New therapeutic strategies in short cervical length: Arabin pessaries

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ABSTRACT

The progress made in the field of ultrasound in the diagnosis of threatened preterm delivery in the case of short cervical length (SCL) are unfortunately not paid advances in therapy, since actual treatment options are confined to the use of progesterone , micronized vaginally or orally, of antibiotics and indomethacin, which are also used vaginally or orally, of nifedipine, used orally, until reaching to promising use of lactoferrin or lactoglobulin, vaginally, or to the packaging of a surgical cerclage procedure now almost obsolete in most European countries because of the many complications that occurred. New perspectives seems to offer the application of silicone vaginal devices specifically designed to modify the cervical plasticity and reduce, with very striking mechanism as will be seen, the possibility of occurrence of segmental uterine contractions; for such features to "cervical support" such devices are called pessaries, whose function is mistakenly equated with classic surgical cerclage, invasive method, bloody, costly and much less effective in preventing preterm birth. Our experience is based on the application of 32 vaginal devices in the period October 2012 -May 2014; of these 28 (p=87.5%) were placed in singleton pregnancies and 4 (12.5%) in twin pregnancies (3 bigemine pregnancies 1 and triplets). In 22/32 pregnant women (p=69%) the application of the pessary has been associated with the use of a medicament, as we shall see later in the specification, while in 10/32 (p=31%) was not associated with any medication. Surprisingly, the outcome of these 2 latter groups did not show substantial changes, so as to lead us to believe that the action of vaginal device is the real creator in obtained benefits. Last notation must be made on gestational period of positioning pessary that in the vast majority of cases occurred between 22 and 28 weeks (n=29, p=90%), while in only 3 cases (p=10%) the time of insertion was greater than 28 weeks. Almost all pregnant women had when inserting a BMI> 25 (n=30, p=94%), while only 2 were ≤25.

Keywords: Arabin pessary, Flabby Cervix, Short Cervix, Preterm Delivery, Premature Rupture Of Membranes, Non-invasive cerclage

SOMMARIO

Ai progressi compiuti in campo ecografico nella diagnosi di minaccia di parto pretermine (MPP) nei casi di short cervical lenght (SCL) non sono purtroppo corrisposti progressi in campo terapeutico, dal momento che le opzioni terapeutiche ad oggi applicate sono confinate all'utilizzo di progesterone, micronizzato per via vaginale o per via orale, di antibiotici e di indometacina, anch'essi utilizzati per via vaginale o per via orale, alla nifedipina, utilizzata per via orale, al promettente utilizzo di lattoferrina o lattoglobulina, per via vaginale, e/o al confezionamento di un cerchiaggio chirurgico, procedura ormai quasi in disuso nella stragrande maggioranza dei Paesi Europei a causa delle numerose complicanze riportate. Nuove prospettive in tal senso sembra offrire l'applicazione di dispositivi vaginali in silicone specificamente progettati per modificare la plasticità cervicale e ridurre, con meccanismo molto suggestivo come si vedrà, la possibilità di insorgenza di contrazioni segmentarie uterine; per tali funzioni di "supporto cervicale" tali dispositivi sono denominati pessari, la cui funzione è erroneamente assimilata al classico cerchiaggio chirurgico, metodica invasiva, cruenta, costosa e molto meno efficace nel prevenire il parto pretermine. La nostra esperienza personale si basa sull'applicazione di 32 dispositivi vaginali nel periodo ottobre 2012- maggio 2014; di questi 28 (p=87.5%) sono stati posizionati in gravidanze singole e 4 (12.5%) in gravidanze gemellari (3 gravidanze bigemine e 1 trigemina). In 22/32 gravide (p=69%) l'applicazione del pessario è stato associato all'utilizzo di un medicamento, come poi vedremo nella specifica, mentre in 10/32 (p=31%) non è stato associato alcun farmaco. Sorprendentemente l'outcome tra questi 2 ultimi gruppi non ha mostrato sostanziali variazioni, tanto da indurci a ritenere che l'esclusiva azione del dispositivo vaginale sia il reale artefice dei benefici ottenuti. Ultima notazione va fatta sull'epoca gravidica di posizionamento del pessario che nella stragrande maggioranza di casi è avvenuto tra la 22ª e la 28ª settimana (n=29 p=90%), mentre in soli 3 casi (p=10%) l'epoca di inserimento è stata maggiore delle 28 settimane. Quasi tutte le gravide presentavano all'atto dell'inserimento un BMI>25 (n=30 p=94%), mentre solo 2 erano ≤25.

