Clinical evaluation and risk assessment of the pessaries of Dr. Arabin GmbH & Co KG, A. Herrhausen Str. 44 58455 Witten based on current literature, only CE-certified products /product families

according to ISO 13485-2016 § 7.2,
products which are now in a process of design and development (see § 7.3) are excluded

1. Overview

A) Gynecological pessaries, CE certified

Product family A-a Pessaries for pelvic organ prolapse grade 1-2 and/or stress incontinence

1. Thick ring
2. Hodge Pessary (with aluminum insert for bending)
3. Shell or sieve shell pessary
4. Urethral shells pessary
5. Urethra pessary,
6. Ring pessary

Product Family A-b) Pessaries for pelvic organ prolapse Grade 2-3 and/or stress incontinence

7. Cube pessary (with button if necessary, firmly welded thread), perforated/unperforated
8. Tandem pessary (with dome of 2 cubes)
9. Club pessary (with support)

Product family A-c) Special features

10. Adjustment set of ring pessaries
11. Vaginal dilator

B) Product Family Obstetric Pessaries, CE certified

12. Cerclage Pessary (perforated and unperforated)

1.1 Responsibility

Clinical evaluation and risk assessment are based on MEDDEV 2.7.1 _Rev.4 and Directive 93/42/EEC.

2. Process description

2.1 Short summary of clinical evaluation/history

Vaginal pessaries were already used by Hippocrates ("**primum non nocere**") and in ancient Egypt. Pessary therapy has been introduced for the treatment of various gynecological and obstetrical conditions related to weakening of the uterine support apparatus, including sedation problems and stress incontinence [1-5]. Last but not least, cervical insufficiency during pregnancy, now diagnosed by transvaginal sonography, has been started to be treated with pessaries [6, 7]. Pessaries were made of various materials such as glass, porcelain, clay and rubber. Today, the material is body-compatible silicone, which is only offered by a few companies.

In product history, pessary therapy was and is the only way to treat symptomatic prolapse and incontinence without risking surgery and anesthesia. Dr. Arabin GmbH & Co KG was not founded out of the need to found a company, but rather Dr. Hans Arabin developed various models of pessaries "at home", initially for the treatment of sedimentation problems. Due to the high mortality rate of premature babies 32 weeks ago, he also developed the cerclage pessary, which should help to keep the cervix as stable as possible and thus prevent premature birth. Only when it became necessary to manufacture larger quantities by assigning problem cases and ordering from colleagues, a so-called KG was founded in 1968, which also made it possible to ship in a limited form. After his death, Dr. Gretel Arabin initially took care of maintaining production and shipping with helpers.

In the meantime, transvaginal sonographic examinations of the cervix were also possible, which objectified the indication of the cerclage pessary, and transperineal ultrasound objectified the indication of gynecological pessaries. Prof. Birgit Arabin has worked in the Netherlands since 1993 and only then realized the value of pessary treatment for pregnant women. Since nobody wanted to take over the further production, she decided in 1997 to found a GmbH & Co KG on the campus of the private university Witten and to transfer the large part of the production first to a handicapped workshop in Zwolle (WEZO) as well as an injection molding company in Heerhugowaard (van Kempen). Work processes were standardized, automated and certified with the help of MDSS Hannover from Med-Cert Hamburg. After a first case-control study published in 2003, a first publication of a randomized study in Lancet (Goya et al. 2012) in single pregnancy and a further randomized study in twin pregnancies (Liem et al. 2013), also in Lancet, appeared. The international teams were able to demonstrate the success of pessary therapy in preventing premature birth and even improving outcomes. This led to other groups dealing with pessary therapy during pregnancy. However, it turned out that the success of the therapy was also significantly linked to clinical experience and personal training. In 2012, a training centre in Berlin was therefore acquired and training courses expanded. Independently of this, the cooperation with urogynecologists was intensified in order to stimulate studies and develop new models. The coordination of science, production and sales is only possible with support of a constantly growing team of reliable employees. It became increasingly clear, however, that in special situations postoperative support of the surgical results and treatment of young women during and after pregnancy with lowering complaints makes further development of the products desirable ("user needs"). In addition, further developments in the manufacturing process were unavoidable. This was an occasion to look for new research opportunities and producers and to strive for certification according to Annex II.

Information material provided by the manufacturer can be found on the home page of Dr. Arabin GmbH & Co KG www.dr-arabin.de as well as in the instructions accompanying the pessaries.
Prof. Arabin herself as well as experienced colleagues regularly conduct numerous further training courses for medical personnel in Germany and abroad outside the training center in Berlin.

