnostic accuracy of the transabdominal approach is even more limited. Finally, the transperineal ultrasound seems to have similar accuracy as the transvaginal one. Based on the aforementioned, all the international guidelines recommend the transvaginal ultrasound when assessing the cervical length (76).

For the transvaginal measurement of the cervical length the patient should have an empty bladder. A longitudinal plane of the cervix is captured, including clearly the internal and external os. The picture is magnified as much to occupy 50-75% of the screen. Caution must be taken not to apply any pressure to the cervix which can produce a falsely long cervix. Due to the physiological dynamic changes of the cervix, three different measurements must be taken over a few minutes and record the shortest one. The measurement is done with a straight line from the internal to the external os, even when the cervical canal is curved (53) (76).

Transvaginal ultrasound measurement of cervical length is safe, reliable, and highly reproducible when performed by trained providers (84). Formal training programs with certification for cervical length measurement are available online (e.g. the Fetal Medicine Foundation's cervical assessment certificate of competence and the Perinatal Quality Foundation's Cervical Length Education and Review (CLEAR) program).







Upper Left: The appropriate measurement of cervical length by transvaginal ultrasound

Upper Right: Measurement of cervical length, note the contraction of the lower uterine segment which can be mistaken for the internal os

Bottom Left: short cervical length of 3.5 mm, note the 'U' shaped funneling

Other ultrasonographic markers

During the transvaginal examination, additional markers should be examined, apart from the cervical length, such as funneling and the present of amniotic sludge, in an attempt to increase the diagnostic value of the assessment.

Funneling

Funneling is the protrusion of the amniotic sac into the cervical canal. The shape of funneling changes based on the cervical length from 'T' shaped in mild cases and subsequently to 'Y', 'V' and finally 'U' in more severe cases. In a study by Berghella et al. it was shown that the progression

over time of the internal os cervical anatomy from a "T" to a "V" to a "U" shape was associated with earlier gestational age at delivery, whereas resolution of "V" shape funnels was associated with term delivery. They also found that although funneling has a significant association with earlier gestational age at delivery, the size of funneling does not constitute an independent risk factor especially in women with short cervix and should not be included in the cervical assessment (85).

A) The different stages of funneling **B)** 'Y' shaped funneling with normal cervical length **C)** Follow up of the same patient 2 weeks later; note the 'U' shaped funneling with short cervix of 7mm.

Amniotic fluid sludge

The amniotic fluid sludge consists of hyperechogenic particles which can be attributed to pus, microorganism, blood clots, fetal vernix, meconium or a combination of the above. In many cases there is co-existing intrauterine infection and therefore higher risk of preterm delivery, especially if the cervix is short (86).

In a recent retrospective cohort, Suff et al. examined asymptomatic patient with known short cervix and amniotic fluid sludge. They concluded that women with amniotic fluid sludge and short cervix were more likely to have a shorter cervical length, to deliver before 24 weeks, to have raised fetal

fibronectin levels and increased cervicovaginal interleukin 8. These findings are consistent with the concept that amniotic fluid sludge is related to infection and inflammatory process (87).

A) amniotic sludge and short cervix

B) amniotic sludge with normal cervical length

Transfundal and Suprapubic Pressure

Application of transfundal or suprapubic pressure while examining the cervical length sometimes cause opening of the internal os and shortening of the cervix. The mechanism is not completely understood but they are thought to be early markers of cervical insufficiency and women with positive transfundal pressure may benefit from cervical cerclage (88). Owen et al. stated that dynamic cervical changes, either spontaneously or after fundal pressure can improve the predictive value of cervical assessment for preterm delivery (77). Different methods to identify those dynamic changes like coughing and standing position were also tested, but none of them was proven useful (89).

We believe that pressure application can expose a ‘soft’ cervix and consequently weak cervix who is unable to maintain its’ shape, and will eventually shorten as pregnancy progresses (90) .

A) Cervix before applying suprapubic pressure

B) Cervix of the same patient after applying suprapubic pressure, note the opening of the internal os

Assessing Cervical Elasticity

Parra et al. introduced in 2011 the Cervical Consistency Index (CCI), which is an ultrasound measurement aiming to identify accelerated cervical softening. The CCI quantifies the change of the anteroposterior diameter of the uterine cervix after deformation induced with the transvaginal probe by the operator (91). CCI has displayed good performance in various clinical scenarios, including low-risk pregnant women, high-risk pregnant women, and twin pregnancies, even outperforming the cervical length measurements typically conducted during mid-trimester evaluations (92) (93). However, it is not readily used as it requires special training.

New data are evolving regarding elastography for evaluating the cervix during pregnancy and its predictive value for spontaneous preterm birth. Elastography is a noninvasive technique in which images of soft tissue stiffness are used to detect or classify masses. It is particulartly useful for the diagnosis and characterization of breast cancer, prostate cancer, and thyroid nodules, which are usually stiffer than normal tissues. In similar way, elastography can assess the cervical tissue stiffness. Despite the promising results, there is still no consensus in the literature and uniformed methodological technique. Different methods have been tested including shear-wave elastography and strain elasgtography, with various elastographic data (strain ratio, elastography index, strain pattern score). Overall, the data are very encouraging and it seems that elastography is also outperforming the cervical length measurements (94) (95).

In conclusion, both CCI and elastography seem to improve the diagnostic value of screening for preterm birth and potentially outweigh isolated cervical length measurement. Standardized techniques and validation process need to be in place before universal spread for clinical use.

Fetal Fibronectin

Fetal fibronectin is an extracellular matrix glycoprotein produced by fetal cells. It is found at the maternal-fetal interface of the amniotic membranes, between decidua and chorion, where it acts like a ‘glue’. Fetal fibronectin is released when there is a disruption between the decidua and chorion before delivery or due to inflammation.

In normal circumstances, fetal fibronectin is detected in high concentrations into the cervicovaginal secretions before 22 weeks and after 36 weeks and in very low concentrations (<50 ng/mL) between 22 and 34 weeks of gestation. Increased levels of fetal fibronectin (>50 ng/mL) between 22 and 34 weeks are associated with preterm labour (96). Between 22 and 24 weeks, high concentration of fetal fibronectin is detected in 5% of the general population and this group includes 25% of women who will deliver spontaneously before 34 weeks.

While the specificity and positive predictive value are poor, fetal fibronectin testing has excellent sensitivity (100%) and negative predictive value (100%). In other words, the negative predictive value of measuring fetal fibronectin is superior since in case of normal low levels the chance of subsequent delivery within the next two weeks is practically none (97).

There are two types of kits for fibronectin levels measurement; the qualitative test which is positive if fibronectin is ≥50 ng/mL and the quantitative test which gives the exact concentration. The EQUIPP study (Evaluation of a Quantitative Instrument for the Prediction of Preterm Birth) was the first to prospectively demonstrate the enhanced value of quantification of fFN (detectable range 0 to >500 ng/ml) using a bedside automatic analyzer, that had a superior positive prediction (38%) compared with the qualitative positive test (14%), while maintaining high specificity (96%) (82).

The test is easily performed with the use of a vaginal swab and a fibronectin test kit. For the accurate performance of this test the following requirements must be in place: intact membranes, minimal cervical dilation (<3cm), gestational age between 22 and 34^{+6} weeks, absence of significant vaginal bleeding, and without cerclage in situ. A false positive fetal fibronectin result can occur if the test is performed after digital examination of the cervix, after having had intercourse, vaginal bleeding, and vaginal lubrication or douching (98). It is important that the swab is taken before a digital cervical examination or more than 24 hours following intercourse or previous examination. There is scant evidence regarding fibronectin test in multiple pregnancies and therefore it should be avoided.

The combination of cervical length and fetal fibronectin is extremely useful when assessing symptomatic women for the diagnosis of threatened preterm labour. If both tests are negative then the chance of imminent delivery is extremely low, and more specifically the chance of not delivering within the next 14 days is 95%. In such cases, hospitalization or further treatment are not recommended (99) (100).

In case of asymptomatic women, the performance of fetal fibronectin test is questionable. In this group, the isolated measurement of cervical length has equal prognostic value, especially for values within the normal range (101).

The QUiPP App Toolkit is a decision support tool that uses medical history and fetal fibronectin or cervical length to give an individualized score for the risk of having a spontaneous preterm delivery. It was developed at King's College London, and Guy's and St Thomas' NHS Foundation Trust in April 2020. It is designed for use in two clinical settings: the first focus on asymptomatic women deemed to be at high risk for preterm birth and the second in women showing symptoms of early labour suggestive by abnormal or premature uterine activity (102).

Additional Tests

Cervical length measurement during the second trimester of pregnancy remains the gold standard method of screening for preterm birth. Different ultrasonographic markers (funneling, amniotic sludge, elastography) have been described over the time, but their exact value as a screening tool remains uncertain. Other tests and examinations to increase the screening performance have been investigated, including screening for infections, vaginosis, periodontal disease and uterine activity monitoring.

Asymptomatic bacteriuria is found in 2-15% of pregnant women. If left untreated can lead to acute pyelonephritis in 30% of the cases, while is also associated with preterm delivery and low birth weight. A Cochrane systematic review of 15 studies, involving over 2000 women showed that treatment with antibiotics seems to reduce the risk for preterm birth (RR 0.34, 95% CI 0.13 to 0.88; 3 studies, 327 women; low-certainty evidence), and low birthweight babies (average RR 0.64, 95% CI 0.45 to 0.93; 6 studies, 1437 babies; low-certainty evidence). Yet, the evidence is weak and should be interpreted with caution (103). It seems however, that screening for asymptomatic bacteriuria and subsequently treating patients with positive results can be useful.

Bacterial vaginosis is observed in 10-25% of all women with 50% of them being asymptomatic. Older studies linked bacterial vaginosis to preterm delivery (104). However, treating bacterial vaginosis during pregnancy does not reduce the risk for preterm delivery as proven with a recent

randomized trial by Subtil et al. (105). A systematic review and individual participant data meta-analysis by Klebanoff et al. confirmed that treatment of bacterial vaginosis during pregnancy did not reduce preterm birth, nor prolong pregnancy, in any subgroup, even when started earlier in gestation (37). Therefore, screening for bacterial vaginosis especially in asymptomatic patients may not be useful for preterm birth prevention, but vaginal swabs remain necessary during pregnancy for detection of Group B Streptoccocus, for which patient will need intrapartum antibiotics.

Periodontal disease during pregnancy has a similar trend to bacterial vaginosis. In other words, although it is associated with preterm delivery, treating periodontal disease does not reduce the chance for delivery before 37 weeks (106). It is worth mentioning that many studies highlight the common pathophysiological mechanism of periodontal disease and vaginosis on preterm birth, since the oral and vaginal flora consist of similar microorganisms. Moreover, recent data dispute a causal relationship between periodontal disease and adverse pregnancy outcome, which indicates that screening for periodontal disease in pregnant women is probably not useful for reducing preterm birth rates (39).

Finally, **uterine activity** can be monitored with tocodynamometer for any contractions. Different devices have been proposed for monitoring of early contractions at home (Home Uterine Activity Monitoring), especially for women at high risk for preterm delivery. The purpose of such devices is the early detection of contractions and possibly treatment, e.g. administration of tocolytic drugs. However, a recent meta-analysis showed that women receiving these devices were more likely to visit the hospital more often and receive tocolysis, while they did not reduce the risk for admission to Neonatal Intensive Care Units (107).

Conclusions

Over the years, several studies have examined and proposed different ways of screening and predicting spontaneous preterm birth.

Honest et al., in 2009, published a systematic review with which they tried to identify combinations of tests and treatments to predict and prevent spontaneous preterm birth. They examined 22 tests,

and only a few tests in asymptomatic women showed a likelihood ratio for a positive test result of >5, the cut-off required to be categorised as a useful test for predicting spontaneous preterm birth before 34 weeks. These were ultrasonographic measurements of cervical length and funnelling as well as cervicovaginal fFN screening (108).

Prevention of Preterm Birth

General Measures

Several preventative measures should be adopted to reduce the risk of preterm birth, even before conception. An example of great significance is the **family planning programs**. Through those programs the following should be promoted:

- *Education regarding the appropriate inter-pregnancy interval*: As mentioned in a previous chapter short interval less than 6 months involves 10.1 times greater odds of a second-trimester loss or spontaneous PTB in subsequent pregnancy (67).
- *Counseling regarding appropriate to conceive maternal age:* Teen pregnancies are associated with multiple adverse pregnancy complications including preterm birth, low birthweight, low Apgar score (109). On the other hand, maternal age >40 years old is also associated with multiple complications including spontaneous and iatrogenic preterm birth, as well as perinatal mortality, intrauterine growth restriction, neonatal death, admission to neonatal intensive care unit, pre-eclampsia, cesarean delivery, and maternal mortality (110).
- *Appropriate dietary habits aiming for a normal body mass index:* overweight and obese mothers are at increased risk of pre-term premature rupture of membrane, extreme pre-term birth, cesarean delivery, gestational diabetes, gestational hypertension, induction of labour, postpartum hemorrhage, pre-eclampsia, and other fetal and neonatal complications. Similarly, the underweight mothers have increased odds for small for gestational age infant and pre-term birth (111).

- *Screening for and treatment of sexually transmitted diseases:* It has been mentioned already in previous section that women with bacterial vaginosis have a >2-fold increased risk for preterm delivery in comparison with those without vaginosis (37).
- *Smoking and recreational drugs cessation:* Smoking-cessation programs in pregnancy have been reported to reduce the rate of preterm birth by 16% (relative risk, 0.84; 95% confidence interval [CI], 0.72–0.98) to 31% (adjusted odds ratio [aOR], 0.69; 95% CI, 0.65–0.74) (112) (113).
- *Appropriate management of chronic diseases*, like diabetes, hypertension or autoimmune disease. Uncontrolled maternal chronic conditions is one of the main indications of iatrogenic preterm birth. For example, chronic hypertension if not controlled appropriately can evolve to preeclampsia and fetal growth restriction, which subsequently have high risk for maternal and neonatal mortality and morbidity, stillbirth and iatrogenic preterm birth.
- *HPV vaccinations:* Human papillomavirus infection increases the risk for cervical intraepithelial neoplasia requiring cervical surgery. As discussed already cervical surgery increases the risk for short cervix during pregnancy and spontaneous preterm birth (50). Therefore, by preventing HPV infection via vaccinations, the need of cervical surgeries will be diminished dramatically. Interestingly, a Danish cohort of 243 136 primiparous females found that women vaccinated against HPV before 17 years old, had lower incidence of spontaneous preterm birth comparing unvaccinated women (114). This observation indicates that there may be a direct causal relationship between HPV infection and PTB, besides the known risk after a cervical surgery.
- *Physical Activity:* Older theories that exercise during pregnancy is linked to adverse pregnancy outcomes like lower birthweight and increased perinatal mortality (stillbirth and neonatal deaths), are now abandoned. The benefits of exercise during pregnancy include lower risk of preterm birth, gestational diabetes, hypertensive disorders of pregnancy, and improvement of maternal mental well-being (115). Excessive gestational weight gain is associated with a wide range of maternal and fetal complications, including gestational diabetes, preeclampsia, spontaneous preterm birth, and fetal macrosomia or large for gestational age fetuses. All of the latter, are additionally linked with iatrogenic preterm birth.

Furthermore, during pregnancy, women at high risk should be monitored regularly and receive appropriate medical care, which includes:

- *Screening and treating sexually transmitted diseases, including HPV*
- *Optimizing chronic conditions*
- *Smoking cessation*
- *Support groups for vulnerable women* e.g., victims of domestic violence or women under poverty
- *Counseling regarding timing of delivery*, meaning not expediting delivery before 39 weeks for non-medical reason, e.g., maternal request
- *Applying screening methods for the general population* with particular focus on women at high risk (e.g., multiple pregnancies, diabetes, hypertension, history of preterm birth)

Bed rest

Old theories, initially by Pinard in 1895 and later by Peller in 1931 supported that bed rest should be encouraged in all women to improve the pregnancy outcome. More specifically, they suggested that bed rest is associated with higher birthweight and reduced perinatal mortality (stillbirth and neonatal deaths) (116). Bed rest is still wrongly recommended by some obstetricians in cases of short cervix.

Several studies prove wrong those benefits of bed rest. On the contrary, bed rest increases the risk for thromboembolic events, adverse psychological effects on the mother and partner with higher rates of postpartum depression. Furthermore, women who were prescribed activity restriction were twice as likely to deliver preterm (117). Additionally, recent evidence suggests that mild physical activity in women with short cervix reduces the risk of preterm delivery by 32% (118).

In a meta-analysis of physical activity and preterm birth, by Aune et al., that included 21 cohort studies and 20 randomized trials (n=171,595 pregnant women), those who reported higher leisure time physical activity had a statistically significant 14% decrease in the relative risk of preterm birth. Likewise, even modest increase in physical activity, meaning 3 hours increase per week, was

also associated with reduction in the incidence of preterm birth by 10% (119). A previous meta-analysis of randomized clinical trials, including 2,059 low risk women in total, showed that there is no association between exercise and preterm birth (RR 1.01, 95% CI 0.68 to 1.50) but women who were allocated to the exercise group were more likely to have a vaginal delivery (73.6% vs. 67.5%; RR, 1.09, 95% CI 1.04–1.15) (120).

Interestingly, a retrospective study of 252 nulliparous women with short cervical length <30 mm in mid-gestation who were prescribed activity restriction since the diagnosis of short cervix, were more likely to deliver before 37 and 34 weeks [aOR 2.37 (95% CI 1.60, 3.53)] (121). Similarly, in a pilot prospective cohort study with 49 patient and cervical length <20 mm in the mid-gestation, it was noted that patient who delivered prematurely were less active than those who delivered at term (122).

A meta-analysis of randomized controlled trials focused on overweight and obese pregnant women, showed that patients who were randomized in early pregnancy to aerobic exercise for about 30-60 min three to seven times per week had a lower percentage of delivery <37 weeks (RR 0.62, 95% CI 0.41-0.95) compared to controls. The study group also had lower risk of gestational diabetes mellitus and no difference was observed for cesarean delivery, birthweight and stillbirth rates (123).

The most recent recommendation by the American College of Obstetricians and Gynecologists (ACOG) in 2020, suggest that pregnant women should engage in 150 minutes of moderate-intensity aerobic, resistance, and stretching activities distributed throughout the week. They warn that some of the contraindications to physical activity are maternal cardiovascular and respiratory diseases, signs of preterm labour, preterm rupture of membranes and other (124).

The Pregnancy Physical Activity Questionnaire (PPAQ) is a reliable instrument and a reasonably accurate measure of a broad range of physical activities during pregnancy. We recently translated and adapted the PPAQ into Greek culture. Through our paper we demonstrated that only 14.8% of Greek women meet the international recommendations about physical activity during pregnancy. Interestingly, women who exercise more, are of higher educational level, higher maternal age, have conceived spontaneously and live in larger cities, while physical activity increased with gestational age (125; 126). Similar findings were published by Xiang et al. in China, who conducted a cross-sectional study also using the PPAQ (127).

Therefore, pregnant women should be encouraged not only to continue their daily activity and avoid bed rest but also to maintain their physically activity as per ACOG guidelines to 150 minutes of moderate exercise per week.