INTRODUCTION

The threatened preterm delivery, or SPB (Spontaneous Preterm Birth), is a syndromic disease that recognizes a variety of causes. Almost 100 years the pessaries have been successfully used in genital prolapse treatment[4,6,8,42]. Different types of pessary have succeeded over the years, from the classic ring pessaries (Figure 1) to Donut pessaries (Figure 2), by Hodge pessary (Figure 3) to Jorde-Hamann pessaries (Figure 4), all used in the symptomatic treatment of genital prolapse and therefore not very considered by gynecologists with higher surgical inclinations that saw, and in some cases can still be seen today, in the packaging of surgical cervical cerclage the only successful attempt to oppose the SPB, regardless of the many failures and multiple complications obtained.

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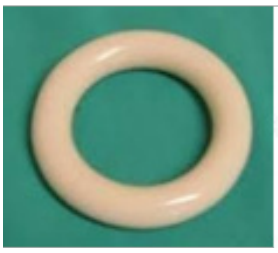


Figure 1.
Ring Pessary.

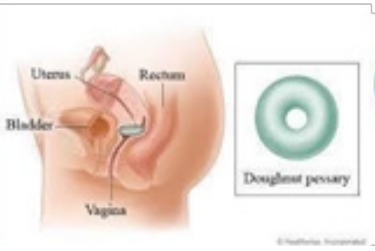


Figure 2.
Donut Pessary

Figure 3.
Hodge Pessary

Figure 4.
Jorde-Hamann Pessary

In 1979 the german gynecologist Hans Arabin devised a flexible silicon device which is well suited to the natural shape of the vaginal fornices, with a circular central space to permit the entire cervix to be included and therefore supported and angulated in a position more suited to the physiological hereinafter of pregnancy. Just this latter point has been to intuition of dr. Arabin, which assumed that he must not forcibly close the cervical canal, the principle on which is based the surgical cerclage, but restore to the cervix the natural angle with the uterine body to ensure that it interrupted the inevitable evolution towards the onset of contractions that ultimately led to preterm delivery. As indeed it himself wrote in his publication "Pessartherapie" (Gynäkologie – ed. Thieme 1991, 263-276), "..the body of the uterus and cervix are 2 entities histologically and functionally different, so different that they can be considered as two bodies which form part of the same apparatus; must be maintained an angulation between 30 and 45 degrees, a prerequisite to the physiological continuation of the pregnancy. In the moment in which this angle is lost, resulting in straightening of the cervix with respect to the body, it triggers a process that ultimately leads to the onset of uterine contractions, almost like a trigger of a mine that is activated when fit together 2 ends normally separate [..]".Therefore the Arabin pessary was designed with the intent not only to hold and squeeze the cervix, but especially to tilt the cervix and rotate it slightly toward the sacred (Figure 5).

Only with the advent of transvaginal sonography has been documented effectively reducing or at least stabilizing the cervical funneling after placement of Arabin pessary in selected patients[2,10,25,26,27,29,30,33,37,39,42] (Figure 6).

There are several hypotheses regarding Arabin pessary purpose in the prevention of premature rupture of membranes (PROM) and then ultimately prevent the spontaneous preterm birth (SPB)[4,7,8,9,11,12,13,14,20,25,28,40].

The evidence which is the starting, documented by studies performed with transvaginal ultrasound (TVS) and with magnetic resonance (RMI), is that the Arabin pessary restores the normal utero-cervical angle, which so it remains until the device stand in place.

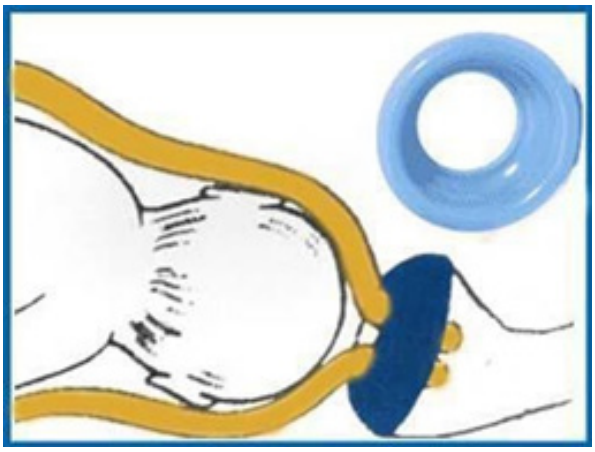


Figure 5.
Arabin pessary and its positioning.