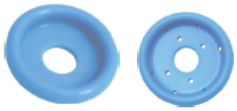
The risk-benefit ratio was initially only determined empirically. A demonstration of the acceptability of the benefit-risk ratio based on the current state of the art and clinical science is increasingly evaluated through cohort studies and randomized trials. For all pessaries the risk is relatively small.
Our obstetric cerclage pessaries were examined in various countries or continents. Since preterm birth is a major cause of infant mortality and morbidity, the benefits could be immense and will be presented in more detail. Almost no risks have been identified **except for application errors**, **Therefore, the European and the German Guideline for prematurity meanwhile demand training courses before application (see below).**

2.2 Precise description of physical/chemical properties with images

Following aspects are shown in Table 1 (2 pages):

- ***Product identification, classification &purpose of the products***
- ***General product descriptions (indications / contraindications, image display with physical and chemical description, technical specifications, functional principle, intended performance and clinical benefit, producers)***
- ***Regulatory Status***
- ***UMDNS code: 13004-13005/ 11267 VD/ GMDN code: 34149 GYN/35260 GEB***

Dr. Arabin GmbH & Co KG is responsible for the final inspection of all products. Each product is examined by a trained reviewer before packing.

Pessary type/classification	Sizes	Duration Therapy	Indications	Contraindications	Silicon/Manufacturer
GYNECOLOGICAL PESSARIES	**UMDNS-13004 GMDN 34149**				
Thick Ring - IIa CE+ since 1970 	50-100 mm Each in 5 mm steps	Up to 28 days	Descensus grade I-II with or without incontinence	Descensus III grade, i.e. no load-bearing pelvic floor	Altropol: Neukasil networker and RTV25 WEZO-NL
Hodge Pessar-IIa CE+ with aluminum since 1968 	55-95 mm Each in 5 mm steps	Up to 28 days	Rare situation that requires an adaptation of the shape, early retroflexion of the uterus	Descensus III Degree i.e. no load-bearing pelvic floor	Altropol: Neukasil networker and RTV25 early tailor
Bowl and sieve bowl pessaries - IIa CE+ since 1968 	55-95 mm Each in 5 mm steps	Up to 28 days	Lowering complaints (Descensus grade I-II), low stress incontinence	Descensus III grade i.e. no load-bearing pelvic floor	Altropol: Neukasil networker Unbd RTV25 WEZO-NL
Urethral cup pessary round - IIa with pressure point for Urethra **CE+** since 1968 	55-90 mm Each in 5 mm steps	Up to 28 days	stress incontinence	Neurogenic incontinence Descensus grade III, i.e. no load-bearing pelvic floor	Altropol: Neukasil networker and RTV25 WEZO-NL
Urethra Pessary -IIa CE+ with steel spring core steel 4301/4310 and pressure point for urethra since 1968  **NEW: without steel spring core** **Standardized compression Since 07-2019**	45-100 mm Each in 5 mm steps	Up to 28 days	stress incontinence	Neurogenic Incontinence, Prolapse / Descensus Grade III i.e. no load-bearing pelvic floor	Until 2019 Altropol: Neukasil networker And RTV25 Now: Silpurane 8020-70 Curing Agent M Elastosil color paste PT dark blue RAL 5010 Elastosil color paste PT white RAL 9010 Wacker AG/ DINO AG
Ring pessary - IIa CE+ with steel spring core Steel 4301/ 4310 since 1970  **NEW: without steel spring core** **Standardized compression Since 07-2019**	50-100 mm Each in 5 mm steps	Up to 28 days	Mild Descensus grade 1-2, low stress incontinence only during exercise	Descensus grade III	Until 2019:Altropol: Neukasil networker And RTV25 Now: Silpuran 8020-70 Curing Agent M Elastosil color paste PT dark blue RAL 5010 Elastosil color paste PT white RAL 9010 Wacker AG/DINO AG