Short Cervix

The primary goal of screening methods (cervical length measurement, fibronectin test etc.) is identifying women who are at high risk of delivering before 37 weeks. Subsequently those women can receive an intervention which may reduce the risk of prematurity, although they can never eliminate it.

As mentioned in a previous chapter, cervical length assessment remains the gold standard technique for preterm birth screening. The cervical length at 20 to 24 weeks of gestation is 34 mm on average and gradually shortens throughout pregnancy. Cervical length of 25 mm which corresponds to the 10th percentile for this gestational age is the cutoff for short cervix (77). The incidence of short cervix (≤25 mm) in the 2nd trimester varies from 0.45% up to 10% and this group of women contains 40% of deliveries before 34 weeks (53).

Once a short cervix is diagnosed during first or second trimester, an intervention should be recommended. The most commonly used interventions for short cervix are progesterone, cervical cerclage and Arabin pessary. The final decision of which intervention to use, is made based on the cervical length, the previous obstetric history and the attending obstetrician's preference.

Progesterone

Progesterone is an endogenous steroid hormone, produced by the adrenal cortex and gonads (ovaries, testes). During pregnancy, progesterone is initially secreted by the corpus luteum and after 10 weeks is produced by the placenta, a transition known as "the luteal-placental shift" (128). The molecule progesterone is a derivative of cholesterol, explaining the commonly observed hypercholesterolemia in pregnant women (129). The plasma progesterone concentration increases

during pregnancy from 40 ng/mL in the first trimester to 160 ng/mL in the third trimester. The placenta at term produces ~250 mg of progesterone per day, of which 90% is secreted to the maternal circulation and 10% into the fetal circulation (130).

Sufficient progesterone levels during pregnancy are of paramount importance. Among others, progesterone decreases the vascular tone into the myometrium and affects the production of inflammatory mediators, like human T-cells within the uterine cavity. Therefore, reduced levels of progesterone are associated with increased myometrial contractility and decreased anti-inflammatory response, leading to a higher risk of pregnancy loss and preterm birth as well as infertility (131). It is therefore believed, that administration of progesterone reduces the aforementioned adverse outcomes (pregnancy loss and preterm birth).

The available forms of progesterone are intramuscular 17α-hydroxyprogesterone caproate (17-OHPC) and natural progesterone as vaginal capsules, vaginal gel or oral tablets and subcutaneous progesterone. Natural compounds are those with chemical structures similar to those produced by living organisms. By contrast, synthetic progestogens (or progestins) are compounds generated in the laboratory whose structures have been modified and do not correspond to a naturally occurring steroid. Progesterone is a natural progestogen; 17α-hydroxyprogesterone caproate (17-OHPC) is synthetic (132).

Initially, studies in women who previously had a spontaneous preterm birth, had shown that the prophylactic administration of progesterone beginning in mid-gestation halves the rate of recurrence. Consequently, large randomized prospective studies showed a significant reduction in the incidence of preterm birth before 34 weeks in women with a short cervix in the mid trimester following the administration of natural progesterone transvaginally (133) (134).

Da Fonseca et al. in 2003 were the first to examine the effect of natural progesterone. They conducted a placebo-controlled double-blind randomized trial with women at high risk of preterm delivery based on their history. Women who had at least one previous spontaneous preterm birth, prophylactic cervical cerclage or uterine malformation were allocate to either vaginal progesterone suppository (100 mg) or an identical-looking placebo. They observed a reduction in preterm birth incidence from 28.1% in the placebo group to 13.8% in the progesterone group (135).

A few years later, Da Fonseca et al. examined for the first time the efficacy of natural progesterone in women with short cervix in the mid-trimester. They conducted another randomized placebo-controlled trial in 413 women with short cervix less than 15 mm. Women were randomly assigned to either vaginal progesterone capsules 200mg each night or placebo until 34 weeks. They concluded that administration of vaginal progesterone in women with cervical length <15 mm reduces the risk of delivery before 34 weeks by 44% (19.2% in placebo group vs. 34.4% in study group; relative risk, 0.56; 95% confidence interval [CI], 0.36 to 0.86) (136).

These findings were confirmed by the team of Hassan et al. in 2011. They randomized 465 women with short cervix 10-20 mm between 19^{+0} and 23^{+6} weeks to either 90mg vaginal progesterone gel or placebo, until 36^{+6} weeks. They found about 45% reduction in the rate of preterm birth before 28, 33 and 35 weeks of gestation and improved neonatal outcome, including respiratory distress syndrome, neonatal morbidity and mortality and low birthweight in women who received progesterone. No statistically significant association was found for preterm delivery before 37 weeks. After adjusting for maternal history of preterm birth, the PTB reduction remained significant for those without prior history but was non-significant for women with prior preterm delivery (137).

An individual patient data (IPD) meta-analysis by Romero et al., comparing vaginal progesterone with placebo in 975 women with cervical length ≤25 mm from five randomized controlled trials, showed that the administration of progesterone significantly reduced the risk of preterm birth <33 weeks of gestation (14% vs. 22%, 38% reduction, RR 0.62; 95%CI 0.47–0.81) and improved neonatal outcomes, including respiratory distress syndrome, neonatal morbidity and mortality, birthweight and risk for NICU admission (134).

A recent meta-analysis of individual participant data from randomised controlled trials included women with short cervix during pregnancy or history of preterm birth and they confirmed the pre-existing evidence about the usefulness of progesterone. They showed that administration of progesterone vaginally reduces the risk of preterm birth <34 weeks in singleton pregnancies (3769 women, RR 0.78, 95%CI 0.68–0.90) and adverse neonatal outcomes. They also demonstrated that 17-hydroxyprogesterone also improves the pregnancy outcome, but the evidence was not statistically significant (3053 women; RR 0.83, 95%CI 0.68-1.01). Finally, they stated that there

is lack of data about oral administration of progesterone and its effectiveness of preterm birth prevention. (138).

Since the initial study of Da Fonseca in 2003, following studies examining the effect of progesterone in high-risk women based on their history, e.g., previous preterm birth, have yielded conflict results, with some of them demonstrating no protective value against preterm birth in current pregnancy. Indeed, a recent meta-analysis of randomised control trials by Conde Agudelo et al., combined all existing evidence and concluded that after adjusting for small-study effects, vaginal progesterone, in women with prior history only, has no effect on preterm birth <34 nor 37 weeks of gestation (139).

Natural progesterone administered as vaginal suppositories or vaginal cream is superior to 17-hydroxyprogesterone which did not reduce the risk of preterm birth compared to placebo in another recent randomised double-blind trial by Blackwell et al. (140). Although the use of intramuscular 17α-hydroxyprogesterone caproate (17-OHPC) in women with history of preterm birth was common practice in the USA since 2011, the FDA (Food and Drug Administration) has withdrawn this indication, since April 2023 based on the latest evidence (141). Indeed, available studies have shown that 17-OHPC does not have any effect on cervical length in patients with a history of ≥1 preterm births (142). Even animal studies demonstrated examining local effects of vaginal progesterone and 17-OHPC in pregnant mice showed that vaginal progesterone, but not 17-OHPC, had anti-inflammatory effects at the maternal-fetal interface (143).

Administration of progesterone is also a common clinical practice for women presenting with first trimester vaginal bleeding and threatened miscarriage. However, a recent randomised clinical trial which randomised 278 women to either progesterone vaginal pessaries or placebo pessaries until 12 weeks, failed to demonstrate a beneficial effect of progesterone on threatened miscarriage. More specifically, they did not find any statistically significant relationship between progesterone and live birth compared to control group, even when adjusting for history or previous miscarriage (144).

Regarding the safety of progesterone administration, a recent report of the OPPTIMUM trial reported no long-term harm observed in the outcomes of the children at 2 years of age whose mothers had taken 200 mg daily of progesterone from 22–24 to 34 weeks of gestation (145). Similar findings regarding progesterone safety were found by the follow-up study of the Triple P

trial who showed no differences in neurodevelopmental, behavioral, health-related and physical outcomes between offspring exposed to vaginal progesterone and those exposed to placebo (146).

During the last years authors and professional organizations around the world have recommended the use of vaginal progesterone in patients with a singleton gestation and a short cervix in the mid-trimester. Nevertheless, a significant proportion of women with short cervix will deliver prematurely despite progesterone treatment. This is probably the result of the multiple different causes of preterm birth and the fact that apparently progesterone is not effective in all the cases. It is possible that in those cases that will deliver prematurely, progesterone treatment fails to stop the delivery process which involves cervical remodeling in which the cervix gradually ripens, shortens and finally dilates.

Fonseca et al. noted that vaginal progesterone reduced the rate of spontaneous preterm delivery <34 weeks of gestation by only 25% in patients with a cervical length of 6-10 mm by 14% in cervical length 1-5 mm, but the effect size was 75% in those with a cervical length between 11-15 mm. Therefore, in cases of very short cervix, a different intervention namely cervical cerclage should be considered (136).

In summary, current evidence suggest that vaginal progesterone in women with short cervix ≤25 mm in mid-trimester, and mainly in those with cervical length between 10-25 mm, reduces the risk for preterm birth <34 weeks by 40%.

Cervical Cerclage

The term “cervical incompetence” was mentioned for the first time in 1865 by Gream, in an article published in the Lancet (147). The first cervical cerclage was performed in 1902 and it was initially used for women with history of second trimester miscarriage or very preterm births which were attributed to cervical insufficiency.

Cervical cerclage was introduced in clinical practice by VN Shirodkar, Professor of Midwifery and Gynecology at the Grant Medical College in Bombay, India, in 1955. He developed this

procedure because of his observation that “some women abort repeatedly between the fourth and seventh months and no amount of rest and treatment with hormones seemed to help them in retaining the product of conception.” Shirodkar referred to a group of 30 women who had had at least four abortions (some between 9 and 11 weeks). He stated that in his opinion, “95% of cases were due to a weak cervical sphincter and the other few to an underdeveloped or malformed uterus, etc.” Shirodkar emphasized that his work was confined to women in whom he could prove the existence of weakness of the internal os by “repeated internal examinations” (148). A few years later in 1957, Ian McDonald, from the Royal Melbourne Hospital, reported his experience with 70 patients who had a suture of the cervix for inevitable miscarriage (149).

Since then, several studies were published regarding the effectiveness of cervical cerclage in preventing preterm birth. Several indications have been examined with often conflict results.

Unlike progesterone, cervical cerclage is a mechanical intervention which supports the cervix reducing the risk for preterm delivery in certain cases. It is believed that apart from the structural support to a ‘weak cervix’, the effectiveness of cerclage lies also on the maintenance of cervical length and endocervical mucus plug which function as a barrier to ascending infection.

It can be placed transvaginally or transabdominally. The most common approach is the transvaginal placement which includes two techniques; McDonald or Shirodkar.

- **Transvaginal Cerclage – McDonald**

A permanent suture is inserted around the exo-cervix as high as possible to approximate to the level of the internal os, at the cervicovesical junction, without bladder mobilization. This is at the junction of the rugose vagina and smooth cervix.

McDonald technique is preferred because of its easier placement and removal and its proven comparative effectiveness.

- **High Vaginal Cerclage – Shirodkar**

This technique involves dissection of the vaginal mucosa and retraction of the bladder and rectum to expose the cervix at the level of the internal os and the suture is then placed above the level of the cardinal ligaments.

A recent meta-analysis by McAuliffe et al., which included 17 studies, showed that Shirodkar cerclage reduces the rate of preterm birth prior to 35, 34 and 32 weeks' gestation when compared with McDonald cerclage. However, the overall quality of the studies in this review is low and the results should be interpreted with caution (150).

The main disadvantage of Shirodkar cerclage is that requires anaethesia for the stich removal. Additionally, it is technically more challenging than McDonald cerclage. Therefore, this procedure is not routinely preferred, although the final decision is always left on the discretion of the surgeon.

- **Transabdominal Cerclage**

Transabdominal cerclage is indicated firstly in previous failed vaginal cerclage with scarring or lacerations rendering vaginal cerclage technically very difficult or impossible and secondly in cases of absent or very hypoplastic cervix with history of pregnancy loss fitting classical description of cervical insufficiency. It can be performed via laparotomy or more rarely with laparoscopy and the stich is placed at the level of cervicoisthmic junction (151).

Sheenan et al. conducted a multicenter randomized controlled trial and demonstrated transabdominal cerclage is superior to low vaginal cerclage in the reduction of early preterm birth and fetal loss in women with previous failed transvaginal cerclage. More specifically, rates of preterm birth at <32 weeks of gestation were significantly lower in women who received transabdominal cerclage (8%) compared with low vaginal cerclage (33%) and high vaginal cerclage (38%) (152).

Tulandi et al. compared the outcome in cases of transabdominal cerclage pre-conceptual versus in early pregnancy. They found no difference in regards of preterm birth rates. Yet, it is recommended to be placed before conception, when possible, due to reduced anesthetic risks and technical advantage of operating a non-pregnant uterus (153).

A meta-analysis including six studies using the laparoscopic approach and 26 studies using laparotomy found no difference in second trimester loss (8.1% laparoscopic versus 7.8%) or birth rates after 34 weeks (78.5% versus 84.8%) in the two groups (154). Additionally, another prospective cohort study comparing the two techniques, observed more complications in the laparotomy group (22% vs 2%) (155).

Cervical cerclage is further distinguished into three categories based on the **indication**:

1. Ultrasound indicated cerclage

From the published data, it is evident that cerclage is not beneficial for all women with short cervix during pregnancy. An individual patient data (IPD) meta-analysis of four RCTs of cerclage versus expectant management in women with a short cervix less than 25mm and no other risk factor for spontaneous preterm birth showed no reduction in the incidence of PTB before 33 weeks (156). Another multicentre, open label 3-arm randomised controlled trial which included cases of CL <25 mm between 14^{+0} and 23^{+6} weeks found similar results for PTB <37 (RD 6.2%, -5.0 to 17.0), <34 and <30 weeks when compared cerclage (n = 128) versus progesterone (n = 132) (157).

It seems though, that cervical cerclage is efficacious in preventing preterm birth, in singleton pregnancies, without history of preterm birth and a very short cervix, <10 mm (39.5% vs 58.0%; RR, 0.68 (95% CI, 0.47-0.98); I2 = 0%; five studies; 126 participants) (158). Furthermore, cerclage should be considered in women with further cervical length shortening despite progesterone (159) (160).

The isolated findings of funneling or sludge, without co-existing short cervix should not promote cerclage placement. In such cases, frequent follow up is recommended (161).

2. History based cerclage

Royal College of Obstetricians and Gynaecologists (RCOG), Society of Obstetricians and Gynaecologists of Canada (SOGC) and International Federation of Gynecology and Obstetrics (FIGO) recommend history-indicated cerclage for women with 3 or more previous preterm deliveries and/or second trimester pregnancy miscarriages, whereas the American College of Obstetricians and Gynecologists (ACOG) suggests the use of cervical cerclage in singleton pregnancies with 1 or more previous second trimester miscarriages related to painless cervical dilation or prior cerclage due to painless cervical dilation in the second trimester (162). It seems that those women, despite the sonographic findings, would benefit from early prophylactic cervical cerclage, which should be performed between 11 to 14 weeks, after confirming fetal viability.

An international multicentre trial, which recruited 1292 women to cerclage or no cerclage, showed that prophylactic cerclage reduces the incidence of PTB before 33 weeks by 50% only in women with history of three or more preterm pregnancies. They also demonstrated no benefit for women with previous cervical surgery or uterine abnormalities (163).

A meta-analysis by Berghella et al. compared women with prior preterm birth who were managed either by cervical length screening and cerclage for short cervical length or history-indicated cerclage. There was no significant difference in the incidence of preterm birth before 37 weeks (31% compared with 32%, RR 0.97; 95% CI 0.73–1.29), preterm birth before 34 weeks (17% compared with 23%, RR 0.76; 95% CI 0.48–1.2) and perinatal mortality (5% compared with 3%, RR 1.77; 95% CI 0.58–5.35) in women with surveillance compared with history-indicated cerclage. In the transvaginal ultrasound group, only 42% developed a short cervix and required cerclage. These data support the recommendation that women with a previous second trimester loss/preterm birth can be safely cared for by serial ultrasound surveillance and that this may reduce the number of cerclages performed (164).

3. Emergency cerclage

Emergency cerclage, also known as rescue cerclage or physical indicated cerclage, is performed in cases of painless cervical dilatation with bulging membranes, without sings of preterm delivery. The diagnosis is made sonographically or via clinical examination (speculum) and it can be performed up to 27^{+6} weeks gestation (165).

The investigation is usually urged by the patient's symptoms, which include increased vaginal discharge, vaginal bleeding or feeling 'pressure' into the vagina.

The technique for placing an emergency cerclage is slightly different than the standard procedure. To avoid preterm premature rupture of membranes (pPROM), the fetal membranes should be moved above the planned suture site. Over the years, moist swabs or Folley catheter filled with saline, have been used for this purpose. Alternatively, filling the bladder with physiological saline in a patient positioned in the Trendelenburg position is also technically effective for draining prolapsed fetal membranes. A full bladder lifts the inferior pole of the fetal membranes, causing

the membranes to withdraw from the vagina. A cervical suture is placed as high as possible over the cervix according to the McDonald's technique (166) (167).

In our meta-analysis in 2020, which compared rescue cerclage with expectant management in women with mid-trimester painless cervical dilatation, we found that cerclage reduces the incidence of preterm birth before 28 and 32 weeks, neonatal death and NICU admission, while it prolongs the pregnancy and women eventually deliver in more advanced gestation (168). The main limitation of this meta-analysis is that the included studies are not randomised control trials. Yet, due to the nature of this condition, with the rare incidence, a randomised controlled trial of significant statistical power, is unlikely to be conducted.

Intra-amniotic infection has been reported in 8-52%, and intra-amniotic inflammation in 81% of such patients with cervical dilatation, when ascertained by amniocentesis (28) (169) (170) (171) (172) and the risk of subsequent delivery within 7 days is about 50% (169). A retrospective study including 17 cases of emergency cerclage, it was reported that C-reactive protein (CRP) value below 4.0 mg/dl and a maternal white cell (WBC) count less than 14 000/microlitre were associated with prolongation of pregnancy compared with women with values above these cutoffs. They also associated higher values of CRP and WBC with more advanced cervical dilatation (173).

Fuchs et al. used multivariate logistic regression methods to develop a score for assessing the risk of early preterm delivery before 32 weeks in singleton pregnancies with emergency cervical cerclage. The authors found that a history of second-trimester pregnancy loss, nulliparity, cervical dilatation more than 4 cm, membranes bulging into the vagina, and infection (i.e., white blood cells (WBC) $\geq$ 13,600/ mm3 or C-reactive protein (CRP) > 15 mg/L) are associated with emergency suture failure (174).

It was suggested by Oh et al. to administer triple course of antibiotics (ceftriaxone 1 gram IV every 24 hours; 2) clarithromycin 500 mg oral every 12 hours; and 3) metronidazole 500 mg IV every 8 hours) in women with painless cervical dilatation to treat cases of subclinical chorioamnionitis or sterile intra-amniotic inflammation. Indeed, they demonstrated that after the antibiotics the incidence of intrauterine inflammation in patients with cervical insufficiency was reduced by 75% and was associated with treatment success in 59% of cases (171) (175). Spontaneous resolution of the dilatation was also observed after the antibiotics (176).