The first consequence of this modification is that it removes the direct pressure of amniotic fluid on the membranes covering the internal uterine orifice (IUO), preventing further cervical dilation triggered by the dissociation between amnion and chorion especially when pregnant is in the upright position [2,3,4,7,8,9,11,12,13,14,16]. It 'also been postulated that genetically determined factors make the amniotic membranes more susceptible to mechanical stress or infection, for which the effect of the device would suffer from subjective factors not quantifiable. Another interesting hypothesis, advanced by N. Becher in 2009 and taken up by DC Lee in 2011 [18,19], is that the device prevents the mobilization of so-called "mucous plug", much studied issue actually, which seems play a very important role in the maintenance of pregnancy because, due to its unique protein structure and

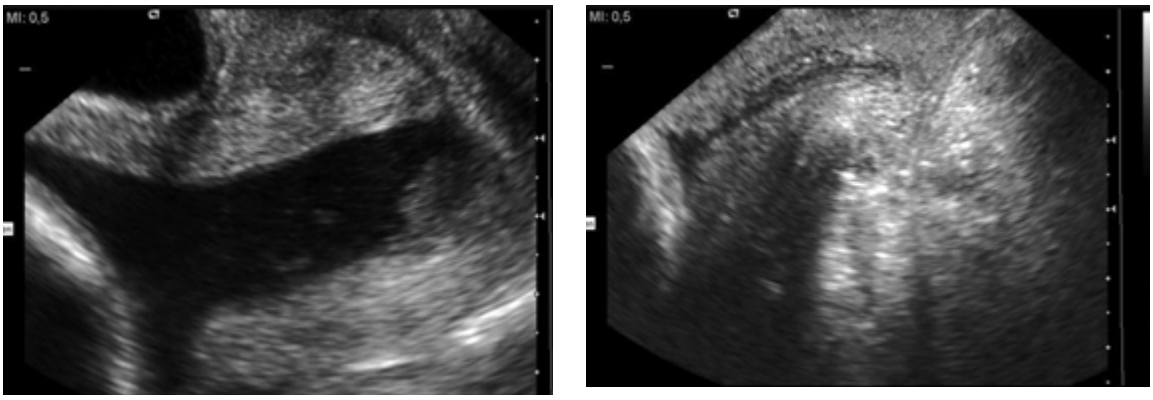
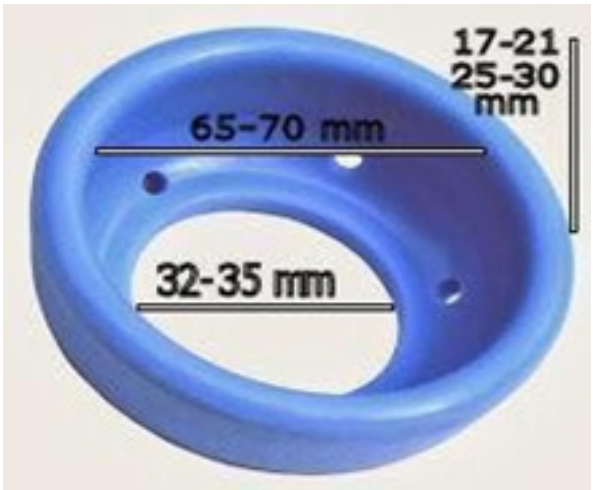


Figure 6.
Large cervical funneling (U-shaped) reduced by positioning of Arabin pessary

immunological capacity would responsible for protecting the uterine cavity by inflammatory and ascending infectious liables for initiation of preterm labor or PROM; it is well known that expulsion of the mucous plug a few hours preceding the onset of spontaneous labor in pregnant women at term. In a study of 2013, Cannie MM demonstrated with MRI aid that more time stationing the pessary and more greater the chances that the cervix will generates focal thickening and edema phenomena, which could complicate the dynamic changes of the cervix during labor[15] . For those headings it is advisable to establish the cut-off tolerance average is 15 weeks, reserving to periodic checks of local conditions any greater permanence. In February of 2013 A. Baschat (pers. com.) has suggested that the pessary may decrease so-called Ferguson reflection, positive feedback that triggers when the cervix or vaginal walls pressure increases inducing production of oxytocin by the hypothalamic-pituitary axle[41].