Cube Pessary –IIa CE+ Perforated / unperforated with button and threat, since 1970 	25-100 mm (edge length) In 5 mm steps	Daily change by patient	Severe genital prolapse (Grade II-III)	Increase incontinence, ulcers, limited capability for daily change	Wacker: Elastosil R+4000 Color paste PT RAL5010 v.Kempen-NL RILSAMID AMNOTLDPA12 (button) DINO-AG Berlin
Tandem pessary-IIa CE+ Two combined cubes 	Customized construction	Daily change by patient	Severe genital prolapse (Grade II-III)	Increase incontinence, ulcers, limited capability for daily change	Wacker: Elastosil R+4000 Farbpaste PT RAL 5010 v.Kempen-NL coppeling Klees
Club (Gelhorn) pessary -IIb CE+, since 1970 	55-90 mm in 5 mm-steps	>28 days	Severe genital prolapse (Grade II-III) when other products do not help	Eventually atrophic sensitive vagina	Altropol: Neukasil-networking + RTV25
Vaginal expander - IIa CE+, since 1970  **UMDNS 11267**	4 sizes: 20/120 mm 26/127 mm 30/112 mm 37/137 mm	Per hour	Wish to dilate the vagina (e.g. after operations, in case of aberrations)	First 2 weeks after an operation	Altropol Neukasil-networking and RTV25
Adaption set-IIa CE+ (soft/green),since 2014 	small:50-65 mm medium::65-80 mm large: 85-100 mm in 5 mm-steps	Only minutes	In case of uncertainty of sizes **Validation for cleaning & sterilization**	None	Wacker: Elastosil FL 6010/ Green color paste RAL v.Kempen-NL
OBSTETRIC PESSARIES	**UMDNS13004 GMDN 35260**				
Cerclage-Pessary - IIb CE+, perforated and unperforated Neukasil since 1975 Silpuran since 2014 	Internal: 32-35mm Height:17-30mm External:65-70mm Compression adapted	During pregnancy > 28 days	Prevention of preterm birth in singleton and twin pregnancies	Chorioamnionitis, PPROM Severe contractions Anatomic deviations	Wacker: Silpuran8020 Color paste PT RAL5010 v.Kempen-NL and DINO AG for ASQ

Table 1) Direct comparison and characterization of the products of Dr.Arabin GmbH &Co KG
Page 1: Product group annular gynecological pessaries genital prolapse I-II and/or stress incontinence
Page 2: Product group gynecological pessaries genital prolapse II-III and/or stress incontinence
Page 2: Product Group Vaginal Stretchers / Product Group Pessaries for Prevention of Premature Birth
Page 2: Product group obstetric pessaries

2.3 *Short summary, justification and type of literature search according to requirements MEDDEV 2.7.1Rev.4, summary advantages & disadvantages, benefit/risk profile, limitations, hazards, current state of knowledge*

The **search date** is the end of June 2019.
For the **methodology and justification of the literature search,** the generally applicable methods for the preparation of a systematic review were used and the following databases were searched using **search** terms (Cervical pessary, preterm birth, pessary and stress incontinence, pessary and genital prolapse):

- The Cochrane Library "evidence on the effects of healthcare" until 06- 2019, issue 1, John Wiley & Sons update.
- PubMed database, up-to-date.
- Personal congress visits and contacts make it possible to always be "up-to-date" here.
- The database "Clinical trials" was searched for ongoing studies.
- In addition, guidelines from various countries were visited.

Background, description, natural course and medical condition with regard to gynecological pessaries: Ring-shaped pessaries for a treatment of genital prolapse grade I-II and/or incontinence as well as cube, tandem and club pessaries for the treatment of women with genital prolapse grade II-III and/or incontinence

Lowering problems and/or incontinence are problems of the pelvic floor that frequently occur after pregnancies/vaginal births and affect about 1/3 of all women. Operations have a risk of recurrence, depending on the surgeon.
There are still a large number of indications, including patients with an increased risk of surgery or patients who do not want surgery or young patients who have problems during active sports or during or after pregnancy, for whom pessary therapy is the treatment of choice[8]
According to recent studies, however, pessary therapy is regarded as the first method of choice for mild symptoms10. In a study by Patel et al., it was shown in symptomatic prolapse that after a treatment period of 6-12 months, symptoms of lowering and one's own body feeling could be improved [9].
Even after reviewing current abstracts and databases summarizing new studies, we found few randomized trials to test pessary therapy in comparison to abstention or surgical therapy in the treatment of stress incontinence or symptomatic genital prolapse [10]. The question whether pessary therapy is used will therefore still depend on the individual experience of the gynecologist and his educational work, and must be made dependent on the individual situation of the patient[11-13].
According to the recommendations of international and national expert committees, however, pessaries in combination with various other "conservative" forms of therapy should always first be presented before surgical therapy is recommended.
For the question of a justification for the existence of pessaries as a medical device, the comparison of the performance of both methods is irrelevant, since in each case a group of patient's remains for whom surgical measures are out of the question. Typical complications of pessary therapy usually depend less on the pessary itself than on proper adjustment and regular replacement. Beyond the menopause, the use of estriol creams may become necessary in order to avoid pressure points and to ensure blood circulation in the mucous membranes. Other creams are also recommended:

Experts recommend to use 50g unscented Oestrogynadion (2x/week), Vagisan-Dr. Wolff Cream (5x/week) and Linova Protection Balm (7x/week).
A Dutch RCT showed that pessary therapy with ring pessaries was successfully maintained in the long term in patients over 72 years of age, while this therapy was rather abandoned in patients with previous hysterectomy or surgical measures for stress incontinence and pelvic organ prolapse (POP) [14]. However, it must be taken into account that the cube pessary was not tested, but only the traditional ring pessaries, which require an intact pelvic floor. The results after treatment with the cube pessary would certainly have been different.
Recently, the cube pessary was also examined in a study examining the quality of life. It turned out that in patients > 60 years the quality of life after therapy with this pessary increased significantly [15].**The Dutch study describes for the first time the comparison of prolapse pessaries and operations, thereby 75% of women decided not to undergo surgery [14].**

With regard to the clinical use of gynecological pessaries there are so far only indications in Canadian guidelines [16]: The summary/recommendation is as follows:
Summary Statements: 1. Most women can be successfully fitted with a pessary when they present with prolapse. (II-2)
2. Complications of pessary use are usually minor, and vaginal discharge is the most common complaint. (II-3)
3. Vaginal erosions can be treated with removal of the pessary and optional vaginal estrogen supplementation. (II-2)
4. Satisfaction rates with pessary use are very high. (II-2)
Recommendations: 1. Pessaries should be considered in all women presenting with symptomatic prolapse and/or urinary stress incontinence. (II-1A)
Side effects of all gynecological pessaries are increased fluorine and, in the case of application errors, very rare infections or incarcerations. With the cube pessaries there can be problems with the thread, which is however only combined with a low medical risk

Historical background, description, natural course and medical conditions with regard to obstetric pessaries, description of available forms of treatment

Premature birth causes the largest proportion of child mortality and morbidity worldwide.
After their first own publication on the significance of Arabin cerclage pessaries in sonographically diagnosed cervical shortening in single and twin pregnancies[17] Dharan and Ludmir published a review article in 2009 on pessary therapy for the treatment of imminent premature birth. Almost all the articles cited in this overview related to the Arabin "cerclage pessary" and the previous and ongoing studies are dealt with there [7].
In the meantime, randomized controlled trials (RCTs) have been performed in single-gravidity with short cervix (< 2.5 cm) or twin-gravidity with or without short cervix.
In April 2012, the first randomized prospective study on our Arabin cerclage pessaries with the indication "Prevention of premature birth in single-gravidity and short cervix" appeared in Lancet [18] with corresponding comment [19]. Both studies are added to this assessment. It could be proven that the pessary not only postponed the premature birth, but also reduced the incidence of diseases in children caused by premature birth. This was preceded by a work of the same group on the technique of sonographic control of cervical length with pessary[20], which could thus strengthen the confidence of the treating physicians in this therapy. For the treatment of cervical insufficiency, comparative studies were conducted between cerclage and pessary, suggesting that pessary treatment is equal to, if not better than, cerclage, but there are no prospective randomized trials both to compare pessaries to no treatment and to compare pessaries to cerclage. What is certain is that even in meta-analyses, cerclage has no visible effect for the prevention or treatment of imminent preterm birth [21, 22]. Due to our activities a first Cochrane review appeared in 2013 [23].

Further studies were completed in 2013 and are currently also available electronically. These include the work of Alfirevic from England, who retrospectively compared the treatment of pessaries, cerclage and progesterone[24], the study of Carreras from Spain on the early birth-lowering effect in twin pregnancies with twin-to twin transfusion syndrome and laser therapy[25], the Protwin trial from the Netherlands, which has now also been published in the Lancet and demonstrates the early birth-preventing effect in twin pregnancies and a short cervix[26, 27], the work of Cannie et al. from Brussels, who was able to determine the angular changes between cervix and uterus by means of nuclear spinning examinations and to show the retraction of egg membranes after pessary therapy[28]. Prof. Arabin herself wrote an overview of the previous use of pessaries as well as a practical guideline with suggestions for studies in the future, which will be made available to all interested parties as "open access". [29] An analysis of costs versus benefits of twin pregnancy was published after the PROTWIN study [30].

Team Hebron published another randomized study in twin pregnancies with short cervix between 20 and 24 SSW for pessary versus no treatment [31]. Births before the 34 SSW were significantly reduced. In another new study, women were randomized after an episode of preterm labor and cervical shortening. The group with pessary treatment had a significantly lower rate of preterm births before 37 SSW [32]. Studies in England, France, Spain, the Netherlands, the USA and Canada are currently being started or planned. In the USA, an IDE (Investigational Device Exemption) approval was granted by the FDA.