Contraindications of cerclage

The contraindications of placing a cervical cerclage are the same for all the aforementioned categories of cerclage and are irrespective of the initial indication. These include the following:

- Ongoing preterm labour
- Clinical suspicion of chorioamnionitis
- Pre-labour preterm rupture of membranes (pPROM)
- Vaginal bleeding
- Fetal distress
- Lethal congenital abnormalities
- Intrauterine fetal death (IUD)

Potential Risks and Complications

As in every surgical procedure, cerclage placement is not without risks. Cases of non-emergency cerclage, namely history- or ultrasound-indicated cerclage, enclosed a small risk, less than 1%, of intraoperative bladder damage, cervical trauma, membrane rupture and bleeding. Postoperatively, no study has shown increased risk of pPROM, chorioamnionitis, preterm birth, second trimester loss, induction of labour or caesarean section. Cervical trauma is a potential risk in cases of spontaneous onset of labour with the suture in situ (177). Fistula formation has been reported as a late, rare complication (178).

Perioperative management

There is limited data suggesting the use of **tocolysis** prior to cerclage insertion. Indeed, a retrospective cohort study of 101 women who had ultrasound-indicated cerclage demonstrated that the rate of delivery <35 weeks was not significantly different in women who received indomethacin for 48 hours following the procedure compared with those who did not (39% versus 34%) (179).

Similarly, there is a paucity of evidence supporting the use of **antibiotic prophylaxis** at the time of cerclage insertion and the decision is left at the discretion of the operator.

In terms of **anaesthesia**, both general and regional can be safely used for cerclage insertion. Overall, general anaesthesia is associated with faster recovery time but has higher demand for post-operative analgesia (180). Therefore, the finally choice should be individualized.

The choice of transvaginal cerclage **technique** (high cervical insertion with bladder mobilization or low cervical insertion) should be at the discretion of the surgeon, but the cerclage should be placed as high as is practically possible. Odibo at al. showed no difference in preterm birth before 33 weeks in women who had a McDonald cerclage compared with those with a Shirodkar suture (181). Furthermore, several studies including that of Scheib et al. showed that the higher the cerclage is placed the lower the incidence of subsequent preterm birth (182). Double or single suture technique are also equally effective, although data is scarce, and the decision is again left at the discretion of the operator (183).

Post-operative management

After cerclage placement, **frequent cervical length** measurement is not recommended. It could be thought useful in individual cases at very high risk of preterm birth or in cases with signs and symptoms of imminent delivery, in order to offer steroids or in utero transfer to a tertiary hospital with appropriate NICU for that gestational age.

Bed rest is also not recommended as it is now known that restriction in physical activity during pregnancy can actually increase complications such as thromboembolic events, adverse psychological effects on the mother and partner with higher rates of postpartum depression, as well as preterm birth (117).

Fetal fibronectin test post cerclage insertion is not routinely recommended due to low specificity (184). However, the high negative predictive value of fetal fibronectin testing for preterm delivery before 30 weeks could provide reassurance to women and clinicians and help the decision for inpatient or outpatient management in certain cases.

In a meta-analysis by Jarde et al. it was shown that the additional administration of **progesterone** in women with cerclage in situ, did not reduce further the incidence of delivery before 37 weeks (185). Current NICE guidelines do not advise progesterone administration following cervical cerclage (186).

In case of pPROM with cerclage in situ between 24 and 34 weeks of gestation, without signs of infections or preterm labour, it is justified to keep the stich for up to 48 hours to administer steroids for fetal lung maturation, magnesium for neurological protection and transfer to tertiary hospital. If pPROM occurs before 23 or after 34 weeks, then the stich should be removed as keeping the stich in situ increases the risk of maternal and neonatal sepsis without improving the ultimate pregnancy outcome.

The transvaginal cerclage is usually removed at around 36-37 weeks unless delivery is planned by elective Cesarean Section (C-Section), in which occasion, stich removal can take place at the same time. If spontaneous onset of labour occurs earlier, the stich should be removed immediately to avoid cervical lacerations. In case of transabdominal cerclage, the indicated modε of delivery is Cesarean Section (C-section) and the stich remains in situ for future pregnancies (177).

Overall, cervical cerclage should be considered for women with cervical length less than 10 mm, for those with history of 3 or more previous preterm deliveries and/or second trimester pregnancy miscarriages and finally for women with painless cervical dilatation.

Arabin Pessary

The vaginal pessary is a silicone ring used traditionally for the conservative management of uterine prolapse. Recent studies have focused on the use of pessaries in Obstetrics and specifically, for the prevention of preterm birth in cases of cervical insufficiency. There are different types of pessaries but the one that is commonly used for this purpose is the Arabin pessary. The Arabin pessary has been approved for the prevention of preterm birth in Europe (CE0482/EN ISO 13485:2003 annex III of the council directive 93/42 EEC) (187).

The use of pessaries in women with suspected cervical insufficiency was firstly descripted back in 1959 (188). The pessary offers mechanical support to the uterus because it holds and prolongs the cervix, while it can also change the angle of the cervix to the uterus turning the cervix towards the sacral bone. In that way, it strengthens the cervical canal and reduces the contact of intact membranes with the vagina.

The pessary placement can be performed without general or regional anesthesia as opposed to the cerclage and therefore does not require hospitalization or recovery time. There are different sizes of Arabin pessary so the appropriate choice for each patient should be made after clinical examination. The decision for appropriate size is made taking into consideration the gestational age, parity, singleton or multiple pregnancy, the cervical length, presence or absence of funneling, as well as patient's height. If the patient is able to feel the pessary or experiences any discomfort that means that the pessary is not placed correctly or the size is inappropriate and it should be readjusted.

The pessary is electively removed at 37 to 38 weeks of gestation unless there are signs of preterm labour, pPROM, infections or bleeding occur earlier. The most common side effect of the pessary is the increased vaginal discharge. In cases of discomfort or bleeding the pessary position should be evaluated and be re-adjusted or replaced by a new one. The contraindications of pessary placement are the same as cerclage, already mentioned previously, including active preterm labour, suspicion of chorioamnionitis, pPROM, vaginal bleeding, fetal distress, lethal congenital abnormalities and intrauterine fetal death.

Arabin Pessary for singleton pregnancies with short cervix

There is conflict evidence regarding the actual efficacy of Arabin pessary in preventing preterm delivery in singleton pregnancies. Two randomised trials (RCT) showed that the Arabin pessary in women with short cervix <25 mm reduced the risk of preterm delivery before 34 weeks (a. 385 women: 6% vs 27%, b. 300 women: 7% vs 15%) (189) (190).

However, the largest RCT performed up to date in singleton pregnancies was the multicentre RCT by Nicolaides et al. who enrolled a sample of 932 patients with CL ≤25 mm between 20 and 24^{+6} weeks and randomised the patients into Arabin pessary versus expectant management. They did

not demonstrate any significant difference in the rate of preterm birth (12% vs 11%) (191), which is consistent with the results of the most recent meta-analysis (192).

Indeed, the most recent multicentre randomised controlled trial by van Dijk et al., who assigned 315 women with short cervix to pessary and 320 similar women to progesterone showed that spontaneous preterm birth at less than 28 weeks occurred more often after pessary than after progesterone (10/62 (16%) vs 3/69 (4%), relative risk 3.7 (95% CI 1.1 to 12.9)) and adverse perinatal outcomes seemed more frequent in the pessary group (15/62 (24%) vs 8/69 (12%), relative risk 2.1 (0.95 to 4.6)). They concluded that for women with singleton pregnancies, a short cervix, and no prior spontaneous preterm birth less than 34 weeks' gestation, superiority of a cervical pessary compared with vaginal progesterone to prevent preterm birth and consecutive adverse outcomes could not be proven (193).

Similar results were found by a multicentre, open label 3-arm randomised controlled trial which included cases of CL <25 mm between 14^{+0} and 23^{+6} weeks. They demonstrated equal efficacy on PTB prevention <37, <34 and <30 weeks when compared cerclage (n = 128) versus pessary (n = 132) [risk difference (RD) -0.7% (-12.1 to 10.7)] and progesterone (n = 132) versus pessary (n = 126) [RD -6.9% (-17.9 to 4.1)] (154).

Arabin Pessary and progesterone for singleton pregnancies with short cervix

Moreover, clinical trials comparing the efficacy of progesterone in combination with Arabin pessary in women with short cervix, showed that the addition of pessary did not reduce further the risk of prematurity compared to the progesterone only group (194) (195).

There is only one retrospective study demonstrating effectiveness of combined Arabin pessary with progesterone in preventing preterm birth before 34 weeks gestation. They included women with cervical length ≤25 mm between 15 and 29 weeks. The study group which received progesterone and Arabin pessary, comprised of 94 women with additional risk factors for preterm birth, like cervical surgery and history of cervical incompetence, as opposed to the 108 patients treated with progesterone only. The rate of preterm delivery <34 weeks gestation was lower in the pessary group (7.4 % vs. 17.6 % respectively, P = 0.036) and they delivered one week later compared to the control group (37.2 ± 2.1 vs. 36.2 ± 3.7 respectively, P = 0.02) (196). It can

therefore be postulated, that the combination of Arabin pessary with progesterone, can be useful in women with multiple risk factors of preterm birth, besides short cervix.

Arabin Pessary and cerclage for singleton pregnancies with short cervix

A retrospective cohort study investigated the efficacy of combined treatment with cervical cerclage and Arabin pessary in high-risk singleton pregnancies with cervical shortening. Wolnicki et al. compared combined therapy (47 women) versus McDonald cerclage alone (34 women) considering delivery before 34 weeks as the primary outcome and found that there were no differences in the rates of preterm birth (27,7 % vs 32.4% p = 0.48) between the two populations. They observed however, that the mean neonatal admission time at the neonatal intensive care unit was shorter in the combined treatment group versus in the cerclage group (p = 0.02) (197).

Shor et al. enrolled 286 pregnant women with short cervical length (25 mm) to four different treatment protocols: combined treatment with cervical cerclage, Arabin pessary and vaginal progesterone (group A), Arabin cervical pessary and vaginal progesterone (group B), cervical cerclage and vaginal progesterone (group C) and vaginal progesterone alone (group D). The authors described similar rates of spontaneous preterm delivery <37 weeks gestation among groups (44.4 % vs 32.5 % vs 36.8 % vs 32.7 % respectively, P = 0.665). Nevertheless, Group A was characterized by patients with higher risk for preterm delivery, having a history of cervical incompetence or cervical procedure and shorter cervical length at recruitment, compared to the other groups (198).

Conclusions

In summary, the published data regarding the efficacy of Arabin pessary in singleton pregnancies in reducing preterm birth have yielded conflicting results. Due to the fact that the studies are extremely heterogeneous, it is impossible to combine and compare their results. Therefore, the Arabin pessary is not recommended by any international guidelines, as a first line preventative measure for preterm birth.

Additional Measures

In cases of short cervix, taking high vaginal swabs for cultures should always be considered, irrespective of the final intervention (progesterone, cerclage or pessary). If abnormal culture is confirmed, then appropriate antibiotic treatment should be given. However, as mentioned in previous chapter, treating bacterial vaginosis during pregnancy does not reduce the risk for preterm delivery nor prolong pregnancy, in any subgroup, even when started earlier in gestation (37) (105).

Multiple Pregnancies

Twin pregnancies represent 3.2% of all births. The risk of spontaneous or iatrogenic preterm birth in multiple pregnancies is much higher compared to singleton pregnancies. More specifically, about 60% of twins are born before 37 weeks and 12% before 32 weeks (199). Overall, 20% of all preterm deliveries happen in twin pregnancies.

Measuring the cervical length between 18 and 24 weeks of gestation remains the gold standard screening method to identify women at high risk. Although some studies suggest using as cutoff for short cervix in multiple pregnancies the 20 mm for better prognostic value, most guidelines use the same cutoff as for singleton pregnancies, which is ≤25 mm (200).

Despite the extensive research about preterm birth prevention, the evidence regarding multiple pregnancies are less encouraging, mainly due to lack of available studies. It seems that none of the known preventative interventions used in singletons (progesterone, cerclage, Arabin pessary) are effective in reducing spontaneous preterm birth before 34 weeks in unselected twin pregnancies, wither in cases of short cervix ≤25 mm (201). The same applies for bed rest.

There is lack of evidence regarding triplets or higher multiples and therefore the following data focus on twin pregnancies.

Progesterone in twin pregnancies

The prophylactic administration of progesterone in twin pregnancies is ineffective which was shown by a meta-analysis of D'Antonio et al. The authors concluded that vaginal progesterone in unselected twin pregnancies do not reduce the risk of PTB before 34 weeks of gestation (6 studies, 2672 pregnancies; RR: 1.04; 95 % CI: 0.84-1.30 - p = 0.7). Similar results were produced by a meta-analysis of Norman et al. of 500 unselected twins who were randomized into vaginal progesterone or placebo and it was shown that that progesterone does not prevent early preterm birth in women with twin pregnancy (pooled OR 1.16, 95% CI 0.89-1.51) (202). Finally, two subsequent RCTs confirmed the previous findings that vaginal progesterone does not reduce the risk of PTB <34 weeks in unselected twin pregnancies (203) (204). Likewise, there was no contribution of intra-muscular 17-OHPC (3 studies, 923 pregnancies; RR: 1.09; 95 % CI: 0.74-1.60 - p = 0.7) in reduction of preterm birth (201).

In cases of short cervix before 24 weeks, the use of progesterone may reduce the risk of prematurity and neonatal mortality and morbidity (205). A recent meta-analysis by Conde-Agudelo et al. demonstrated that among twin gestations with a transvaginal sonographic cervical length <30 mm (6 studies; 306 women), vaginal progesterone was associated with a significant decrease in the risk of PTB <28 and <32 gestational weeks (RR, 0.48-0.65; moderate- to high-quality evidence), neonatal death (RR, 0.32; 95% CI, 0.11-0.92; moderate-quality evidence), and birthweight <1500 g (RR, 0.60; 95% CI, 0.39-0.88; high-quality evidence) (206).

Cervical Cerclage in twin pregnancies

In terms of cerclage, some studies suggested that cerclage in twins may actually increase the risk of PTB (207). On the contrary, a multicentre retrospective cohort study in twins showed that the subgroup of women with cervical length less than 15 mm (cerclage n = 32 and controls n = 39) had prolonged interval between diagnosis to birth (12.5 ± 4.5 versus 8.8 ± 4.6 weeks, $P < 0.001$) and reduced risk of spontaneous preterm birth less than 34 weeks (16 versus 31 adjusted OR 0.51; 95% CI 0.31–0.83) (208). However, another individual patient data (IPD) meta-analysis by Saccone et

al. explored the role of cerclage in twin pregnancies with a short cervical length <25 mm, reported no difference in the rate of PTB between women undergoing cerclage and controls (209).

The most robust data regarding cerclage is about asymptomatic dilatation before 24 weeks, in which case, cervical cerclage in combination with antibiotics and tocolysis reduces the risk of delivery before 28 weeks by 50% and the risk of neonatal mortality by 78% (210). Additionally, a meta-analysis by Hulshoff et al. showed that singleton and twin pregnancies, after emergency cerclage, have similar survival, with a pregnancy prolongation of 37 days and a gestational age at delivery of 28 weeks, in cases of twin pregnancies. The authors concluded that compared with expectant management, emergency cerclage significantly increased overall survival by 43%, fetal survival by 17% and neonatal survival by 22%, along with a significant pregnancy prolongation of 37 days and reduction in delivery at <28 weeks of gestation of 55% (211). Therefore, emergency cerclage should be considered with the same indications as in singletons.

Arabin Pessary in twin pregnancy

Finally, several studies about the use of Arabin pessary revealed conflict evidence, similarly to singleton pregnancies. While some randomised trials showed improvement in the rates of PTB (212), other studies including a meta-analysis by Norman et al. could not replicate those results (213).

The Dutch ProTWIN trial, which was the first study to evaluate the use of Arabin pessary in twin pregnancies showed that in women with a cervical length less than the 25th percentile, the risk of PTB < 28 weeks (4% versus 16 %, RR 0.23, 95 % CI 0.06–0.87, P = 0.0158) and < 32 weeks (14 % versus 29 %, RR 0.49, 95 % CI 0.24–0.97, P = 0.0476) were significantly reduced in the pessary group compared with the expectant management group (214).

The PECEP-Twins trial, a prospective, open-label, multicentre RCT published in 2016, randomized 137 women with a short cervix (defined as 25 mm) to cervical pessary (68 patient) or expectant management (66 patient) with a 1:1 ratio. Spontaneous preterm birth before 34 weeks of gestation was significantly reduced in the pessary group as compared to expectant management

(16.2 % vs 39.4 % RR 0.41, 95 % CI 0.22–0.76, P = 0.003), whilst no differences were found between the two groups in terms of neonatal morbidity or mortality (189).

On the other hand, the largest randomised controlled trial (RCT) performed up to date, by Nicolaides et al., included 1180 unselected twin pregnancies (between 20 and 24 + 6 weeks) who received either a cervical pessary (588 patients) or an expectant management (589 patients). This RCT found no significant differences in incidence of delivery before 34 weeks of gestation (13.6 % vs 12.9 % RR 1.05, 95 % CI 0.79–1.41; P = 0.722), or perinatal morbidity and mortality, between the two groups. Moreover, a post hoc analysis in a subgroup of 214 women with short cervix (25 mm) showed no increase in prolongation of pregnancy in the pessary group (106 patients) as compared to control group (108 patients) (sPTB < 34 weeks: 31.1 % versus 25.9 %, RR 1.201, 95 % CI 0.784–1.839) (215).

A more recent open label multicentre randomised controlled trial, STOPPIT 2, allocated women with twin pregnancies and short cervix <35 mm to Arabin pessary (n=230) or to standard care alone (n=253). The rate of spontaneous preterm birth before 34 weeks was similar in both groups, and specifically was 18.4% (46/250) in the intervention group and 20.6% (52/253) in the control group (adjusted OR 0.87, 95% CI 0.55 to 1.38; p = 0.54) (213).

In 2016 Fox et al., in a retrospective cohort study that included 21 patients treated with Arabin pessary plus vaginal progesterone and 63 matched controls on progesterone only treatment, at 28 weeks of gestation or less with a cervical length less than 20 mm, found that cervical pessary was associated with the prevention of delivery before 32 weeks (4.8 % vs 28.6 %, P = 0.033) (216).

Conclusions

In summary, based on the existing data, in cases of twin pregnancies and short cervix in the mid-gestation, the first line intervention is the vaginal progesterone capsules. If further shortening is noted then cerclage could be beneficial. In case of painless cervical dilation then cerclage should be performed. Finally, the use of Arabin pessary should lie on the individual's expertise.

Cost-effectiveness

Unfortunately, evidence is conflicting regarding the utility, feasibility, and cost-effectiveness of universal transvaginal cervical length screening in low-risk populations. Since many institutions have implemented universal cervical length screening protocols, evidence regarding the effectiveness of this approach continues to evolve.