Whatever the actual mechanism of pessary action, it is very important to evaluated the correct size to be placed. There are several sizes of Arabin pessary, and it's important to stick to pragmatic criteria in the choice of device that may be specifically adapted to peculiar characteristics of each specific patient. The latest generation devices are made in soft silicone with multiple circumferential perforations that allow secretions outflow that accumulates in the fornices, but the factor that distinguishes them is exclusively the size. The proximal hole diameter varies from 32 to 35 mm, while distal hole diameter goes from 65 to 70 mm; the height can be of 17-21-25 and 30 mm. In general a size of 32 mm is used when the pessary is applied during the first trimester of singleton pregnancy or after surgical conization or even in the second and third trimesters without significant cervical funneling (Y-shaped)[9,16,25,42] .



In pregnants with large and edematous cervix or wide cervical funneling (U-shaped or V-shaped) is preferred devices with inner hole of 35 mm in order to avoid increases in focal pressure on the membranes and the release of prostaglandins during placement. Moreover, in physically smaller woman or nulliparous is advisable an outer diameter of 65 mm, to reserving 70 mm in constitutionally large patients or in multiparous. About the height of the Arabin pessary is advisable to use the small sizes of 17-21 mm in singleton pregnancies, the 25 mm in pregnants with uterine distension (multiple pregnancies and/or polyhydramnios), and finally the 30 mm in patients with uterine prolapse during pregnancy (Table I). It's guessed that greater is device diameter and the more frequently the pregnant may complain of discomfort, due to distension of fornices operated from normal secretions which inevitably accumulate behind the pessary; this problem has been largely overcome to use of drilled devices[1,7,11,12,13,14,20,25,28,30,31,32,34,42].

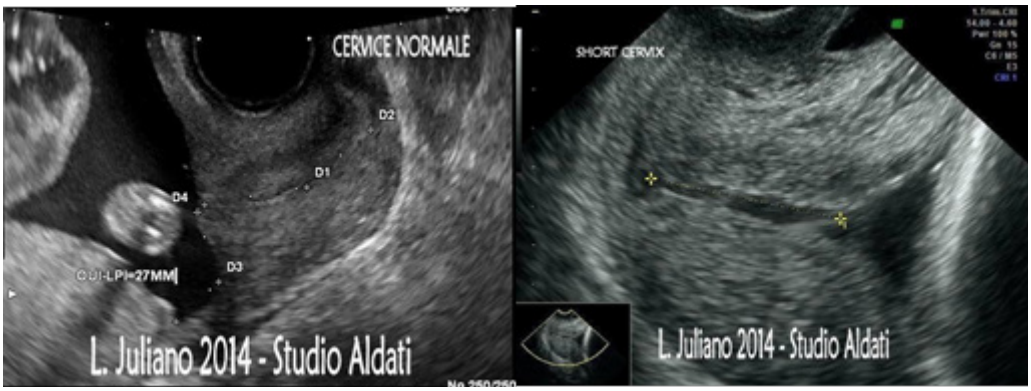
Table I.
Sizes of Arabin pessaries

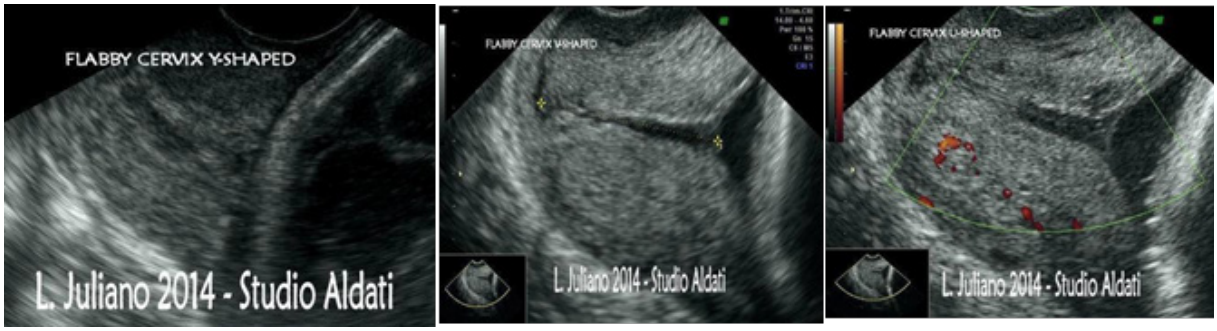
	Proximal hole diameter		Distal hole diameter		Height (mm)			
Clinical state	32 mm	35 mm	65 mm	70 mm	17	21	25	30
Short or Flabby cervix at II trimester ≤ 25 mm								
Singleton Pregnancy								
o With or without Y-shaped funneling								
Nulliparous	o		o			o		
Pluriparous	o			o		o		
o With V- or U-shaped funneling (Flabby cervix)								
Nulliparous		o	o			o		
Pluriparous		o		o		o		
Twins								
o Without funneling								
Nulliparous	o		o				o	
Pluriparous	o			o			o	
o With V- or U-shaped funneling (Flabby cervix)								
Nulliparous		o	o				o	
Pluriparous		o		o			o	
Short or Flabby cervix at I trimester or after surgical conization								
o Singleton Pregnancy								
Nulliparous	o		o		o			
Pluriparous	o			o	o			
o Twins								
Nulliparous	o		o			o		
Pluriparous	o			o		o		
o With genital prolapse								
Nulliparous		o	o					o
Pluriparous		o		o				o