A Cochrane analysis carried out in 2013 showed that there was still insufficient data at that time to be able to draw up precise sub-analyses of the pessary indication in pregnancy [23] . However, this is due to the fact that new meta-analyses of the Cochrane Group are not carried out at standardized intervals. In addition, retrospective meta-analyses, which sprout out of the soil like fungi, have the disadvantage that a bias is created by the selection of the studies. This could be circumvented in a meta-analysis by including only pre-registered studies. Then a significant advantage of the cerclage pessary over no treatment was shown [33].

Since 2014 there have also been meetings of a group (PROMT) planning a prospective meta-analysis: Prospective Individual Patient Data Meta-Analysis of Pessary Trials. The project is supported by the Global Obstetrics Network (GONet) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the Maternal-Fetal Medicine Units (MFMU) Network.

First, this group has defined a unified OUTCOME of preterm births through a worldwide Delphi survey of patients, midwives and physicians. All groups planning studies give their consent to provide the patient record file to a central commission in Washington for examination. With appropriate approval, joint examinations in subgroups should then be possible at a later date.

Between 2016 and 2017, in addition to the work of Goya (positive), a study by Nicolaides et al. on the significance of the pessary in twin pregnancies was published, although Nicolaides admitted that he had not carried out careful teaching. This also applies to the study by Nicolaides et al. on singleton pregnancies. Due to the lack of monitoring of insertion, follow-up and removal, the study results, which did not demonstrate any effect, should be [31, 34-38]. In the meantime, secondary analyses of the Pro-Twin study have also been published which showed that good teaching [39, 40]. Therefore, clinical instruction was recommended as a measure for pessary therapy in pregnancy[41].

Also in singleton pregnancies Saccone et al. found a significant effect of the pessary in preventing preterm birth [42]. The most convincing results are those of an RCT comparing progesterone and pessary in twin pregnancies [43] (see Table 2).

Table 2) Direct comparison of vaginal progesterone and cerclage pessary in twin pregnancy using important child outcome parameters (Dang et al, 2919)

Women with a cervical length < 28 mm					
Outcome	**Arabin pessary**		**Vaginal progesterone**		**RR (95%CI)**
Birth < 34.SSW	10/49	20.4%	16/34	44.0%	0.46 (0.24-0.89)
Birth < 37.SSW	23/49	46.9%	26/36	72.2%	0.65 (0.45-0.93)
Weight <2500 g	50/98	51.0%	51/72	70.8%	0.72 (0.23-0.82)
Recording NICU	14/90	15.6%	28/63	44.4%	0.35 (0.11-0.49)
RDS	12/90	13.3%	21/63	33.3%	0.40 (0.14-0.69)
neonatal sepsis	6/90	6.7%	33/285	23.8%	0.28 (0.08-0.63)
Women with a cervical length < 38 mm					
outcome	**Arabin Pessary**		**Vaginal progesterone**		**RR (95%CI)**
Birth < 34SSW	24/159	16.0%	35/150	22.0%	0.73 (0.45-1.17)
Birth < 37SSW	73/150	48,7%	91/159	60.7%	0.8 (0.65-0.83)
Weight< 2500g	143/300	47.7%	181/300	60.3%	0.79 (0.43-0.83)
Admission NICU	39/280	13.9%	66/285	23.2%	0.60 (0.35-0.83)
RDS	32/280	11.4%	51/285	17.9%	0.64 (0.37-0.95)
neonatal sepsis	17/280	6.1%	33/285	11.6%	0.52 (0.27-0.9)

Another study compared the therapy with progesterone and cerclage pessary in single pregnancies and found no significant difference in the prevention of preterm birth [44]. In addition, a significant effect of reducing bleeding and prolonging gestation in pregnant women with placenta praevia was described [45].

With regard to the clinical application of obstetric pessaries, there is so far only information on this in the European **guideline [41].** The summary reads as follows: "Although promising and with a potentially favorable cost-benefit ratio, there is a need for further RCTs. Proper training to apply the pessary should be homogenized and encouraged in further investigations".

Last but not least, we have succeeded in having the German Society for Gynecology and Obstetrics include an **addendum to the** practical use of pessaries as an addition to **the guideline on premature birth (Kyvernitakis et al., in press)**. This text was indirectly co-designed by us, as it is based on our recommendations published on the internet - preferably on our instructions and FAQs.

Side effects of obstetric pessaries are predominantly increased fluorine and, in the case of application errors, very rare lesions of the cervix.

Background, description, natural course and medical condition with regard to the product group of vaginal dilators, description of the available forms of treatment.

A conservative enlargement of the vagina is indicated for congenital anatomical abnormalities, constriction of the vagina after surgery or transsexual constellations.