A randomised trial in 2023 by Saccone et al. included 1334 asymptomatic women with singleton pregnancies and without prior preterm birth, who were assigned to either cervical length screening or no screening between 18^{+0} and 23^{+6} weeks of gestation. Women with short cervix ≤25 mm were offered 200mg vaginal progesterone daily along with cervical pessary. The did not find a significant difference in preterm birth incidence before 37 weeks between the two groups (relative risk, 0.86; 95% confidence interval, 0.59-1.25), neither for preterm birth less than 34, 32, 30, 28, and 24 weeks of gestation. They concluded that introduction of a universal transvaginal ultrasound cervical length screening program at 18^{+0} and 23^{+6} weeks of gestation in lower risk women did not result in significant lower incidence of preterm delivery than the incidence without the screening program (217).

On the contrary, a very recent meta-analysis of 8 studies (447,864 pregnancies), showed that although universal screening of all women between 16-25 weeks did not reduce the risk of spontaneous preterm delivery before 37 weeks, it was associated with lower incidence of PTB before 32 weeks (odds ratio, 0.84 [95% confidence interval, 0.76-0.94], P=.002). In a secondary analysis of low-risk women without prior preterm delivery they found a significantly lower risk of spontaneous PTB before 37 weeks as well (odds ratio, 0.88 [95% confidence interval, 0.79-0.97], P=.01). Based on that, they concluded that universal transvaginal ultrasound cervical length screening before 24 weeks in singletons without a prior spontaneous preterm birth, is associated with a significant reduction in spontaneous preterm birth <37 weeks, compared to no screening (218).

Other clinical practices suggest screening only women at high risk for preterm birth based on their history, e.g. prior preterm delivery, cervical surgery, congenital uterine anomalies etc. However, Miller et al. in their cohort of 18,250 women found that if women with at least one risk factor were

screened, 63% of transvaginal ultrasonograms could be avoided, but 40% of women with a short cervix will not be identified and would miss the corresponding chance of averting a preterm birth through progesterone treatment (219). Of note, only 10% of spontaneous preterm births occur among women with a history of preterm delivery (220).

When it comes to screening after 24 weeks, a cohort study with 2728 women by Seravalli et al. showed that in asymptomatic women with singleton pregnancy at low risk for spontaneous preterm birth, the predictive value of cervical length after 24 weeks of gestation is low and therefore, cervical length screening in these women should be discouraged (221).

Several studies have demonstrated that universal second trimester cervical length screening and subsequent progesterone administration for those with short cervix is the most cost-effective strategy when compared to other strategies as screening only high-risk population, treatment based only on history or no screening at all (222).

Cahill et al. conducted a decision analysis in 2010, comparing the cost-effectiveness of four strategies: (i) universal ultrasound screening by cervical length measurements, combined with treatment by vaginal progesterone; (ii) ultrasound screening to measure cervical length among women with an increased risk of preterm delivery, and treatment with vaginal progesterone; (iii) treatment among high-risk women by 17 alpha-hydroxyprogesterone caproate (17-OHPC), without ultrasound screening; (iv) no screening and no treatment. They demonstrated that universal ultrasound screening and treatment with vaginal progesterone was the dominant strategy and led to the greatest reduction in preterm births before 34 weeks. They calculated that in the USA the universal screening would save nearly $13 billion and would avoid 95 920 preterm births each year (223).

Another decision analytic model by Einerson et al., compared the cost and effectiveness of 3 cervical length screening strategies in a population of women with no prior preterm birth; risk-based screening compared to universal cervical length screening or no screening. They concluded that universal screening in the USA would result in 2.19 million more transvaginal ultrasounds, 11,027 more women treated with vaginal progesterone, 913 fewer preterm births <35 weeks gestational age, and 63 fewer neonatal deaths at an additional cost of $51,936,699 annually. Despite costing more, the additional health benefits of universal screening resulted in that strategy being more cost-effective than risk-based screening, with an incremental cost-

effectiveness ratio of $21,144 per quality-adjusted life-year (224). In other words, the reduction of preterm births and improvement in the quality of life of those neonates add on the economic benefits of universal screening.

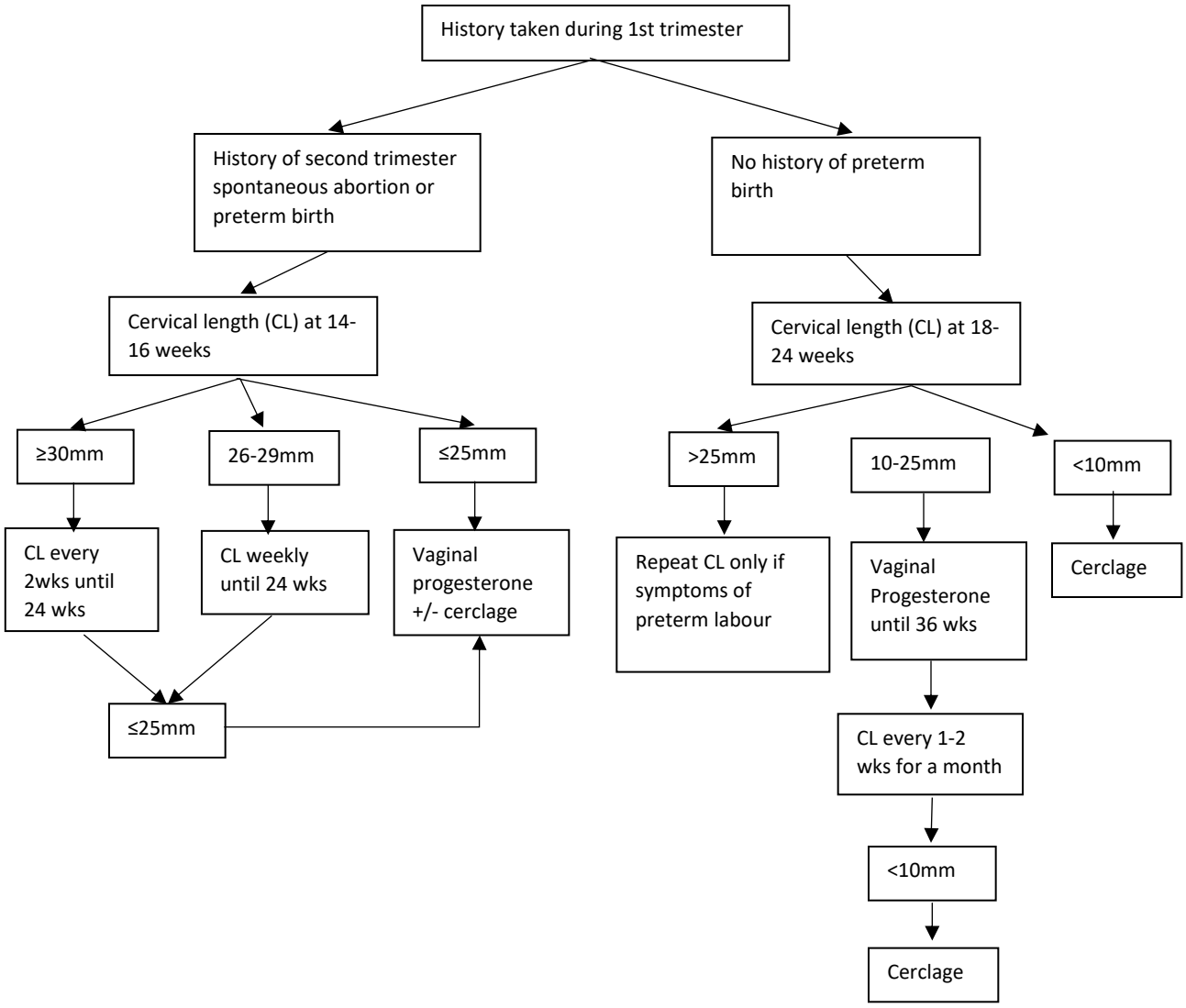
Leshno et al. recently examined the cost-effectiveness of universal routine sonographic cervical-length measurement at 19 to 25 weeks' gestation, which is implemented in Israel since 2010. They estimated that the national savings from screening for short cervical length and subsequent treatment with vaginal progesterone, when compared with no cervical length screening amounted to $8.31 million annually (225).

Recommended Screening Method and Management

In 2022 the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) suggested an algorithm regarding screening for preterm birth, according to our protocol which was published in 2019 (226; 160).

Screening by a combination of obstetric history and cervical length provides a higher detection rate than either method alone. For a screen positive rate of 10%, the respective detection rates are about 80% and 60% in identifying extreme and early preterm birth (227).

Figure 1: Screening for preterm birth, by the International Society of Ultrasound in Obstetrics and Gynecology



Management of Threatened Preterm Labour

Threatened preterm labour (TPL) is the progression of cervical dilatation and ripening caused by regular uterine contractions occurring before 37 weeks of pregnancy, which may result in preterm birth.

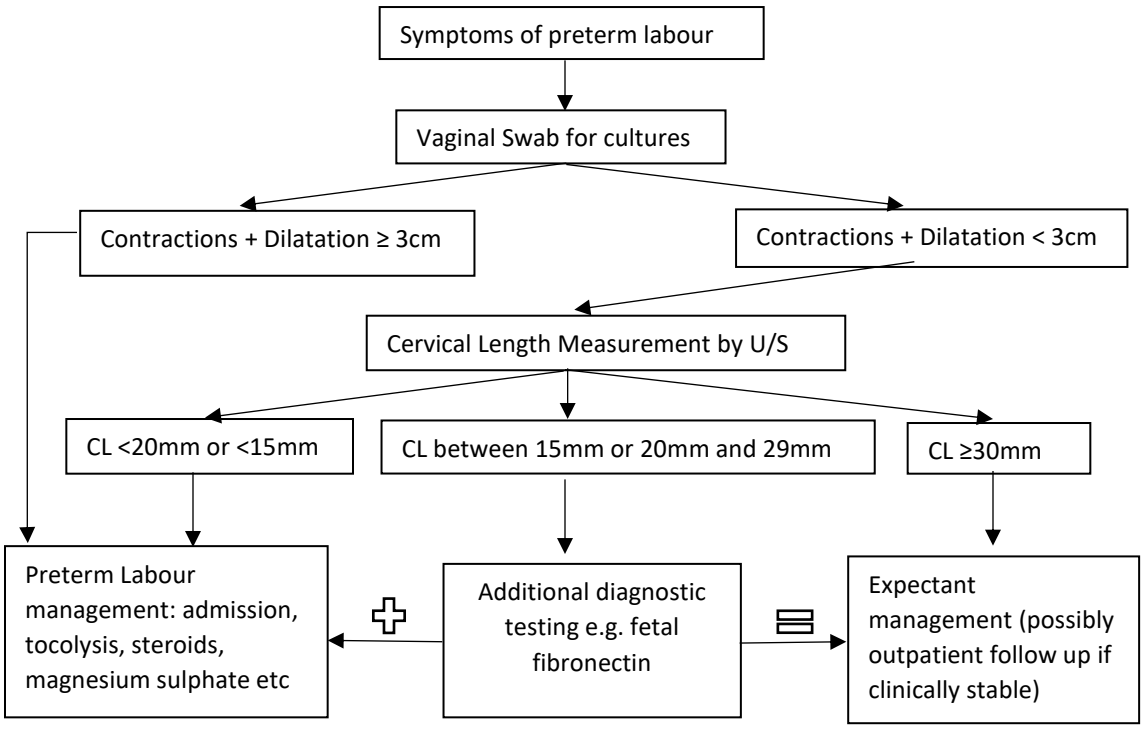
The two most important elements in the management of threatened preterm labour are:

1) The accurate pregnancy dating which should take place ideally in the first trimester between 11 and 13^{+6} weeks using the crown rump length (CRL) or by the conception date in pregnancies conceived with assisted reproductive technology (ART).

2) The accurate diagnosis of threatened preterm labour.

The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) recommends the following algorithm for the diagnosis and management of such cases (226):

Figure 2: Diagnosis and Management of threatened preterm labour, by International Society of Ultrasound in Obstetrics and Gynecology



The appropriate management of threatened preterm labour improves significantly the neonatal prognosis. Pregnancy prolongation, even for a few days in order to administer steroids and magnesium sulfate can dramatically reduce the neonatal morbidity. Furthermore, the administration of antibiotics in cases of pPROM can be lifesaving.

Tocolysis

Tocolysis is the procedure followed to inhibit uterine contractions and prolong gestation. It is achieved through different medications and is practically used for pregnant women experiencing preterm labour. From a physiologic perspective, the myometrium is responsible for the contractional effort of childbirth. Like all smooth muscle, this process is calcium-mediated. It´s believed that this switch to a contractional uterus is caused by an equilibrium change of proinflammatory and anti-inflammatory cytokines and is initiated by several factors as discussed in previous chapter, for example uterine overdistention, infection and others (22).

ACOG warns that women with preterm contractions but without cervical change, especially those with a cervical dilation of less than 2 cm, generally should not be treated with tocolytics. This recommendation is derived by several studies demonstrating that the majority of women presenting with preterm contractions will not actually deliver prematurely. More specifically, a study of 763 women who had unscheduled triage visits for symptoms of preterm labour, only 18% gave birth before 37 weeks of gestation and only 3% gave birth within 2 weeks of presenting with symptoms (228). No evidence exists to support the use of prophylactic tocolytic therapy.

There is a plethora of medications which can be used for tocolysis including **b2-selecive agents or sympathomimetic** (ritodrine, terbutaline, salbutamol), **calcium channel blockers** (nifedipine), **prostaglandin inhibitors** (indomethacine), **ocytoxin antagonists** (atosiban) and **nitric oxide donors** (nitroglycerine).

WHO suggests the use of tocolytic agents in cases of threatened preterm labour between 24 and 33^{+6} weeks of gestation. It does not seem to directly improve the neonatal outcome because it is

not intended to increase gestation of the fetus to term. Therefore, it is not recommended to use tocolytic medications as prophylaxis, as it hasn´t been shown to reduce neonatal morbidity. However, it should be used to prolong the pregnancy for a short period of time to administer steroids and in utero transfer to a tertiary hospital with appropriate Neonatal Intensive Care Unit (NICU) if necessary. This additional time is also used to determine the group B streptococcus (GBS) status of the pregnant woman, and provide prophylaxis if needed.

Tocolysis has also been used in the setting of external cephalic version, uterine tachysystole, and suspected fetal distress. For the external cephalic version in cases of abnormal fetal presentations, betamimetics are the most efficient in increasing the rate of cephalic presentation and reducing the frequency of cesarean section. A dose of 0.25 mg of terbutaline is given subcutaneously or intravenously 30 minutes before the attempted procedure. There is no difference between intravenous and subcutaneous administration of terbutaline (229). Uterine tachysystole is defined as more than 5 contractions in 10 minutes averaged for 30 minutes. Betamimetics, like salbutamol are effective at aborting uterine contractions in this emergent setting (230).

Tocolysis is contraindicated in cases when delayed delivery can be harmful for the mother of the fetus, for example vaginal bleeding with or without placental abruption, intrauterine infection/ chorioamnionitis, severe preeclampsia, intrauterine death and non-reassuring cardiotocography (CTG). Pre-labour rupture of membranes (PROM) is a relative contraindication, so it should be used with caution only when absolutely necessary to gain sometime, up to 24 hours, for steroids or in utero transfer, if there are no signs of maternal infection. Tocolysis should not be used after 34 weeks of gestation or in cases of lethal fetal anomaly, as there is no benefit.

Ideally, tocolysis should be used for up to 48 hours, but it can be justified for up to 7 days if the benefits outweigh this delay, mainly to achieve in utero transfer to an appropriate tertiary hospital. Longer use of tocolytic medications for more than 7 days, does not improve the neonatal outcome, while it increases the chance of maternal complications.

The decision of which medication to use is made by each clinician individually and based on the maternal medical history, local protocols, drugs availability and cost. There is no definitive first-line tocolytic agent proposed by the American College of Obstetrics and Gynecology (ACOG). They suggest the use of first-line tocolytic treatment with beta-adrenergic receptor agonists, calcium channel blockers, or NSAIDs for short-term prolongation of pregnancy, but in reality

nifedipine and indomethacin are the most commonly used (231). The guidelines by WHO and NICE indicate that nifedipine should be the first line, followed by the oxytocin antagonists, which however have a significantly high cost. Indomethacin should be avoided during the third trimester of pregnancy because is associated with premature closure of the ductus arteriosus. They also suggest that although beta2-selective agents are equally effective with nifedipine, they should be avoided due to numerus side effects (232).

Calcium channel blockers specifically work on T-type calcium channels by inhibiting the entry of calcium into the uterine smooth muscle. The lack of free calcium directly affects the ability of myometrium to contract. The most common medication in this class is nifedipine. Sublingual administration of nifedipine can achieve tocolysis faster than oral route. Maternal side effects include flushing headaches, dizziness, nausea, transaminasaemia, suppression of heart rate and contractility and hypotension, while there is no evidence suggesting fetal risks from the use of nifedipine. It should, however be used with caution in patients with hypotension and cardiac problems. A recent review published by Hanley et al., suggested that nifedipine is probably the best tocolytic agent (233). WHO propose the commonly used regimen for nifedipine (immediate release) as an initial oral dose of 20 mg followed by 10 mg every 6 hours for 3–7 days or until transfer is completed, whichever comes first (234).

Oxytocin inhibitors (atosiban and retosiban) work by competitively acting at the oxytocin receptor site. The medication is delivered intravenously and nor maternal, nor fetal side effects have been described for this tocolytic. It has, however, a significantly high cost and is therefore preferred as a second line treatment, after nifedipine.

B2-selecive agents work by increasing the cyclic AMP which cause smooth muscle relaxation. This drug category also activates the beta-1 receptors, which are located in cardiac muscle. Therefore, maternal risks include but are not limited to cardiac arrhythmias, tachycardia, hypotension, tremor, shortness of breath, pulmonary edema, nausea and vomiting. Fetal risks include but are not limited to tachycardia (231). Studies have suggested the tocolytic agents in this family might confer a risk of the development of childhood asthma (235). Overall, NICE guidelines suggest not to use sympathomimetic due to maternal cardiac complications (8).

Nonsteroidal anti-inflammatory medications (NSAIDs) work by inhibiting cyclooxygenases (COX), which is responsible for production of prostaglandins. The most common representative

of this category is indomethacin, which can be given per os or per rectum. NSAIDs are contraindicated in women who have history of bleeding disorders, gastritis, aspirin hypersensitivity, and hepatic impairment. Indomethacin is also contraindicated after 32 weeks of gestational age because of premature closure of the ductus arteriosus (236). Other fetal effects from indomethacin include oligohydramnios due to renal dysfunction, necrotizing enterocolitis, patent ductus arteriosus in newborn, gastric perforation, and pulmonary hypertension.