Some considerations should be taken prior to placement of vaginal device, regardless of type and size used. We have to carefully evaluate the cervical characteristics by transvaginal ultrasonography (TVS).[10,14,16,22,23,26,29,30,37,39,42]

The cut-off of 25 mm so far considered in the definition of short cervix should not be the only discriminating; this parameter might not be to treatment if just isolated finding in gestational age ≥32 weeks in nulliparous with singleton pregnancy, while it might be an adequate criterion when combined with funnelling cervix and/or cervical hypoechoic pattern. In our experience, lowest is cervical echogenicity and worst is the prognosis in terms of progression to generalized cervical incompetence that led to the triggering of preterm labor for activation of Ferguson reflection. The reasons should be sought in the histological characteristics of the cervix, very poor in muscle fibers which, due to prostaglandins release secondly oxytocic effect of Ferguson reflection, loosen increasing distance between them and making the ultrasound cervical pattern objectively less compact, just hypoechoic. So rather than using short cervix as a marker, we propose to introduce the term of flabby cervix to define by ultrasound (TVS) a cervical length ≤ 25 mm with hypoechoic parenchymal pattern and funneling (Y, U or V-shaped).

Essential aspect to consider prior to placement of the pessary is the lack of previous vaginal infections by performing a vaginal swab, which excludes the presence of Chlamydia, β-hemolytic Streptococcus, Mycoplasma spp and Candida albicans, Gardnerella and Trichomonas. The secretions which inevitably accumulates in fornices where is placed the Arabin pessary, if copious may creates focal increases of pressure responsible for the Ferguson reflection, with increased risk of amnionitis and PROM[1,2,3,7,14,17,24,25,34,38]. To complete prevention against vaginal infections, the pessary should be covered with antibacterial





cream before insertion, also for lubricant effects that facilitates the positioning and minimizes the discomfort complained of by pregnant. There is no need to use anesthetics or analgesics[42], partly because the sensations reported by all patients at approximately 30 minutes from the introduction of the device was a subjective "sense of relief". In any case it was decided to recommend the resting after the introduction of Arabin pessary, even in cases of marked flabby cervix.

MATERIALS AND METHODS

Our experience is based on the application of 32 Arabin pessary of ASQ type in the period October 2012 -May 2014. In 28/32 cases (p=87.5%) they were singleton pregnancies and in 4/32 cases (p=12.5%) were twins pregnancies (3 bigemine pregnancies and 1 triplets). Only in 3 patients (p=90.6%) was the first pregnancy (1 triplets, 1 twins and 1 singleton pregnancy), while the others were all multiparous.

Regardless the number of fetuses, in all pregnancies the pessary has been positioned between the 22nd and 23rd week due to an apparent shortening of the cervix measured with TVS (average length 23 mm); in 3 cases the shortening was an isolated finding (short cervix) while in the remaining cases were associated sonographic signs of flabby cervix (funnelling and hypoechoic stromal).

In the remaining singleton pregnancies (28/32 cases, p=87.5%) the device was inserted between the 22nd and 28th weeks on the basis of ultrasound flabby cervix (short cervix, funnelling and hypoechoic stromal); only in 4/28 cases (p=14.3%) was considered discriminating the presence of only short cervix. In 26/32 cases (p=81%) the pessary was removed between 36th and 37th weeks with spontaneous delivery at 38 weeks (7/26 cases, p=27%), at 39th weeks (12/26 cases p=46%) and at 40th weeks or over (7/26 cases, p=27%); in 2/7 patients who delivered spontaneously were twins pregnancies.