Research of this product group is sparse, but describes a successful application of vaginal extensors in Mayer-Rokitansky-Küster-Hauser syndrome with congenital absence of a uterus and at least the upper part of the vagina. This method was further developed by Ingram (1981) and Edmonds (2012), who described 245 patients with a 95% success rate in anatomical outcome. Few patients did not follow the therapy because of psychological or cultural problems. Experts of the American College of Obstetricians and Gynecologists described in their "Committee Opinion" (2013): "Non-surgical creation of the vagina is the appropriate first line approach in most patients".
Patel et al. described 2018 experiences with vaginal stretchers in vaginal agenesis. Over 50% of users reported success with regular sexual intercourse. Complications were maximal discomfort or pain during therapy. There is one Cochrane review on the use of vaginal dilators during radiotherapy. It is concluded that "there is no reliable evidence to show that routine, regular vaginal dilation during radiotherapy treatment prevents stenosis or improves quality of life. More studies are needed" [46].

2.4 Evaluated product/product groups, presentation of comparability Safety/benefit/risk ratio requirement (MDD ER 1), performance (MDD ER 3), acceptance of undesired side effects (MDD 6)

The pessary treatment follows the principle **"primum non nocere"**.
The assessment of the risks in comparison to the benefits is favorable in comparison to medicinal and surgical procedures and depends mainly on the correct application.
Accordingly, the acceptance of undesirable side effects (mainly fluorine) is high. This applies to all product groups. The following should be said in detail for product groups:
Product group annular gynecological pessaries genital prolapse I-II / stress incontinence
The conservative treatment is much **less expensive than** surgical procedures and has not only a short-term symptomatic but also a **long-term therapeutic effect**. After adaptation and indication, nurses can also be included in the care [47]. The individual situation of the patient must be taken into account during the consultation, because she must decide whether she prefers conservative or surgical therapy. The side effects of an operation as well as the recurrence rates and complications of the operations should be mentioned during informative talks. The decision can then only be made by the patient herself. The advantage of pessary treatment is that it can also be used by experienced auxiliary staff, which is particularly effective in developing countries and in care of the elderly [8]. At least 75% of women who receive a pessary as a result of prolapse then refrain from surgical treatment, as a new RCT has shown [14] (EVIDENCE IA). In a RCT of the group of Thakar, the World president of urogynecology, there was no difference in satisfaction of operative or conservative (pessary) treatment in the satisfaction of pessaries [48].

Product group gynecological pessaries genital prolapse II-III / stress incontinence
Due to complaints about torn out threads of the **cube pessary** we have decided to use only cubes with central button and firmly welded nylon thread from 2018 onwards, a test of the cube pessary with this new nylon button and nylon thread for biocompatibility and cytotoxicity was carried out.

A theoretical problem is the recommended daily change and the domestic preparation or storage, here we have proposed as a design doses for storage. Another problem is leaving the pessary for too long, contrary to the recommendations, which can lead to irritation of the vagina.
With the **club pessaries,** the thick wall leads to great durability and possible use with heavy depressions, but the pessaries are very difficult to change, so we are in the process of manufacturing these pessaries with the help of a guided procedure and a collegial team (PD Dr. Baessler/Dr. Fink Berlin), even with a smaller wall thickness.
At least 75% of women who receive a pessary as a result of prolapse then refrain from surgical treatment, as a new RCT has shown [14] (EVIDENCE IA). In a RCT of the group of Thakar, the World president of urogynecology, there was no difference in satisfaction of operative or conservative (pessary) treatment in the satisfaction of pessaries [48] (EVIDENCE IA). The most reported "complication" is an increase of discharge.

On demand we are allowed to produce customized pessaries.
Together with the Charite Berlin, PD Dr. Baessler), Prof. Kalder University Marburg as well as PD Dr. Koscizewski Hospital Hagen Haspe (Team "input"), We are testing new devices in the treatment of incontinence and early prevention of prolapse during pregnancy or as a combined treatment with operations (under research conditions).