The exact mechanism of **magnesium sulfate** is not completely clear but it has been described to inhibit the entry of calcium into the uterine smooth muscle. It also has vasodilatory effects on uterine blood vessels (237). WHO reports that while magnesium sulfate has a tocolytic effect (delaying birth by 48 hours), other tocolytic agents have greater benefits and fewer side-effects. On the contrary, other studies demonstrated that while magnesium sulfate has a neuroprotective effect on the newborn, it does not prolong pregnancy in the setting of preterm labour and should not be used solely for that reason (238). It should not be used in conjunction with calcium channel blockers and beta-adrenergic receptor agonists when possible, due to risk of maternal respiratory depression. Other risks of magnesium toxicity are flushing, nausea, reduced deep tendon reflexes, blurred vision, reduced cardiac contractility and cardiac arrest (231).

Finally, **nitroglycerine** works by producing cyclic GMP, which halts intracellular calcium levels from rising and subsequently inhibit contractions. It can be administered intravenously or transdermal. A meta-analysis by Conde Agudelo et al. showed that when compared with β2-adrenergic-receptor agonists, transdermal nitroglycerin was associated with a significant reduction in the risk of preterm birth <34 and <37 weeks of gestation, admission to the neonatal intensive care unit, use of mechanical ventilation, and maternal side effects. However, there were no significant differences between transdermal nitroglycerin and nifedipine and magnesium sulfate in delivery within 48 hours of treatment and pregnancy prolongation, respectively (239). Overall, current evidence does not support its routine use as tocolytic agent for the treatment of preterm labour.

Corticosteroids

Endogenous glucocorticoids are essential for normal fetal development, and a surge of circulating glucocorticoids in late pregnancy facilitates normal maturation of the fetal lungs, heart, brain, and kidneys (240).

Liggins in 1969 while researching the effects of the steroid dexamethasone on premature labour in fetal sheeps, incidentally found that there was some inflation of the lungs of lambs born at gestations at which the lungs would be expected to be airless (241). Liggins and Howie subsequently performed in 1972 the first randomised controlled trial in humans on the effect of betamethasone on the prevention of respiratory distress syndrome (RDS) (242) and then Crowley et al. in 1990 were the first to examine corticosteroids in preterm birth. The latter, showed for the first time that corticosteroids in preterm labour reduce the risk of RDS, intraventricular haemorrhage and neonatal mortality (243). Subsequent studies confirmed those findings and nowadays, administration of corticosteroids in cases of TPL is considered standard practice by all international guidelines.

It is believed that corticosteroids promote rapid maturation of the preterm fetal lung and surfactant production, manifesting as improved lung compliance and enhanced gas exchange because of increased stability when breathing out, which prevent collapse of the alveoli. All the above, result in a reduction in the risk of morbidity (principally RDS) and mortality in cases of preterm birth before 32 weeks (244).

Potential Benefits of Antenatal Corticosteroids

It is well established that the administration of corticosteroids in cases of imminent preterm birth promote fetal lung maturation. It is also proven, that steroids improve tremendously the neonatal outcome with reduction in the incidence of respiratory distress syndrome as well as perinatal and neonatal mortality. Finally, it seems that steroids reduce by a certain degree, the chance of intraventricular hemorrhage (IVH) and long term neurodevelopmental delay (245).

More specifically, a Cochrane systematic review showed that neonates whose mothers receive antenatal corticosteroids have significantly lower risk of perinatal death (risk ratio (RR) 0.85, 95%

confidence interval (CI) 0.77 to 0.93), neonatal death (RR 0.78, 95% CI 0.70 to 0.87) and respiratory distress syndrome (RR 0.71, 95% CI 0.65 to 0.78). They also suggest that antenatal corticosteroids probably reduce the risk of IVH (RR 0.58, 95% CI 0.45 to 0.75) and probably lead to a reduction in developmental delay childhood (RR 0.51, 95% CI 0.27 to 0.97). Finally, there was no statistical association between antenatal corticosteroids and maternal death, chorioamnionitis and endometritis (246).

Low quality evidence also suggest that prophylactic administration of corticosteroids in term elective cesarean sections, appear to decrease the risk of respiratory distress syndrome (RDS) (risk ratio (RR) 0.48; 95% confidence interval (CI) 0.27 to 0.87; 4 studies; 3817 participants), transient tachypnoea of the neonate (TTN) (RR 0.43; 95% CI 0.29 to 0.65; 4 studies; 3821 participants), admission to the neonatal intensive care unit (NICU) for respiratory morbidity (RR 0.42; 95% CI 0.22 to 0.79; 3 studies; 3441 participants). The authors of this meta-analysis highlight that consideration should be given to the balance between statistical significance and clinical significance, particularly in view of the low event rates of significant respiratory morbidity (RDS or admission to NICU for respiratory complications) in this population. In addition, further trials on the long-term outcomes of these infants are needed (247).

Treatment Regime

The vast majority of official guidelines suggest the use of steroids in pregnancies between 24 and 34 weeks, when imminent delivery within 7 days is expected. Some guidelines also recommend considering steroids up to 36 weeks.

WHO reports that high likelihood of preterm birth within 7 days may be assessed using the following criteria: preterm membrane rupture without preterm labour, spontaneous preterm labour with intact membranes (where preterm labour is defined as at least six regular uterine contractions per hour and at least one of the following: cervix ≥3 cm dilated or ≥75% effaced), or planned preterm birth by induction or caesarean section. Antenatal steroids should also be considered in cases of iatrogenic preterm birth, mainly in women with hypertensive disorders and fetuses with intrauterine growth restriction (248).

If delivery occurs after those 7 days, then the beneficial effect of steroids on lung maturation is eliminated. The complete course includes 24mg of betamethasone or dexamethasone split equally into two doses within 12 or 24 hours depending of the progression of preterm labour. Treatment with corticosteroids for less than 24 hours is still associated with significant reductions in neonatal morbidity and mortality, and therefore the first dose of antenatal corticosteroids should always be administered even if the ability to give the second dose is unlikely because of imminent delivery before the 12 hours interval (231).

A repeat course (a single rescue course) can be considered if delivery does not occur within the first 7 days, but no more than two courses of steroids should be administered in such cases. A multicentre randomised double-blind placebo-controlled trial examining the effect of repeat course of steroids in cases of TPL before 34 weeks, showed a significant reduction in the primary outcome of composite neonatal morbidity < 34 weeks in the rescue steroid group vs placebo (43.9% vs 63.6%; OR 0.45; 95% CI 0.27-0.75; P = 0.002) and significantly decreased respiratory distress syndrome, ventilator support, and surfactant use (249).

In cases of preterm premature rupture of membranes, steroids should be given only when severe maternal infection is excluded. In cases of chorioamnionitis or serious systematic maternal infection (sepsis, tuberculosis etc), steroids should be avoided. In any case, if infection is present, delaying delivery for steroids maturation can be more harmful (232).

Caution should be taken in women with diabetes mellitus when administer corticosteroids and should be accompanied by inpatient glucose level monitoring (245). Caution should also be taken when administering corticosteroids in women with gestational diabetes due to the maternal hyperglycemic effect of antenatal corticosteroids. It is however agreed, that when the potential benefits for the baby are higher, appropriate measures can be taken to ensure glycemic control (248).

Potential Risks from Antenatal Corticosteroids

A study based on data from seven randomised controlled trials and 10 population studies involving 1.6 million infants born since 2000, shows that around 40% of infants treated with antenatal corticosteroids are actually born at term (250). This observation indicates that a significant

proportion of antenatal steroids are given in cases where is not actually needed. Although it is a common belief in clinical practice, to administer steroids even with small suspicion of imminent preterm delivery, recent data suggest that corticosteroids may not be us harmless as previously thought.

This study by Ninan et al. also noted that exposure to antenatal corticosteroids was associated with an increased chance of short- and long-term health issues, such as admission to neonatal intensive care, breathing problems, and reduced growth (250). Another study based on data from the National Health Insurance Research Database (NHIRD) in Taiwan for nearly 2 million children born between 2008 and 2019, showed that exposure to antenatal corticosteroids compared with no exposure is associated with an increased risk of serious infection, including sepsis and pneumonia, during the first 12 months of life (251).

Other studies have linked steroids exposure to potential developmental delays in childhood. A cohort study from Taiwan identified a significant association between use of corticosteroids and increased risk of childhood mental disease (252). A long-term follow-up of the 2005 Stutchfield et al. study cohort, found that children exposed to steroids were twice as likely to be in the bottom quartile of academic ability as those who did not receive steroids (17.7 vs 8.5%) (253). Raikkonen et al. demonstrated that exposure to steroids was associated with the diagnosis of any mental and behavioral disorder (12.01 vs 6.45%, $P < 0.001$), including intellectual disability, psychological development disorders, autism spectrum disorders, attention-deficit/hyperactivity disorders, and psychotic, mood, neurotic, stress-related, or somatization disorders (254).

Short-term effects of antenatal corticosteroids include neonatal hypoglycemia, which was further found to be associated with a child's longer-term risk of development delay, including poor cognitive and motor function and continuation in adverse health outcomes into adulthood (255). Several studies showed an association between antenatal corticosteroids and intrauterine growth restriction, especially in cases of repeated courses. However, the results were inconsistent and indeed a Cochrane review in 2020, of 19 RCTs, found that reductions in birthweight were only minor and not significantly different from age-matched infants who did not receive corticosteroids, with differences in weight resolved by discharge (256).

Taking this into account, extra caution should be taken when assessing a patient and diagnosis of threatened preterm labour should be made using strict criteria to avoid unnecessary interventions which enclose uncertain risks.

Magnesium Sulfate

Magnesium sulfate was traditionally used in cases of severe preeclampsia and as tocolytic agent. Nelson et al. in 1995 were the first to describe the neuroprotective effect of magnesium sulfate. They examined infants at the age of three, who had a low birthweight <1500gr and they observed that children with cerebral palsy were less likely to had been exposed to magnesium sulfate in utero (257).

After that, several studies examined this observation and in 2009, a meta-analysis combined all that data in a Cochrane systematic review which showed that antenatal magnesium sulfate in women at risk of preterm delivery reduces the risk of cerebral palsy in their offspring (RR 0.68; 95% CI 0.54 to 0.87; five trials; 6145 infants) and the risk of substantial gross motor dysfunction (RR 0.61; 95% CI 0.44 to 0.85; four trials; 5980 infants) (258). Interestingly, none of the trials demonstrated significant pregnancy prolongation when magnesium sulfate was given for neuroprotection and therefore in no longer used for tocolysis but only for neonatal neuroprotection.

Magnesium sulfate is used in cases of preterm delivery before 32-34 weeks. There is enough evidence now that magnesium sulfate has a neuroprotective impact on preterm neonates since it reduces the risk of complications such us cerebral palsy and motor disabilities. It should be administered only in cases of imminent delivery within 24 hours and the mother should be closely monitored for possible side effects, such as peripheral vasodilatation with flushing, vertigo, vomiting, palpitations, tachycardia, headache, hypotension, generalized muscle weakness, ischemia, pulmonary edema, reduced uterine artery velocity, oliguria and renal failure (232).

NICE (National Institute for Health and Care Excellence) guidelines recommend initial bolus intravenous administration of 4gr magnesium sulfate within 15 minutes and then continues intravenous administration of 1gr per hour until delivery or for 24 hours; whatever comes first (8).

Antibiotics in PROM

Preterm Premature Rupture of Membranes (pPROM) is the spontaneous rupture of fetal membranes before 37 weeks of gestation without established labour. One of the most common causes associated with pPROM is intrauterine infections and inflammation, which is often subclinical. On the other hand, infection may occur secondary to membrane rupture. Ascending infection may lead to occult deciduitis, intra-amniotic infection or fetal infection.

A meta-analysis of 22 trials involving over 6000 women demonstrated that the use of antibiotics following pROM is associated with a statistically significant reduction in chorioamnionitis (RR 0.66, 95% CI 0.46 to 0.96,). They also found a reduction in deliveries within 48 hours (average RR 0.71, 95% CI 0.58 to 0.87) and seven days of randomization (average RR 0.79, 95% CI 0.71 to 0.89). Additional reduction was observed in neonatal infection (RR 0.67, 95% CI 0.52 to 0.85), use of surfactant (RR 0.83, 95% CI 0.72 to 0.96), oxygen therapy (RR 0.88, 95% CI 0.81 to 0.96), and abnormal cerebral ultrasound scan prior to discharge from hospital (RR 0.81, 95% CI 0.68 to 0.98) (259).

Therefore, in cases of pRPOM, maternal antibiotics are indicated and the gold standard is erythromycin (250mg x 4 per day, for 10 days). Therefore, if erythromycin is not available or is contraindicated, then the alternative choice is penicillin for 10 days or until delivery (8) (232).

Amoxicillin with clavulanic acid (Augmentin) is not recommended during third trimester because it is associated with neonatal necrotizing enterocolitis (RR 4.72, 95% CI 1.57 to 14.23). One plausible mechanism of pathogenesis of neonatal necrotising enterocolitis is abnormal microbial colonisation of the intestinal tract. Co-amoxiclav, because of its large spectrum may influence such colonisation. Furthermore, the immature gut is sensitive to bacterial toxins, resulting in mucosal damage and the initiation of necrotizing enterocolitis (259).

Antibiotics in preterm labour with intact membranes

The use of antibiotics in preterm labour with intact membranes is controversial topic. It is known that infection and inflammation can trigger preterm delivery, as mentioned already in previous chapter. Therefore, it was theorized and examined whether administration of antibiotics during preterm labour can prolong the pregnancy.

Studies have demonstrated that antibiotics reduce the risk of maternal infection but do not reduce the incidence of preterm birth (260). Additionally, a Cochrane meta-analysis of 14 randomised controlled trials, including 7837 women, that compared antibiotic treatment with placebo for patients with documented preterm labour found no difference between the antibiotic treatment and placebo for prolonging pregnancy or preventing preterm delivery and in perinatal or infant mortality (261).

On the contrary, a study which examined infants at the age of 7, the mothers of whom had received antibiotics (erythromycin +/- amoxicillin/clavulanic acid) in the context of preterm labour with intact membranes, showed that those children had higher chance of neurodevelopmental complications, such as cerebral palsy. A possible explanation reported by the authors is that antibiotics can mask intrauterine infection and subsequently delay the delivery (262). Similar findings are suggested for beta-lactam antibiotics which were associated with more neonatal deaths (RR 1.51, 95% CI 1.06 to 2.15; NNTH 143, 95% CI 1250 to 63) and cerebral palsy (RR 1.67, 95% CI 1.06 to 2.61; NNTH 79, 95% CI 909 to 33). The authors emphasize that based on these evidence antibiotics should not be routinely given to women in preterm labour with intact membranes in the absence of overt signs of infection (261).

Therefore, the American College of Obstetricians and Gynecologists (ACOG) and the WHO discourage the use of antibiotics as routine practice in such cases (263). NICE guidelines recommend the use of antibiotics only for Group B Streptococcus prophylaxis in cases of known colonization (8).

Table 2: Different Guidelines on Threatened Preterm Labour Management

	ΕΜΓΕ	***ACOG***	**RCOG**	**WHO**
pPROM	**<34 weeks** - Erythromycin 500mg x4 PO, 10 days - Alternative: Ampicillin 2gr x 4 iv and Erythromycin 250mg x 4 iv for 2 days and then 5 days PO + Steroids +/- GBS prophylaxis **34-37 weeks:** consider IOL +/- GBS prophylaxis **>37 weeks:** IOL	**24-34 weeks** - Ampicillin 2gr x 4 iv και Erythromycin 250mg x 4 iv for 2 days and then 5 days PO + Steroids +/- GBS prophylaxis during labour **34-37 weeks:** consider IOL +/- Steroids +/- GBS prophylaxis during labour **>37 weeks:** IOL +/- GBS prophylaxis during labour	- Erythromycin 250mg x4 PO, 10 days - Alternative: Penicillin 10 days - Avoid: amoxicillin/ clavulanic acid + Steroids +/- GBS prophylaxis during labour **34-37 weeks:** IOL if GBS (+) +/- Steroids **>37 weeks:** IOL	- Erythromycin 250mg x4 PO, 10 days + Steroids +/- GBS prophylaxis during labour
Antibiotics in preterm labour	No in the absence of: PROM, GBS, chorioamniotis	No in the absence of: PROM, GBS, chorioamniotis	Yes, for everyone for GBS prophylaxis (Penicillin G ή Vancomycin)	No in the absence of: PROM, GBS, chorioamniotis
Magnesium Sulfate	24-30 weeks Consider 33+6 wks.	24-32 weeks	24-30 weeks	24-32 weeks
Corticosteroids	24 – 33+6 weeks Consider at 22-23+6 and 34-36+6 weeks	24-33+6 weeks Consider at 23 wks	24- 33+6 weeks Consider up to 35+6 wks	24-34 weeks

GBS: Group B hemolytic Streptococcus, wks: weeks, IOL: induction of labour, wks: weeks

ΕΜΓΕ: Greek Society of Obstetrics and Gynecology: Guidelines No 53 July 2021 (PRETERM LABOUR), Guidelines No 7 July 2013 (PRETERM RUPTURE OF MEMBRANES)

ACOG: The American College of Obstetricians and Gynecologists, Practice Bulletin 188, January 2018 (Pre-labor Rupture of Membranes), Practice Bulletin 159, January 2016 (Management of Preterm Labor)

RCOG: The Royal College of Obstetricians and Gynecologists, Green-top Guideline No. 73, June 2019 (Care of Women Presenting with Suspected Preterm Prelabour Rupture of Membranes from 24+0 Weeks of Gestation), Green-top Guideline No. 36, September 2017 (Prevention of Early-onset Neonatal Group B Streptococcal Disease) Green-top Guideline No. 74, July 2022 (Antenatal corticosteroids to reduce neonatal morbidity and mortality)

WHO: World Health Organization, 2015, WHO recommendations on interventions to improve preterm birth outcomes

CHAPTER 2: AIM AND METHODS

The multifactorial nature of preterm delivery is now well established as described in the previous chapter. Short cervical length (CL) ≤25 mm in the mid gestation is the strongest risk factor for preterm birth before 34 weeks. The therapeutic options for preventing preterm birth in such cases include progesterone, cervical cerclage and Arabin pessary. During the last years, authors and professional organizations around the world have recommended the use of vaginal progesterone in patients with a singleton gestation and a short cervix in the mid-trimester.

Despite the intensive research on the topic, a significant proportion of women with short cervix will deliver prematurely despite progesterone treatment. More specifically, a recent meta-analysis has shown that the administration of progesterone in women with cervical length ≤25 mm will reduce the rate of preterm birth only by 35%. A possible explanation could lie on the different causes of preterm birth and apparently on the fact that progesterone is not effective in all the different cases.

In order to investigate this hypothesis, we performed a prospective observational study involving women with CL ≤ 25 mm in the mid trimester. The aim of this study was to examine the effect of the progesterone administration in the CL and furthermore to investigate the effect of cervical shortening in the rate of preterm birth. Furthermore, we aimed to assess if the following management protocol of women with short cervix can reduce further the rates of PTB <37, 34 and 32 weeks of gestation.