In remaining 5/32 cases (p=16%) the device was removed at 34 weeks with cesarean delivery for the 36th to 37th weeks in twins pregnancies in previous cesarean sections (2/5 cases, p =40%) or multiple previous cesarean sections in 3/5 cases (p=60%); in 1/32 case (p=3%) the pessary was removed after cesarean section for forgetfulness. In 2/26 cases (p=7,6%) the pessary was not removed despite premature rupture of membranes at 28 and 31 weeks, but until the complete removal at the term (37 and 38 weeks), we performed weekly vaginal swab, blood count and serum PCR to

exclude corionamnionitis onset.

In 22/32 pregnant women (p=69%) application of pessary has been associated with the use of (GROUP A):

- Progesterone [21,22,23,24,34,40], micronized vaginally or orally, 400 mg bid in 18/22 patients (p=82%);
- Magnesium [24,40], orally 400 mg m.i.d. in 18/22 patients (p=82%);
- Nifedipine[21,23], orally 20 mg b.i.d. in 4/22 patients (p=18%);
- Lactoferrine o Lactoglobuline[40,42], vaginally 300 mg m.i.d. in 4/22 patients (p=18%).

In 10/32 cases (p=31%) was not associated any medications (GROUP B).

So let's see how to insert and remove the Arabin pessary.

The Arabin pessary, covered with antibacterial cream on the surface that will contact with fornices, is squeezed between thumb and forefinger with the larger hole facing up and plugged intake vagina with the major axis parallel to the major axis of the vagina. Within the vagina the device opens and with 2 fingers gently pushing towards fornices and place it so that cervix is completely included in the smaller hole. Once obtained the positioning, remains the most important act, or give the right angle to the cervix in order to maintain the cervix-uterine angle at a value comprised between 30° and 45°[16,42]. To achieve this objective to push with the index finger on the front edge of the rear toward the sacral bone. Immediately after insertion, the patient is asked to walk for a few minutes and to report any unpleasant sensations; the presence of a prolonged and worsening sense of discomfort should make us reconsider the size or type of device placed[9,16,42].

Usually the device has been removed around the 37th week, except the onset of contractions or PROM before that period; in our series in 2 cases the pessary was not removed despite premature rupture of membranes at 28 and

31 weeks, but until the complete removal at the term (37 and 38 weeks), we performed weekly vaginal swab, blood count and serum PCR to exclude corionamnionitis onset.

Of course the use of the pessary should not be extended to all women with flabby cervix, but there are some conditions that contraindicate the use of the pessary.

Should be considered absolute contraindications[9,14,36,42]:

- presence of major fetal malformations incompatible with life;
- corionamnionitis known or suspected;
- protrusion of the amniotic membranes over an external uterine gaping orifice;
- valid and rhythmic uterine contractions;
- bleeding of uterine origin;
- placenta praevia major;
- previous cervical conization with the remaining cervix of <30%;
- premature rupture of membranes;
- gestational age <22 or> 30 weeks.

Instead should be considered relative contraindications[9,14,36,42]:

- marginal or partial placenta praevia;
- rupture of the membranes with small eccentric outflow of amniotic fluid and no sign of amnionitis;
- further uterine malformations, such as a uterus bicolle in which the positioning of the pessary may be very problematic;
- previous cervical conization with residual cervix of ≤ 50%;
- gestational age between 30 and 32 week.

RESULTS

We've applicated 32 Arabin pessary of ASQ type in the period October 2012-May 2014.

In 28/32 cases (p=87.5%) they were singleton pregnancies and in 4/32 cases (p=12.5%) were twins pregnancies (3 bigemine pregnancies and 1 triplets).

Only in 3 patients (p=90.6%) was the first pregnancy (1 triplets, 1 twins and 1 singleton pregnancy), while the others were all multiparous.