Product Group Obstetric Pessaries
The conservative treatment of **cervical insufficiency** with pessaries seems to be promising as compared to other therapies due to its non-invasive character, the cost-effectiveness and a number of positive RCTs.
For singleton pregnancies, there are two positive trials which prove the effectiveness of the cervical pessary in opposite to control cases with expectant management only to prevent not only preterm birth but also neonatal morbidity (Goya et al Lancet 2012 , Saccone et al. JAMA 2017, both et al, Lancet 2013).
For twin pregnancies, there are two RCTs showing an effect of the cervical pessary versus expectant management to prevent preterm birth (Goya et al, AJOG 2016 [18], Liem et al, Lancet 2013 [27]) and to reduce neonatal morbidity and mortality by the factor of 6 (3 versus 18 deaths) [27]).
Although RCTs have been published showing a positive effect of progesterone in singleton pregnancy on the rate of early preterm births and a reduction in premature birth-associated diseases [49-52], the results have also been questioned by the FDA report and the work of Prior et al. [53] and the Opptimum Trial [54]. The effect of progesterone in twin pregnancies or after an "episode of premature labor" is doubtful [55].
In singleton pregnancies one RCT compared the pessary versus vaginal progesterone – there were no significant differences (Cruz- Melguizo et al. Obstet & Gynecol 2018 [44],
In twin pregnancies, one RCT compared pessary versus vaginal progesterone showing clear benefit of the pessary versus vaginal progesterone in the total group of twin pregnancies but more clearly in those where the CL was shortened < 25th centile in terms of reduction of preterm birth and neonatal outcome (Dang et al. Obstet Gynecol 2019 [43].

Two recent RCTs also show a favorable effect of cerclage pessaries after an episode of preterm labor in singleton and twin pregnancies (Pratcorona et al. AJOG 2016 [56], Merced et al. AJOG 2019), where no other method could show a meaningful effect [57], and even a demonstrable effect on the outcome of children after 3 years with a NTT (number to treat) of 1/6, in avoiding a childhood death or handicaps [58].
The advantage is that pessary therapy can also be combined with pharmacological therapy.

Here we have shown first results in a pilot study in which progesterone had no further effect on the duration of pregnancy in single pregnancies [59] (Stricker et al.AJOG 2016).
Two RCTs both of the group of Nicolaides, who did not teach nor audit pessary treatment in multi-continental trials showed no benefit and no harm of the cervical pessary in either singleton (Nicolaides et al, NEJM 2016 [37]) or twin pregnancies (Nicolaides et al. AJOG 2016 [38]).
However, the authors themselves admitted that it was not controlled whether the pessary was placed the right way, similarly no teaching was performed what to do in specific situations.
Recently, we have shown that the application of the pessary when it is placed upside down as falsely indicated even on the cover of the AJOG 2016, does not have the effect of pressure relief [60].
This is why the European and German guideline demand some kind of teaching by courses, internet and instructions. It has been shown that there is also a learning curve and that the rate of successful treatments increase with increasing experience within one center.
Three underpowered RCTs could similarly not prove any benefit ([61-63]. However, these studies do not fulfil the basic quality requirements (AMSTAR or ROBIS) for a RCT and did not use the Arabin pessary but non-certified devices designed for urogynecology.

Product Group Vaginal Dilators
Since these pessaries are only used for a short time by patients themselves, who can also determine the duration and strength of use themselves, complications are rare and hardly described, at best it can lead to discomfort, in case of pain the patients can interrupt the therapy themselves at any time.

Analysis of clinical/technical data and associated risks

As stated in the international clinical guidelines, the risks of pessary therapy are negligible if the instructions for use are observed.
Serious systematic hazards to patients are not yet known, but individual case reports are described which may theoretically be based on the following influences:

- *Lack of material compatibility, e.g. residual monomers*
- *Mechanical irritations due to surface roughness, webbed membranes, exposed inlays*
- *Injuries or irritations caused by exposed inserts*
- *Mechanical irritation due to pressure on the vaginal mucosa*
- *Infection by contaminated pessaries lying too long*
- *Inclusion or pinching of tissue (e.g. in the cerclage pessary at the beginning of birth or lowering or if the pessary is forgotten during birth)*
- *Pressure points on the previous part of the child during pregnancy (previously described only once if the pessary was not removed at the start of birth)*
- *Increased vaginal discharge, this was described in almost all studies.*

The risk of pressure points cannot be completely excluded, since these are less caused by the material and shape of the pessary than by the anatomical conditions, especially if pessaries lie disproportionately long and/or no additional therapy (e.g. estrogenization) is applied. This is pointed out in the accompanying papers, and there is also extensive literature. This risk can be prevented by controls of the physician.
There are very rare complications, recently a case has been published in the literature in which a ring pessary has been left lying around for 16 years and forgotten without any complications occurring [64]. In the past, however, such application errors have also described the development of rectovaginal and vesicovaginal fistulae [65-70].

In the case of cerclage pessaries, few cases of cervical lesion have been reported. In all cases, it was a medical error on the part of the doctors involved, who left the pessary unlawfully under the birth for a long time, during bleeding or rupture of the bladder or removed it by force. We've adjusted our instructions accordingly.