All women who attended our unit for their routine anomaly scan, between 19^{+0} and 23^{+6} weeks, were offered a transvaginal scan to assess the cervical length. Those with CL between 25 and 10 mm received pessaries of natural progesterone 200mg transvaginally and were offered four consecutive weekly transvaginal scans for CL measurement. In women whose CL remains ≥10 mm no further actions were performed. Women with shortening cervix ≤10 mm were offered placement of cervical cerclage or Arabin pessary, based on the gestational age. More specifically, if shortening cervix to ≤10 mm was noted before 28 weeks then cervical cerclage was performed, while for cases after 28 weeks, Arabin pessary was the treatment of choice. Administration of corticosteroids and or tocolytics were considered, on the preference of the treating physician.

We needed to examine a minimum of 30 patients with short cervix. In the general population about 2.5% will have a cervix between 10 and 25 mm. Therefore, about 1200 women must be screened to identify 30 with short cervix. From those 30 about 6-7 would deliver < 34 weeks if left without treatment. Progesterone administration would reduce preterm birth rate by about 35% therefore we expected 4-5 women to deliver <34 weeks.

Inclusion Criteria

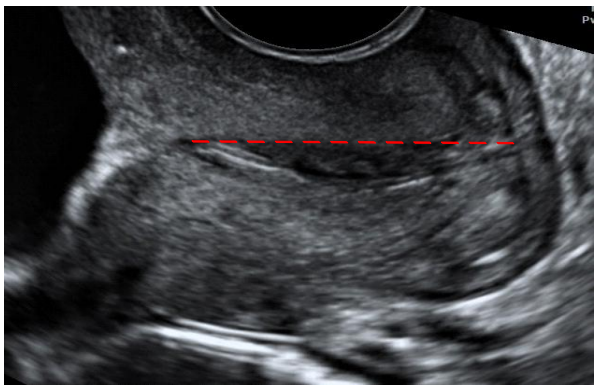
The study included women between 19^{+0} and 23^{+6} weeks of gestation at enrolment, undertaking routine screening for preterm birth by measuring the CL, who met the following criteria:

1. Singleton pregnancy
2. CL ≤ 25 mm
3. No signs or symptoms of preterm labour.

Gestational age was determined by the CRL measured at the 11- 14 weeks scan.

All operators were FMF certified for cervical length assessment (Fetal Medicine Foundation's cervical assessment certificate of competence). For accurate and standardized measurement of the cervical length, transvaginal ultrasound was used and the following steps were followed, as per international guidelines:

- The patient should have an empty bladder.
- A longitudinal plane of the cervix is captured, including clearly the internal and external os. The picture is magnified as much to occupy 50-75% of the screen.
- Caution was taken not to apply any pressure to the cervix which can produce a falsely long cervix.



- Three different measurements were taken over a few minutes and the shortest one was recorded.
- The measurement was done with a straight line from the internal to the external os, even when the cervix was curved (53) (76).

Exclusion Criteria

Women with cervical cerclage at the initial assessment, allergy to progesterone, major thromboembolic disorders, liver disease, major fetal anomaly, uterine malformation, chorioamnionitis or vaginal bleeding were excluded from the study.

Data Collection

Data was collected prospectively using a fetal database software (Astraia).

Recorded parameters included

1) Maternal age
2) Maternal ethnic origin
3) Method of conception (spontaneous / IVF or ICSI / other ART)
4) Maternal weight (1st trimester)
5) Maternal height
6) Smoking in pregnancy
7) Parity
8) Previous term births (at or above 37+0 weeks)
9) Previous spontaneous preterm births (<37 weeks)
10) Previous second trimester loss
11) Previous cervical surgery (i.e., LLETZ)
12) Gestational age at enrolment, (at initial cervical screening)

13) Cervical length at enrolment
14) Presence of amniotic fluid “sludge” and “vanishing amniotic sludge” at the internal cervical os
15) Suprapubic Pressure test
16) Estimated fetal weight at enrolment
17) Follow up CL measurements
18) Additional interventions in case of CL shortening less than 10mm (cerclage or Arabin pessary)
19) Outcome of pregnancy
    a. Gestational age at birth
    b. Birth weight
    c. Fetal sex
    d. Mode of delivery and indication
    e. Antenatal complications (GDM, PE, PPROM)
    f. NICU admission

Other Interventions

Antenatal corticosteroids or tocolytics were prescribed at the attending physician’s discretion.

Statistics

We produced descriptive statistics for the whole group.

The primary outcomes of this study were:

- The % change in CL and its contributing factors. We calculated the % CL change in each individual during the study time (4 weekly measurements) and we explored its associations with initial CL and maternal characteristics.
- Spontaneous preterm birth <37, <34 and <32 weeks in women whose CL remained $\geq$ 10 mm and received progesterone only, and their contributing factors.

The secondary outcomes include:

- CL less than 10mm at the end of the 4-weeks study period and its contributing factors.
- Spontaneous preterm birth <37, <34 and <32 weeks in women with CL <10 mm who received an additional therapy, apart from progesterone (cervical cerclage, Arabin pessary) and their contributing factors.
- Secondary analysis on the outcome and rates of spontaneous preterm birth <37, <34 and <32 weeks in women with painless cervical dilation who had an emergency cerclage.

Continuous variables were described as mean and standard deviation (SD) for normally distributed data, or as median and interquartile range (IQR) for non-normally distributed data. The distribution of continuous variables was assessed through visual inspection of histograms and the Kolmogorov-Smirnov test. Categorical variables were summarized as percentages. Comparisons between groups were performed using the independent sample t-test or the Mann-Whitney U-test for continuous variables, depending on their distribution, and the chi-square test or Fisher's exact test for categorical variables.

Linear regression analysis was employed to evaluate factors influencing the change in cervical length (delta), expressed in absolute millimeters or as a percentage, as well as the final cervical length measurement (dependent variables). The independent variables included maternal age, use of assisted reproductive technology (ART), maternal body mass index (BMI), parity, smoking status, history of cervical surgeries, gestational age at the diagnosis of short cervix, presence of sludge or vanishing amniotic sludge, history of spontaneous preterm birth, and the application of suprapubic pressure.

Logistic regression was utilized to identify factors associated with preterm birth before 37, 34, and 32 weeks of gestation. The same independent variables (maternal age, ART, maternal BMI, parity,

smoking status, history of cervical surgeries, gestational age at diagnosis of short cervix, presence or resolution of sludge, history of spontaneous preterm birth, suprapubic pressure and additionally the initial cervical length measurement) were included in the model.

CHAPTER 3: RESULTS

Between November 2018 and October 2024, 1804 patients accepted to participate in this study. 91 women were excluded as they did not meet the eligibility criteria; 74 women had twin pregnancies, 15 had a cerclage in situ at the time of assessment and 2 had intrauterine fetal death at that time, leaving 1713 eligible for inclusion. All of them were offered a transvaginal scan in order to measure the cervical length. 28 of them declined and 10 were further excluded from the final analysis due to intrauterine death later in pregnancy (no=3) or termination of pregnancy due to fetal abnormalities (n=7). The final sample consisted of 1675 women (mean CL: 34 mm; Range 0-48 mm).

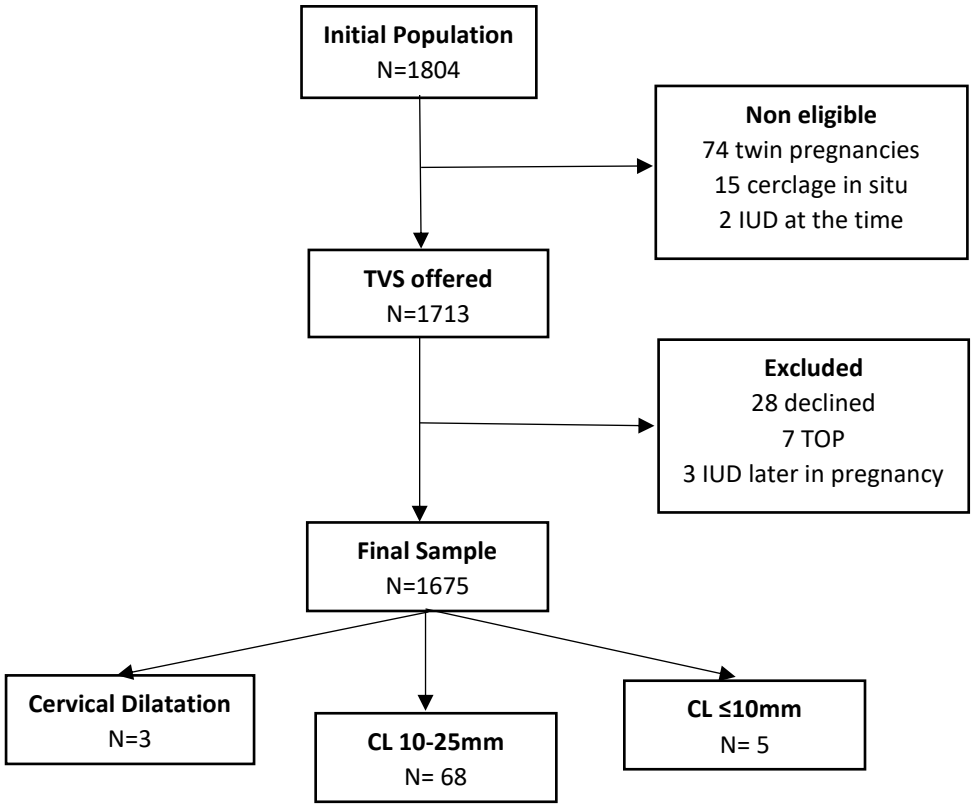
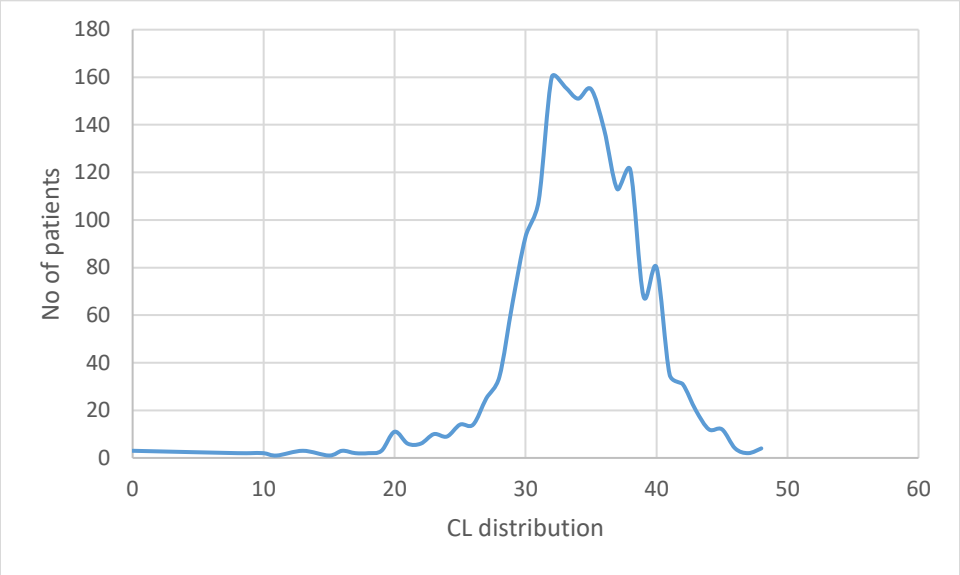


Figure 3: Flowchart of Study selection, IUD: intrauterine death; TOP: termination of pregnancy; CL: cervical length

Figure 4: Distribution of Cervical Length measurements among all women (no: 1675)



No: number; CL: cervical length

The prevalence of short cervix ≤25 mm in our population was 4.5% (76/1675). The characteristics of this population are found in table 3. Five women had initial CL ≤10 mm and had an ultrasound indicated cerclage, while three women had painless cervical dilatation with bulging membranes. The remaining 68 out of 1703 (4%) had a short cervix between 10 and 25 mm and were suggested to use 200 mg natural progesterone transvaginally every day up to 36 weeks of gestation. They were also offered four additional transvaginal scans every one to two weeks, to assess the rate of cervical shortening.

Table 3: Characteristics of study population (women with short cervix ≤25mm)

Characteristics	**Study population (CL ≤25mm) N=76**
Maternal age (years)	33.1 (24-45)
Maternal weight (kg)	66.6 (41-121)
Maternal Height (cm)	165.1 (150-180)

Racial origin Caucasian	 76 (100%)
Mode of conception Spontaneous In-vitro fertilization Ovulation drugs	 66 (86.8%) 9 (11.8%) 1 (1.3)
Parity Nulliparous Parous	 50 (65.8%) 26 (34.2%)
Smoking	
History of cervical surgeries	4 (5.26%)
History of PTB or second trimester loss	4 (5.26%)
History of short cervix in previous pregnancy	6 (7.9%)
Gestational age at enrolment (weeks)	21.3 (19.1-23.9)
Cervical length at enrolment (millimeters) 10-25mm ≤10mm 0mm (cervical dilatation)	19.7 (0-25) 68 (89.4%) 5 (6.6%) 3 (3.9%)
Presence of amniotic sludge	6 (7.9%)
Presence of vanishing amniotic sludge	4 (5.26%)
Positive Suprapubic Pressure test	10 (13.15%)

CL: cervical length, PTB: preterm birth

Primary Outcomes

Overall results for women with initial CL 10-25 mm

In the group of 68 women with initial CL between 10 and 25 mm and irrespective of the final management, the rates of preterm birth (PTB) <37 weeks, <34 weeks and <32weeks were 15/68 (22%), 4/68 (5.9%) and 4/68 (5.9%), respectively. Over the follow up period, in 46 cases the CL

remained above 10 mm, while 22 women had progressively shorter cervix equal or less than 10mm and required additional intervention. More specifically, 14 had a cervical cerclage and 8 received an Arabin pessary, either because they were beyond 28 weeks of pregnancy (n=6) or because cervical cerclage was contraindicated due to vaginal bleeding (n=2).

Linear regression analysis was employed to evaluate the influence of several factors on the change of cervical length (delta) on the subsequent follow up assessments, expressed in absolute millimeters and as a percentage. Those factors were the maternal age, use of assisted reproductive technology (ART), maternal BMI, parity, smoking status, history of cervical surgeries, gestational age at the diagnosis of short cervix, presence of sludge or vanishing amniotic sludge, history of spontaneous preterm birth, and the application of suprapubic pressure. Results are shown in table 4 and table 5.

We found a marginally significant association between gestational age at diagnosis and the cervical length change (delta) when expressed in absolute millimeters (2.08, 95% CI: 0.00-4.16; P: 0.05). None of the examined parameters was significantly associated with the percentage of CL change (table 5). When examining the influence of these factors on the final CL at the end of the observational period, we demonstrated a strong relationship with the initial CL measurement (1.52, 95% CI: 0.90 – 2.14; P: <0.001), and a statistically significant relationship with gestational age at diagnosis (2.58, 95% CI: 0.45 – 4.71; P: 0.02) and parity (4.43, 95% CI: 0.26 – 8.59; P: 0.03) (table 6).

Table 4: Variables affecting the delta of CL in women with initial CL 10-25 mm

Variable	Estimate	95% CI	P-value
Maternal Age	-0.33	-0.78 0.11	0.146
ART	5.27	-1.03 11.59	0.099
BMI	-0.05	-0.35 0.24	0.706
Parity	3.57	-0.53 7.68	0.087
Smoking Status	-2.35	-8.00 3.29	0.406
Hx of cervical surgery	-0.77	-8.81 7.25	0.846

GA at diagnosis	2.08	-0.00 4.16	**0.050**
Sludge	-3.83	-10.92 3.26	0.283
Vanishing amniotic sludge	1.00	-7.02 9.03	0.802
Hx of spontaneous PTB	-0.52	-17.16 16.10	0.949
Positive suprapubic pressure test	-0.00	-5.75 5.73	0.998

CL: cervical length; ART: assisted reproductive techniques; BMI: body mass index; Hx: History; GA: gestational age; PTB: preterm birth

Table 5: Variables affecting the percentage of CL change in women with initial CL 10-25 mm

Variable	Estimate	95% CI	P-value
Maternal Age	-0.01	-0.03 0.01	0.134
ART	0.24	-0.05 0.54	0.104
BMI	-0.00	-0.02 0.01	0.470
Parity	0.15	-0.04 0.34	0.119
Smoking Status	-0.11	-0.38 0.14	0.379
Hx of cervical surgery	-0.11	-0.49 0.26	0.533
GA at diagnosis	0.08	-0.01 0.17	0.101
Sludge	-0.14	-0.47 0.19	0.399
Vanishing amniotic sludge	0.01	-0.36 0.38	0.961
Hx of spontaneous PTB	-0.05	-0.84 0.72	0.879
Positive suprapubic pressure test	-0.04	-0.31 0.22	0.726

CL: cervical length; ART: assisted reproductive techniques; BMI: body mass index; Hx: History; GA: gestational age; PTB: preterm birth

Table 6: Variables affecting the final CL in women with initial CL 10-25 mm

Variable	Estimate	95% CI	P-value
Maternal Age	-0.33	-0.78 0.10	0.129
ART	5.69	-0.53 11.91	0.072
BMI	-0.01	-0.30 0.29	0.965
Parity	4.43	0.26 8.59	**0.037**
Smoking Status	-2.74	-8.31 2.82	0.327
Hx of cervical surgery	1.33	-6.93 9.60	0.747
GA at diagnosis	2.58	0.45 4.71	**0.018**
Sludge	-5.34	-12.53 1.84	0.141
Vanishing amniotic sludge	1.93	-6.02 9.88	0.628
Hx of spontaneous PTB	0.79	-15.61 17.21	0.922
Positive suprapubic pressure test	2.42	-3.89 8.75	0.444
Initial CL	1.52	0.90 2.14	< **0.001**

CL: cervical length; ART: assisted reproductive techniques; BMI: body mass index; Hx: History; GA: gestational age; PTB: preterm birth

Women with CL >10 mm only with progesterone

The majority of patients with initial CL 10-25 mm were treated only with progesterone, as their CL remained above 10 mm (46/68; 67.6%). The incidence of PTB <37 weeks, <34 weeks and <32weeks in this group was 13% (6/46), 2.1% (1/46) and 2.1% (1/46), respectively.

In order to identify factors associated with preterm birth before 37, 34, and 32 weeks of gestation in this group of women whose CL remained >10 mm only with progesterone, logistic regression was utilized. The independent variables examined were maternal age, ART, maternal BMI, parity,

smoking status, history of cervical surgeries, gestational age at diagnosis of short cervix, presence of sludge or vanishing amniotic sludge, history of spontaneous preterm birth, positive suprapubic pressure test and the initial cervical length measurement. Results were yield only for PTB <37 weeks (table 7), as there was only one case of PTB <34 and <32 weeks. The only significant association was between maternal age and PTB <37 weeks (OR: 1.82, 95% CI: 1.16 – 4.21; P: 0.05), while a trend with BMI was also noted (OR: 1.71, 95% CI: 1.15 – 4.46; P: 0.06). None of the other examined parameters was statistically significant.