All patients showed flabby cervix or simply short cervix, but all of them have reached the end of pregnancy despite initial expectations. In 26/32 cases (p=81%) the pessary was removed between 36th and 37th weeks with spontaneous delivery at 38 weeks (7/26 cases, p=27%), at 39th weeks (12/26 cases p=46%) and at 40th weeks or over (7/26 cases, p=27%); in 2/7 patients who delivered spontaneously were twins pregnancies. In remaining 5/32 cases (p=16%) the device was removed at 34 weeks with cesarean

delivery for the 36th to 37th weeks in twins pregnancies in previous cesarean sections (2/5 cases, p =40%) or multiple previous cesarean sections in 3/5 cases (p=60%); in 1/32 case (p=3%) the pessary was removed after cesarean section for forgetfulness. In 2/26 cases (p=7,6%) the pessary was not removed despite premature rupture of membranes at 28 and 31 weeks, but until the complete removal at the term (37 and 38 weeks), we performed weekly vaginal swab, blood count and serum PCR to exclude corionamnionitis onset.

We already said that in 22/32 pregnant women (p=69%) application of pessary has been associated with a medication (GROUP A), while in 10/32 cases (p=31%) was associated anything (GROUP B).

Surprisingly, the outcome of these 2 latter groups did not show substantial changes, so as to lead us to believe that the exclusive action of the vaginal device is the real creator of obtained benefits.

Last notation should be made on the weight of pregnant women at insertion; the majority of pregnant women showed when inserting a BMI> 25 (n =30, p =94%) while only 2 were ≤25, which account for the increased risk of preterm delivery in pregnant women are overweight.

All the foregoing is however a speech in constant evolution; thus, for example, as squeezing and angling the cervix prevents the mobilization of the cervical mucus, whose key role in the stabilization of collagen tissue and extracellular matrix by the hydration of the fibers is still today under study, both through the new techniques of PCR molecular biology both by promising transvaginal sonoelastography.

DISCUSSION

While as claimed by anglosaxon authors "to do nothing is not an option any longer" [42], the American College of Obstetricians and Gynecologists (ACOG) underlines the risk of unnecessary interventions in single pregnancies without a history of childbirth spontaneous preterm.

In one of the most important study published by Goya in Lancet on 2012[14], a multicenter study on the use of the pessary in women with short cervical length selected (<25mm) aged between 18 and 22 weeks showed that the use of the pessary increases the pregnancy rate come to term with respect to control. In this study, 385 women were recruited: 192 was placed an Arabin pessary, while 193 were adopted alternative therapeutic measures. Were excluded women with a higher fetal malformation, those with actual uterine contractions, vaginal bleeding, and premature rupture of membranes, placenta previa, or a history of conization or cerclage in situ. In the group with pessary has had the lowest rate of births before 34 weeks (6% vs27%), before the 37th week (22% vs 59%) and before the 28th week (2% vs 8%).

Of course the use of the pessary should not be extended to all women with flabby cervix, but there are some conditions that contraindicate the use of the pessary, conditions, as already mentioned, unanimously shared by the various authors consulted in indexed publications.

As mentioned in our experience the sensation reported by all patients at approximately 30 minutes from the introduction of the Arabin pessary has been enjoyable and a subjective "sense of relief".

The Arabin pessary is officially indicated in all cases of preterm delivery threatened, certified registered with the

Ministries of Health in all countries of the European Union (Identification number: MED/ CERT0482 EN ISO13485

Council directive 93/42/EEC reg. medical devices), in Scandinavia, the Russian Federation, Indonesia and the United Arab Emirates[9,14,36,42].

It's necessary to confirm the correct positioning of the pessary after insertion through a clinical and sonographic examination. In all cases of expulsion of device, operator independent, the pessary can be repositioned; a further expulsion should lead one to consider a change of measure or type of pessary.

In general, the pessary should be kept in place for up to 37 weeks if there are no indications for early removal. The patient will be asked to notify the obstetrician in case of discomfort, contractions or vaginal bleeding.

The pessary should always be considered a foreign body in the vagina, so it is important to carefully observe periodic prophylactic hygienic washes and ovules antiseptic of chlorhexidine.

As regards the combination of tocolitic and/ or colpotonic therapies, has already been said that in our report 69% of cases has been associated with use of progesterone, magnesium, nifedipine and lactoferrin, while in 31% of cases was not associated with any medications.

In case of hospitalization prior to the planned removal of the pessary, you should always inform the staff of the structure in order to allow the inevitable premature removal if deemed necessary[9,14,36,42].

All the foregoing is however a speech in constant evolution; new techniques of PCR molecular biology and promising transvaginal sonoelastography will certainly contribute to the development and refinement of new knowledges for the prevention of preterm birth.

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