Table 7: Variables affecting the rates of PTB<37 weeks in women whose CL remained >10 mm only with progesterone

Variable	OR	95% CI	P-value
Maternal Age	1.82	1.16 4.21	**0.050**
ART	0.01	0 4.21	0.284
BMI	1.71	1.15 4.46	0.061
Parity	4.29	0.05 6530.18	0.571
Smoking Status	0.00	NA	0.998
Hx of cervical surgery	0.00	NA	0.999
GA at diagnosis	1.13	0.04 43.50	0.935
Sludge	0.00	NA	0.998
Vanishing amniotic sludge	0.00	NA	0.999
Hx of spontaneous PTB	6948209924.77	NA	0.999
Positive suprapubic pressure test	4.64	0.00 998333.5	0.711
Initial CL	1.00	0.26 4.67	0.988

CL: cervical length; ART: assisted reproductive techniques; BMI: body mass index; Hx: History; GA: gestational age; PTB: preterm birth; NA: not applicable

Secondary Outcomes

Women with shortening CL ≤10 mm despite progesterone treatment

At the end of the assessment period, 22/68 (32.4%) women had further shortening of their CL to equal or less than 10 mm. The rate of PTB <37 weeks, <34 weeks and <32 weeks in this group was 41% (9/22), 13.6% (3/22) and 13.6% (3/22), respectively. All of these patients had additional intervention apart from progesterone; 14 had a cervical cerclage and 8 received an Arabin pessary, because they were beyond 28 weeks of pregnancy (n=6) or because cervical cerclage was contraindicated due to vaginal bleeding (n=2).

Regression analysis was utilized once again to examined the association of maternal age, ART, maternal BMI, parity, smoking status, history of cervical surgeries, gestational age at diagnosis of short cervix, presence of sludge or vanishing amniotic sludge, history of spontaneous preterm birth, positive suprapubic pressure test and the initial cervical length measurement with the shortening CL in this group of patients and none of them was significant. A small trend was noted for the parameters maternal age (OR: 1.16, 95% CI: 0.98 – 1.39; P: 0.09) and ART (OR: 1.30, 95% CI: 0.00 – 1.12; P: 0.09).

Similarly, logistic regression analysis on the contributing factors for PTB <37 weeks in this group of patients, showed no association with the examined parameters. Regression analysis for PTB <34 and <32 weeks could not be performed due to limited cases.

Women with shortening CL ≤10 mm despite progesterone treatment vs Women with CL >10 mm with progesterone

Lastly, we compared the two groups; those whose CL shortened to ≤10 mm despite progesterone to those whose CL remained >10 mm with progesterone only. We aimed to demonstrate any factors with predictive value on subsequent shortening despite progesterone. The only significant parameter was the initial CL (19.2, SD: 4.98 vs 22.4, SD: 2.07, P: 0.008). Results are shown in table 8.

Table 8: Comparison of women with shortening CL ≤10 mm despite progesterone treatment vs Women with CL >10 mm with progesterone

Variable	≤10mm (SD)	10-25mm (SD)	P-value
Maternal Age	33.9 (3.88)	32.7 (5.36)	0.276
ART	2/22 (9.1%)	6.46 (13 %)	0.943
BMI	24.8 (7.32)	24.2 (5.06)	0.679
Parity	7/22 (31.8%)	17/46 (37%)	0.885
Smoking Status	4/22 (18.1%)	5/46 (11%)	0.923
Hx of cervical surgery	3/22 (13.6%)	1/46 (2.2%)	0.184
GA at diagnosis	21.2 (1.13)	21.3 (0.89)	0.629
Sludge	3/22 (13.6%)	2/46 (4.33%)	0.380
Vanishing amniotic sludge	1/22 (4.5%)	2.46 (4.33)	0.976
Hx of spontaneous PTB	1/22 (4.5%)	1/46 (2.2%)	0.946
Positive suprapubic pressure test	4/22 (17.2%)	4/46 (8.7%)	0.463
Initial CL	19.2 (4.98)	22.4 (2.07)	**0.008**

ART: assisted reproductive techniques; BMI: body mass index; Hx: History; GA: gestational age; PTB: preterm birth; CL: cervical length

Results for all women with short cervix ≤25 mm

Linear regression analysis was once again employed to evaluate the same factors as modifiers of the change in cervical length (delta), expressed in absolute millimeters or as a percentage, and the final cervical length measurement (dependent variables) in the whole group of women with short cervix.

There was a marginal but non-significant association between the parity (3.47, 95% CI: -0.64 – 7.6; P: 0.09) and gestational age at diagnosis (1.96, 95% CI: -0.11 – 4.05; P: 0.06) with the delta change in CL (table 9). No effect of the examined variables on the percentage of CL change was seen (table 10). Finally, the ultimate CL measurement was affected by the initial CL measurement (1.19, 95% CI 0.67-1.72, P<0.001), with a non-significant trend with gestational age at diagnosis (2.11, 95% CI -0.01-4.24, P:0.05) (table 11).

The PTB rates for all different group of patients can be found in table 12.

Table 9: Variables affecting the delta of CL in women with short cervix ≤25mm

Variable	Estimate	95% CI	P-value
Maternal Age	-0.34	-0.79 0.10	0.132
ART	5.19	-1.14 11.52	0.105
BMI	-0.05	-0.35 0.24	0.712
Parity	3.47	-0.64 7.60	0.096
Smoking Status	-2.52	-8.18 3.13	0.374
Hx of cervical surgery	-0.90	-8.96 7.14	0.821
GA at diagnosis	1.96	-0.11 4.05	0.063
Sludge	-3.91	-11.02 3.19	0.274
Vanishing amniotic sludge	0.80	-7.23 8.84	0.842
Hx of spontaneous PTB	-0.48	-17.15 16.19	0.953
Positive suprapubic pressure test	0.03	-5.71 5.79	0.989

CL: cervical length; ART: assisted reproductive techniques; BMI: body mass index; Hx: History; GA: gestational age; PTB: preterm birth

Table 10: Variables affecting the percentage of CL change in women with short cervix ≤25mm

Variable	Estimate	95% CI	P-value
Maternal Age	-0.03	-0.14 0.07	0.520
ART	0.11	-1.41 1.64	0.883
BMI	-0.003	-0.07 0.07	0.918

Parity	0.01	-0.98 1.00	0.982
Smoking Status	-0.37	-1.74 0.99	0.586
Hx of cervical surgery	-0.31	-2.25 1.62	0.746
GA at diagnosis	-0.08	-0.59 0.41	0.726
Sludge	-0.25	-1.97 1.45	0.763
Vanishing amniotic sludge	-0.29	-2.23 1.64	0.759
Hx of spontaneous PTB	0.006	-4.01 4.02	0.997
Positive suprapubic pressure test	0.02	-1.36 1.41	0.975

CL: cervical length; ART: assisted reproductive techniques; BMI: body mass index; Hx: History; GA: gestational age; PTB: preterm birth

Table 11: Variables affecting the final CL in women with short cervix ≤25mm

Variable	Estimate	95% CI	P-value
Maternal Age	-0.35	-0.80 0.10	0.125
ART	5.31	-1.06 11.68	0.100
BMI	-0.03	-0.34 0.27	0.811
Parity	3.76	-0.44 7.97	0.078
Smoking Status	-2.73	-8.45 2.98	0.341
Hx of cervical surgery	-0.16	-8.5 8.16	0.968
GA at diagnosis	2.11	-0.01 4.24	**0.051**
Sludge	-4.50	-11.82 2.81	0.221
Vanishing amniotic sludge	1.07	-7.04 9.17	0.792
Hx of spontaneous PTB	0.02	-16.79 16.84	0.997

Positive suprapubic pressure test	0.96	-5.32 7.26	0.758
Initial CL	1.19	0.67 1.72	**<0.001**

CL: cervical length; ART: assisted reproductive techniques; BMI: body mass index; Hx: History; GA: gestational age; PTB: preterm birth

Table 12: PTB rates in the different study groups

PTB	***CL ≤25mm***	***CL 10-25mm***	***CL≥10mm only PRG***	***CL<10mm despite PRG***	***CL ≤10mm***	***Cervical Dilatation***
<37 weeks	26% (19/73)	22% (15/68)	13% (6/46)	41% (9/22)	80% (4/5)	66.6% (2/3)
<34 weeks	6.8% (5/73)	5.9% (4/68)	2.1% (1/46)	13.6% (3/22)	20% (1/5)	66.6% (2/3)
<32 weeks	6.8% (5/73)	5.9% (4/68)	2.1% (1/46)	13.6% (3/22)	20% (1/5)	66.6% (2/3)

PTB: preterm birth; CL: cervical length; PRG: progesterone

Women with painless cervical dilation who had an emergency cerclage

Three women were found to have painless cervical dilatation with bulging membranes. They were then admitted to hospital and commenced on the triple course of antibiotics as suggested by Oh et al. (ceftriaxone 1 gram IV every 24 hours; 2) clarithromycin 500 mg oral every 12 hours; and 3) metronidazole 500 mg IV every 8 hours) (171). One of them miscarried the day after. Since the other two did not deliver in the following 5 days, an emergency cerclage was performed. One delivered at 29 weeks and the other at 38 weeks. Due to limited number of cases no statistical analysis could be performed.

CHAPTER 4: DISCUSSION

The prevalence of short cervix (≤25 mm) in our study was 4.5%. Of note, our sample reflects the general population, as we included singleton pregnancies between 19 and 23^{+6} weeks of gestation, with or without risk factors for preterm birth. The reported incidence of short cervix (≤25 mm) in the 2nd trimester varies significantly from 0.45% up to 10%. This can be attributed to the numerous other factors affecting the cervical length, depending on the study population, like maternal characteristics, lifestyle, racial and socioeconomic factors, the different cut-offs for short cervix used in the literature, different gestational age window for the examination as well as technical aspects and the operator's competence when assessing the cervical length. Indeed, a metanalysis of 57 articles with data from 158,346 women examining the association of cervical length with population characteristics, showed that the CL was shorter in women from Africa and Asia, in those from low-income countries and with a lower body weight (264).

For example, Cho et al. reported a similar incidence of short cervix (3.8%) and their definition was CL ≤25 mm, between 20 and 24 weeks (81). On the other hand, Moroz et al. reported a higher incidence of 7.2% in the general population, probably because they included women from 21 - 28 weeks of gestation (83). Finally, a Chinese study of 25 328 asymptomatic women between 20 and 24 weeks showed that the prevalence of short cervix in their population was only 0.45% (265).

A large Dutch cohort study reported a lower prevalence of short cervix ≤30 mm (1.8%) and a high mean CL of 44.2 mm (mean CL in our population was 34 mm). However, they used only low risk women without history of spontaneous preterm birth, which could explain their findings. Furthermore, they reported a significant difference in mean cervical length between primary and tertiary care institutions ($P < 0.001$) and between secondary and tertiary care institutions ($P < 0.001$), indicating that training and different level of expertise can influence the incidence of short cervix in each study (266). Lastly, they included a relatively high number of women with advanced maternal age and European origin, maternal characteristics which have been found to contribute to a slightly longer mean cervical length (267).

The available interventions for women with short cervix are vaginal natural progesterone, cervical cerclage and Arabin pessary, which generally reduce the risk for PTB but do not eliminate it.

Most of the available studies are focused on the efficacy of progesterone, although there is no consensus on the cut-offs used. Fonseca et al. were the first to demonstrate that progesterone in women with short cervix <15 mm reduces the risk of PTB < 34 weeks by 44% (136). Similarly, Hassan et al. showed a 45% reduction in the rate of PTB < 28, 33 and 35 weeks in cases of short cervix 10-20 mm (137). Romero et al., showed a 38% reduction of PTB <33 weeks in women with cervical length ≤25 mm (134). Finally, from the initial study of Fonseca et al. it is evident that vaginal progesterone is less effective in very short cervical length. More specifically, progesterone reduces the rate of spontaneous PTB <34 weeks of gestation by only 25% in patients with a cervical length of 6-10 mm and by 14% in cervical length 1-5mm, but the effect size was 75% in those with a cervical length between 11-15 mm (136).

Cervical cerclage does not seem to be beneficial for all women with short cervix. An individual patient data (IPD) meta-analysis of four RCTs of cerclage versus expectant management in women with short cervix less than 25 mm and no other risk factor for spontaneous preterm birth showed no reduction in the incidence of PTB before 33 weeks (156). However, cervical cerclage is efficacious in preventing preterm birth, in singleton pregnancies, without history of preterm birth and a very short cervix, <10 mm (39.5% vs 58.0%) (158). In our population cerclage was performed for women with CL ≤10 mm either at enrolment or due to continuous shortening despite progesterone treatment. The rate of PTB < 34 weeks was 20% in women with initial CL ≤10 mm and 13.6% for those with shortening despite progesterone, which is significantly lower than other studies.

There is conflict evidence regarding the actual efficacy of Arabin pessary in preventing preterm delivery in singleton pregnancies. Although two randomized trials showed that the Arabin pessary in women with short cervix <25 mm reduced the risk of preterm delivery before 34 weeks (189) (190), two subsequent and larger randomized trials failed to show any superiority over progesterone (16% vs 4%) (193), or even expectant management (12% vs 11%) (191). There are no studies examining though the efficacy of Arabin pessary if placed during the third trimester of pregnancy. In our study, Arabin pessary was used in cases when cerclage was contraindicated, either due to advance gestational age or due to vaginal bleeding. In 6 cases of continuous cervical shortening to less than 10 mm beyond 28 weeks, Arabin pessary was used and we achieved

pregnancy prolongation from 3 to 11 weeks. The rate of PTB < 34 weeks in this latter group of women was 16% (1/6).

Our protocol included screening for PTB at mid-gestation by measuring the cervical length. Those with CL 10-25 mm were administered vaginal suppositories of natural progesterone 200mg and weekly follow up assessments. In cases of further shortening ≤10 mm, additional intervention was performed (either cerclage or Arabin pessary) depending on the gestational age at the diagnosis of very short cervix. In other words, if shortening ≤10 mm occurred before 28 weeks then cervical cerclage was performed, while after 28 weeks an Arabin pessary was placed. Women with initial CL ≤10 mm had cervical cerclage directly. With this approach, the PTB rates before 34 weeks in our population was 6.8%, which is much lower than the 26% mentioned in other studies where no specific management was used (81). It is worth mentioning that a similar protocol was proposed by ISUOG in 2022, after the initiation of our study (226).

Our protocol was firstly published as a letter to the editor in 2019 and our initial results showed that none of the five women who had cervical cerclage due to CL ≤10 mm despite being on progesterone delivered prematurely (160).

A study with similar management approach by Enakpene et al. showed that women who received cervical cerclage due to shortening of CL <10 mm despite progesterone compared to those who remained on progesterone treatment had a lower risk of PTB <35 weeks (38.2% vs 81.6%), and PTB <32 weeks (23.5% vs 78.9%) (159).

Akar et al. included women with cervical length 20-30 mm between 18 and 24 weeks of gestation. Those women were commenced on natural progesterone and if further shortening below 20 mm noted, then cervical cerclage was performed. There results showed that 10% of women had cerclage due to CL <20 mm and 56% of those had preterm delivery <34 weeks (268).

In our study the incidence of PTB < 34 weeks in this group of women with continuous CL shortening was much lower than the results of Enakpene et al. and Akar et al. (13.6% vs 38.2% and 56%) (159) (268). A possible explanation for this observation is that in our study we followed up the patients for a longer period and offered additional intervention for extreme short cervix <10 mm even in the third trimester. The maximum gestational age at which we offered an additional intervention was 32 weeks. On the other hand, Enakpene et al. mentioned that the upper gestational

age of extreme short cervix diagnosis and subsequent cerclage placement was 23.3 weeks (159). In the study of Akar et al., it is not clear up to which gestation cerclage was performed. Additionally, Akar et al. used the cutoff of 20 mm for performing cerclage but they failed to demonstrate a superiority over the cutoff of 10 mm (268). Lastly, we should acknowledge that the operator's training and competence may also affect the cerclage efficacy.

Despite extensive research on the efficacy of progesterone in women with short cervix, there is limited data regarding which women will not benefit from progesterone treatment and will eventually deliver prematurely.

A recent retrospective cohort study in 197 women with a short cervix treated with vaginal progesterone, demonstrated that a 20% reduction in CL on a subsequent ultrasound scan can predict PTB $\leq$ 34 and < 37 weeks (269).

Overall, our study suggests that in women with short cervix ($\leq$25 mm) in mid-trimester, the only factors associated with the final cervical length (CL) is the initial CL (1.19, 95% CI 0.67-1.72, P<0.001). Same effect between initial and final CL was also noted for the subgroup of women with CL 10-25 mm (1.52, 95% CI 0.90-2.14, P<0.001). Finally, the initial CL is the only significant characteristic differ between women who were treated only with progesterone versus those who required further intervention due to shortening of CL to less than 10mm. Therefore, we concluded that beyond the initial CL measurement, none of the other characteristics (demographics, ultrasonographic markers, obstetric history) can be used to predict which women will require additional interventions such as cerclage.

When assessing the different groups separately, we firstly observed that in women with intermediately short cervix; 10-25 mm, the final CL was influenced by parity, gestational age at diagnosis as well as the initial CL. More specifically, the chance of having shorter CL is about 4 times higher in multiparous women (4.43, 95% CI: 0.26-8.59, P: 0.03) and almost three-fold higher with more advance gestational age at diagnosis (2.58, 95% CI: 0.45-4.71, P: 0.01). In both cases, the results should be interpreted with caution due to the wide confidential internal (95% CI).

Secondly, in women whose CL remained above 10mm while using only vaginal progesterone, we demonstrated that the odds of PTB <37 weeks is almost twofold higher in cases of more advance maternal age (OR 1.82, 95% CI: 1.16-4.21, P:0.05).

Finally, maternal age and ART seem to slightly increase the risk of continuous shortening of the cervix despite progesterone, but those associations were not statistically significant in our study.

The EPPPIC study, a meta-analysis of individual participant data from randomised controlled trials included women with short cervix during pregnancy or history of preterm birth and examined if different forms of progestogens reduced the risk of PTB. They also examined different maternal risk factors as potential effect modifiers for the use of vaginal progesterone and 17-OHPC. The maternal characteristics examined were maternal age, BMI, smoking status, diabetes, hypertension and gestational age at randomization.

The authors suggested a greater risk of composite maternal complications with increasing BMI in the vaginal progesterone group (OR: 1.03, 95% CI: 1.02- 1.04, P<0·001) but no statistically significant association between BMI and PTB rates before 37, 34 and 28 weeks. Unexpectedly, they found a protective effect of smoking on PTB rates before 37 weeks (OR: 0.598, 95% CI: 0.39 -0.91, P: 0.018).

When comparing the results from the above study to ours, we found a small trend with BMI and PTB <37 weeks in women using only vaginal progesterone, although this effect was not significant (OR 1.71, 95% CI: 1.15-4.46, P: 0.06). Lastly, we could not correlate smoking status with any of our outcomes of interest.

It is clear that there is still no adequate way to predict which women treated with progesterone will deliver prematurely. The authors of a very recent prospective study of 228 pregnant women, published a few months ago, used cervical elastography to examine different parameters and their association with spontaneous preterm birth in women with short cervix treated with progesterone. They showed that after two weeks of progesterone treatment, women who had spontaneous PTB had significantly higher levels of elasticity contrast index (ECI), cervical hardness ratio, mean internal os strain (IOS), mean external os strain (EOS) (p = 0.0108, 0.0001, 0.016), and lower hardness ratio (p = 0.011) compared to those who had a full-term birth. They also found that that the IOS and EOS, were associated with a 3.38-fold and 2.29-fold increase in the risk of spontaneous PTB before 37 weeks (p = 0.032, 0.047, respectively). The authors concluded that the predictive value of a combined model including CL and cervical stiffness is higher that CL alone (270).

There is a general agreement that a follow up of women with short cervix is needed to improve our prediction regarding PTB. A recent retrospective cohort study in 2023, showed that for high-risk women prescribed vaginal progesterone therapy, either due to short cervix of history of PTB, serial measurement of the cervix at 16 and 19 weeks improves clinical ability to predict PTB from 61.7 to 70.2% (271). Another retrospective cohort study of women with singleton pregnancies with a short CL ≤ 25 mm between 16 and 22 weeks gestational age, showed that about 20% of them will have experienced significant shortening on follow up with dilatation or pregnancy loss before 24 weeks, despite treatment (progesterone, cerclage or pessary). Of note, they highlighted that the risk is higher, approaching 50%, in women with CL <15 mm (272).

In our population, 32.4% of patients with CL 10-25 mm had further shortening and required additional intervention. Our significantly lower rates of PTB overall could be explained from the fact that we followed up the patients for a longer period and offered additional intervention for extreme short cervix <10 mm even in the third trimester.

CHAPTER 5: CONCLUSIONS

Preterm birth is the leading cause of both neonatal and child mortality, in children less than 5 years old, accounting for around 16% of all deaths, and 35% of deaths among newborn babies (up to 28 days old) (9). Cervical length assessment remains the gold standard technique for preterm birth screening. The incidence of short cervix (≤25 mm) in the 2nd trimester varies from 0.45% up to 10% and this group of women contains 40% of deliveries before 34 weeks. (53).

In summary, current evidence suggest that vaginal progesterone in women with short cervix ≤25 mm in mid-trimester, and mainly in those with cervical length between 10-25 mm, reduces the risk for preterm birth <34 weeks by 40%. Cervical cerclage should be considered for women with cervical length less than 10 mm, for those with history of 3 or more previous preterm deliveries and/or second trimester pregnancy miscarriages and finally for women with painless cervical dilatation. There is limited data on Arabin pessary to conclude in any recommendations. Further research on the use of pessaries in the third trimester is needed, as the results from our study are promising.

Future research should focus on identifying which women will benefit from each intervention, based on several parameters, such as maternal characteristics, obstetric history and others. Only then we will be able to personalize the treatment and management of women with short cervix.

It is evident though from our study, that in women with short cervix in mid-trimester, frequent cervical length re-assessments until the third trimester of pregnancy are essential and beneficial in further reducing the risk of preterm birth. Even when the gestational age is too advanced to offer cervical cerclage, the pessary should be considered.

CHAPTER 6: ABSTRACT

Introduction: Preterm birth is the leading cause of both neonatal and child mortality. Preterm birth is a syndrome attributable to multiple pathological processes, including infection, vascular disorders, uterine overdistension, a decline in progesterone action, cervical disease, stress, uterine abnormalities, reduction in feto-maternal tolerance and short cervical length.

Short cervical length (CL) ≤25 mm in the mid gestation, measured by transvaginal ultrasound, is the strongest risk factor for preterm birth before 34 weeks. The therapeutic options for preventing preterm birth in such cases include progesterone, cervical cerclage and Arabin pessary. During the last years, authors and professional organizations around the world have recommended the use of vaginal progesterone in patients with a singleton gestation and a short cervix in the mid-trimester.

Despite the intensive research on the topic, a significant proportion of women with short cervix will deliver prematurely despite progesterone treatment. More specifically, a multiple trials and meta-analyses have shown that the administration of natural progesterone in women with cervical length ≤25 mm will reduce the rate of preterm birth by 35-45%. A possible explanation could lie on the different causes of preterm birth and apparently on the fact that progesterone is not effective in all the different cases.

Methodology: In order to investigate this hypothesis, we performed a prospective observational study involving women with CL ≤ 25 mm in the mid trimester. The aim of this study was to examine the effect of the progesterone administration in the CL and furthermore to investigate the effect of cervical shortening in the rate of preterm birth and their association with maternal characteristics and obstetric history. Furthermore, we aimed to assess if the following management protocol of women with short cervix can reduce further the incidence of PTB <37, 34 and 32 weeks of gestation.

All women who attended our unit for their routine anomaly scan, between 19^{+0} and 23^{+6} weeks, were offered a transvaginal scan to assess the cervical length. Those with CL between 25 and 10 mm received pessaries of natural progesterone 200mg transvaginally and were offered four consecutive weekly transvaginal scans for CL measurement. In women whose CL remains ≥10 mm no further actions were performed. Women with shortening cervix ≤10 mm were offered

placement of cervical cerclage or Arabin pessary, based on the gestational age. More specifically, if shortening cervix to ≤10 mm was noted before 28 weeks then cervical cerclage was performed, while for cases after 28 weeks, Arabin pessary was the treatment of choice.

Overall, 1675 singleton pregnancies, between 19-23^{+6} weeks, without symptoms of labour and without cerclage in situ were eligible for inclusion and had a transvaginal scan to assess the cervical length. 76 out of 1675 (4.5%) women had short cervix ≤25 mm and were included in our study.

For each patient, the following data were recorded: maternal age, weight and height, ethnicity, mode of conception, smoking status, previous term and spontaneous preterm deliveries, history of cervical surgeries, cervical length and gestational age at admission, presence of amniotic sludge or vanishing amniotic sludge, follow up cervical length measurements and finally the pregnancy outcome (gestational age at delivery, birthweight, sex, mode of delivery, pregnancy complications such GDM, PE, PPROM, admission to NICU).

We produced descriptive statistics for the preterm birth rates < 37, <34 and <32 weeks for the whole group (CL ≤25 mm, ≤10 mm, 10-25 mm treated only with progesterone and 10-25 mm with further shortening to ≤10 mm requiring additional intervention).

Linear regression analysis was employed to evaluate factors influencing the change in cervical length (delta), expressed in absolute millimeters or as a percentage, as well as the final cervical length measurement (dependent variables). The independent variables included maternal age, use of assisted reproductive technology (ART), maternal body mass index (BMI), parity, smoking status, history of cervical surgeries, gestational age at the diagnosis of short cervix, presence of sludge or vanishing amniotic sludge, history of spontaneous preterm birth, and the application of suprapubic pressure.

Logistic regression was utilized to identify factors associated with preterm birth before 37, 34, and 32 weeks of gestation. The same independent variables (maternal age, ART, maternal BMI, parity, smoking status, history of cervical surgeries, gestational age at diagnosis of short cervix, presence or resolution of sludge, history of spontaneous preterm birth, suprapubic pressure and additionally the initial cervical length measurement) were included in the model.

Results: The prevalence of short cervix ≤25 mm in our population was 4.5% (76/1675). Five women had initial CL ≤10 mm and had an ultrasound indicated cerclage, while three women had painless cervical dilatation with bulging membranes. The remaining 68 out of 1675 (4%) had a short cervix between 10 and 25 mm and were suggested to use 200 mg natural progesterone transvaginally every day up to 36 weeks of gestation. They were also offered four additional transvaginal scans every one to two weeks, to assess the rate of cervical shortening. At the end of the assessment period, 22/68 (32.4%) women had further shortening of their CL to equal or less than 10 mm. All of these patients had additional intervention apart from progesterone; 14 had a cervical cerclage and 8 received an Arabin pessary, because they were beyond 28 weeks of pregnancy (n=6) or because cervical cerclage was contraindicated due to vaginal bleeding (n=2).

In this study we demonstrated that with our protocol, which included close follow up of women with short cervical length ≤25 mm and additional intervention for shortening CL to ≤10 mm the overall incidence of PTB < 34 weeks was significantly lower than the one reported in the literature (6.8% vs 26%). Even in the subgroup of women with continuous CL shortening, the PTB rates were much lower than the results from two studies with similar protocol (13.6% vs 38.2% and 56%)

When it comes to the effect of the examined variables on the final cervical length, the only consistently significant association among all different categories of women, was observed with the initial cervical length. Additionally, advance maternal age seems to double the risk of PTB <37 weeks in women with CL 10-25 mm who were treated only with progesterone.

Conclusions: In conclusion, our protocol of follow up patients with short cervix managed with vaginal progesterone and further intervention in cases of CL ≤10 mm, result in significantly lower incidence of preterm birth.

CHAPTER 7: ABSTRACT IN GREEK

Τίτλος Διδακτορικής Διατριβής:

«Παρακολούθηση εγκύων γυναικών υπό αγωγή με προγεστερόνη λόγω κοντού τράχηλου»

Ευθυμίου Αθηνά

Εισαγωγή: Ο πρόωρος τοκετός αποτελεί την κύρια αιτία νεογνικής και παιδικής θνησιμότητας. Ο πρόωρος τοκετός αποτελεί ένα σύνδρομο που οφείλεται σε πολλαπλές παθολογικές διεργασίες όπως λοιμώξεις, αγγειακές νόσους, υπερδιάταση της μήτρας, μειωμένη προγεστερονική δράση, παθήσεις τραχήλου, στρες, και άλλα.

Ο κοντός τράχηλος, που παραδοσιακά ορίζεται με διακολπικό υπερηχογράφημα ως τράχηλος ≤25 mm κατά το δεύτερο τρίμηνο της εγκυμοσύνης, αποτελεί ένα σημαντικό παράγοντα κινδύνου για πρόωρο τοκετό και έχει αναδειχθεί ως ένας από τους ισχυρότερους προγνωστικούς δείκτες πρόωρου τοκετού <34 εβδομάδες κύησης σε ασυμπτωματικές γυναίκες με μονήρη ή δίδυμη κύηση. Οι θεραπευτικές επιλογές σε περίπτωση κοντού τραχήλου συμπεριλαμβάνουν την φυσική προγεστερόνη, περίδεση τραχήλου και τον πεσσό του Arabin.

Έχει αποδειχτεί από πολλές κλινικές δοκιμές ότι η χορήγηση φυσικής προγεστερόνης σε γυναίκες υψηλού κινδύνου μειώνει τον κίνδυνο πρόωρου τοκετού κατά 35-45%. Παρόλα αυτά, ένα σημαντικό ποσοστό γυναικών με κοντό τράχηλο, παρά την θεραπεία με προγεστερόνη γεννάνε πρόωρα. Αυτό πιθανών να οφείλεται στην πολυπαραγοντική αιτιολογία του πρόωρου τοκετού και έτσι η προγεστερόνη δεν είναι αποτελεσματική σε όλες τις περιπτώσεις. Είναι πιθανόν πως σε αυτές τις περιπτώσεις που ο τοκετός επέρχεται πρόωρα, η θεραπεία με προγεστερόνη αποτυγχάνει να αναστείλει την διαδικασία του τοκετού που περιλαμβάνει την αναδιαμόρφωση του τραχήλου μέσω της προοδευτικής εξάλειψης και τελικά διαστολής του.

Μεθοδολογία: Προκειμένου να διερευνήσουμε αυτή την υπόθεση, πραγματοποιήσαμε μια προοπτική μελέτη παρατήρησης με γυναίκες με μονήρεις κυήσεις με μήκος τραχήλου ≤25 mm κατά το δεύτερο τρίμηνο της εγκυμοσύνης. Σε γυναίκες με μήκος τραχήλου ≤10 mm πραγματοποιήθηκε περίδεση τραχήλου. Γυναίκες με μήκος τραχήλου μεταξύ 25 και 10 mm

έλαβαν κολπικά υπόθετα φυσικής προγεστερόνης 200mg και 4 συνεχόμενες εβδομαδιαίες μετρήσεις του μήκους του τραχήλου, με διακολπικό υπερηχογράφημα. Σε γυναίκες που το μήκος τραχήλου ελαττώθηκε περαιτέρω ≤10 mm πραγματοποιήθηκε περίδεση τραχήλου ή τοποθέτηση πεσσού Arabin, ανάλογα με την ηλικία κύησης, πριν τις 28 εβδομάδες έλαβαν περίδεση ενώ μετά τις 28 εβδομάδες τοποθετήθηκε πεσσός. Σε γυναίκες που το μήκος τραχήλου παραμείνει ≥10 mm, δε πραγματοποιήθηκε επιπλέον αγωγή ή επέμβαση.

Στόχοι της παρούσας μελέτης ήταν η εξέταση της επίδρασης του συγκεκριμένου πρωτοκόλλου παρακολούθησης των γυναικών με κοντό τράχηλο στην μείωση της επίπτωσης πρόωρου τοκετού. Παράλληλα εξετάστηκε η επίδραση της προγεστερόνης στο μήκος του τραχήλου της μήτρας καθώς και η συσχέτιση της ελάττωσης του μήκους τραχήλου με την εκδήλωση πρόωρου τοκετού αλλά και τα διάφορα χαρακτηριστικά της μητέρας (δημογραφικά, ιστορικό παραγόντων πρόωρου τοκετού).

Συνολικά, εξετάστηκαν 1675 γυναίκες κατά το υπερηχογράφημα ρουτίνας Β επιπέδου που πληρούσα τα κριτήρια ένταξης στην μελέτη, δηλαδή με μονήρεις κυήσεις, 19-23^{+6} εβδομάδες κύησης, χωρίς σημεία τοκετού ή περίδεση in situ. Από αυτές 4.5% (76/1675) είχαν κοντό τράχηλο ≤25 mm και εντάχθηκαν στην μελέτη. Κατά την εισαγωγή καταγράφηκαν τα εξής στοιχεία: ηλικία της μητέρας, εθνική καταγωγή της μητέρας, μέθοδος σύλληψης, βάρος μητέρας (στο 1ο τρίμηνο), ύψος μητέρας, το κάπνισμα κατά την εγκυμοσύνη, προηγούμενοι τελειόμηνοι τοκετοί, ιστορικό αυτόματου πρόωρου τοκετού, ιστορικό επεμβάσεων του τραχήλου, η ηλικία κύησης κατά την εισαγωγή στην μελέτη, μήκος τραχήλου, παρουσία αμνιακής λάσπης στο έσω τραχηλικό στόμιο, έκβαση της εγκυμοσύνης (ηλικία κύησης κατά τη γέννηση, βάρος γέννησης, φύλο εμβρύου, τρόπος τοκετού και ένδειξη, επιπλοκές κατά την κύηση (GDM, PE, PPROM, εισαγωγή στην NICU).

Κατά την στατιστική ανάλυση εξετάστηκαν ως περιγραφικά στοιχεία τα ποσοστά πρόωρου τοκετού <37, <34 και <32 εβδομάδες για όλες τις ομάδες γυναικών (CL ≤25 mm, ≤10 mm, 10-25 mm μόνο με προγεστερόνη και 10-25 mm όπου ακολούθησε ελάττωση του μήκους ≤10 mm). Επιπλέον χρησιμοποιήθηκε ανάλυση λογιστικής παλινδρόμησης (Logistic regression) για να εξεταστούν πως διάφοροι παράγοντες (ηλικία μητέρας, μέθοδος σύλληψης, BMI προηγούμενοι τοκετοί, κάπνισμα, ιστορικό επεμβάσεων τραχήλου, ηλικία κύησης κατά την εισαγωγή, ύπαρξη αμνιακής λάσπης, αρχικό μήκος τραχήλου) επηρέασαν την πιθανότητα πρόωρου τοκετού πριν τις

37, 34 και 32 εβδομάδες. Τέλος με τη χρήση ανάλυσης γραμμικής παλινδρόμησης (Linear regression) εξετάστηκαν παράγοντες που επηρέασαν τις μεταβολές του μήκους τραχήλου ηλικία μητέρας, μέθοδος σύλληψης, BMI προηγούμενοι τοκετοί, κάπνισμα, ιστορικό επεμβάσεων τραχήλου, ηλικία κύησης κατά την εισαγωγή, ύπαρξη αμνιακής λάσπης), εκφραζόμενο σε χιλιοστά και ποσοστό.

Αποτελέσματα: Ο επιπολασμός του κοντού τραχήλου ≤25 mm στον πληθυσμό μας ήταν 4.5% (76/1675). Πέντε γυναίκες είχαν αρχικό CL ≤10 mm και έλαβαν απευθείας περίδεση τραχήλου, ενώ τρεις είχαν ανώδυνη διαστολή τραχήλου με προβολή θυλακίου. Οι υπόλοιπες 68/1675 (4%) είχαν μήκος τραχήλου μεταξύ 10 με 25 mm και έλαβαν κολπικά υπόθετα προγεστερόνης 200 mg καθημερινά έως τις 36 εβδομάδες. Επιπλέον, τους προσφέρθηκε επανέλεγχος ανά μία με δύο εβδομάδες, για αξιολόγηση περαιτέρω μείωσης του μήκους του τραχήλου. Στο τέλος της περιόδου αξιολόγησης, 22/68 (32.4%) είχαν περαιτέρω μείωση του μήκους του τραχήλου ≤10 mm και έλαβαν κάποια επιπλέον παρέμβαση. Συγκεκριμένα, 14 έλαβαν περίδεση τραχήλου και σε 8 έγινε τοποθέτηση πεσσού Arabin, γιατί ήταν μετά τις 28 εβδομάδες κύησης (n=6) είτε λόγω αντένδειξης της περίδεσης τραχήλου λόγω κολπικής αιμόρροιας (n=2).

Στη μελέτη αυτή, διαπιστώθηκε ότι με το συγκεκριμένο πρωτόκολλο παρακολούθησης γυναικών με κοντό τράχηλο και την περαιτέρω παρέμβαση σε περίπτωση μείωσης του μήκους τραχήλου ≤10 mm, το ποσοστό πρόωρου τοκετού πριν τις 34 εβδομάδες ήταν σημαντικό μικρότερο από το αναφερόμενο στην βιβλιογραφία (6.8% vs 26%). Ακόμη και στην υποομάδα των γυναικών με συνεχή μείωση του τραχήλου ≤10 mm τα ποσοστά πρόωρου τοκετού ήταν σημαντικά μικρότερα από δύο μελέτες με συναφές πρωτόκολλο και διαχείριση των ασθενών αυτών (13.6% vs 38.2% και 56%).

Όσο αφορά την επίδραση των διαφόρων παραγόντων στο τελικό μήκος τραχήλου, ο μόνος στατιστικά σημαντικός παράγοντας, σε όλες τις υποκατηγορίες γυναικών ήταν το αρχικό μήκος τραχήλου. Επιπλέον, η προχωρημένη ηλικία μητέρας φαίνεται να διπλασιάζει την πιθανότητα πρόωρου τοκετού πριν τις 37 εβδομάδες στην ομάδα των γυναικών με τράχηλο 10-25 mm που έλαβαν μόνο αγωγή με προγεστερόνη.

Συμπεράσματα: Συμπερασματικά, το προτεινόμενο πρωτόκολλο παρακολούθησης γυναικών με κοντό τράχηλο, με την συχνότερη παρακολούθηση και την επιπλέον παρέμβαση σε περίπτωση

ελάττωσης του μήκους τραχήλου ≤10 mm, οδήγησε σε σημαντικά χαμηλότερα ποσοστά πρόωρου τοκετού.

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