Tested **materials are used, of** which the compatibility is known in principle. Since monomer residues cannot be completely ruled out, the products are "post-cured" after hot vulcanization. This results in good tolerability, which is also underlined by cytotoxicity studies. Only in the case of serious mixing errors would this not be achieved. In this case, however, the Shore hardness of the finished product could be expected to deviate from the specifications. The Shore hardness is tested batch by batch.
For the ring urethra and cerclage pessaries, which are to be manufactured by DINO AG from 20189 onwards, additional compression measurements (given in Newton for compression to 1/2) are carried out to provide information on handling.

During the **production of** the pessaries, a check is carried out for irregularities and an optical check for proper surface quality. In principle, it cannot be ruled out that inserts located just below the surface may be exposed by damage during use. This is visible to the user. However, due to the softness of the edges and the physiological harmlessness of the inlay materials used, this does not pose any serious hazards, at most irritations.
With regard to the **useful life of** our pessaries, we have indicated a period of 10 years. This date refers to the time of manufacture and is based on many years of experience with the products. It is evident from our documentation since certification in 1998 that there have been no complaints regarding material fatigue, even if older pessaries have been used.
Primarily exposed **inserts** are excluded by the optical inspection of the pessaries before delivery. However, the silicone sheath may tear after long use if pessaries have to be strongly deformed during insertion and removal. The cracks that then appear open clearly when the pessary is deformed and close again when it relaxes. The probability that they will be noticed and the pessary will then be discarded is very high. If they are not noticed, it is conceivable that irritations of the vaginal mucosa may occur when the pessary is relaxed if it gets into the closing crack. Due to the softness of the material, however, little more than an unpleasant sensation can be expected here. There are no reasons for the inserts to be exposed over a large area, this would also be noticed. No further risk of injury is to be expected as the inserts have no sharp edges or hooks. The exposure of metallic materials is also harmless. Neither stainless steel 4301 or 4310 nor aluminum have toxic effects. The expected corrosion products of aluminum are also harmless.
Although metal should theoretically not be taken along in nuclear spinning machines, there has never been a problem in practice even when carrying our metal-containing pessaries - not even in the image quality.

As far as **hygiene is concerned, the** pessaries are delivered clean and low in germs and are not sterilized. The everyday germs to which the pessaries are exposed usually do not pose a problem for the physiological vaginal flora. Even if the pessary is changed by the doctor or patient, it should only be washed off. Treatment with disinfectants is not necessary; it may cause irritation of the vaginal mucosa. We therefore no longer recommend the use of disinfectants that can irritate the mucous membrane unnecessarily, and we cannot guarantee the cleanliness of these products everywhere. Accordingly, we have adapted the instructions for pregnant women.
In addition, we have classified our cerclage pessaries as **PRODUCTS FOR SINGLE USE ONLY.** We have done this primarily as a precaution, since a renewed insertion in the same patient or even in other women brings with it an increased risk of too high a germ load.

The vagina has an individual germ spectrum (microbiome) similar to the mouth or intestine. Nevertheless, restricted or overstimulated local immunological defense and non-compliance with the instructions can lead to increased vaginal discharge. However, since infection is usually caused by everyday germs without selection, treatment is normally not a problem.
In the randomized study, bacteriological smears were taken from untreated patients and treated patients before and after pessary use20. The rate of inflammation such as bacterial vaginosis between the groups was comparable. Despite the discharge described above, women treated with pessaries did not experience an increased rate of chorioamnionitis and even a lower rate of premature rupture of the bladder [18]. Since the cerclage pessaries remain "unchanging" in the vagina for the longest time in comparison, we also expect our other pessaries, which usually have a smaller contact surface and are also changed much more frequently (usually daily), not to present an increased risk of infection.

Evaluation of medical devices

Type of assessment

For literature research, the generally applicable methods for the compilation of a systematic review were used, using mesh terms (cervical pessary, preterm birth, pessary and stress incontinence, pessary and genital prolapse) databases. Due to the many years of own clinical experience with all products, not only the statistical but also the clinical quality criteria can be analyzed.

Representation of equivalence

In the case of gynecological pessaries, there is an alternative to pessary therapy in the form of physiotherapy or surgery; the forms of therapy can also be used in combination with pessaries.
In obstetric pessaries, pharmacological substances (progesterone) and operations (cerclage) are alternatives. The direct comparison after completion of an RCT is shown in Table 2 and is convinced of pessary therapy to reduce child morbidity and mortality.
Alternative pessary products exist, but are mostly imitations of our models.
In the future, however, the production of new (oval) pessaries should also be designed by us.

Clinical data from the manufacturer

Own clinical experiences with all models of gynecological pessaries exist and correspond to the summary of the Canadian guideline. In addition, there is clinical experience with gynecological pessaries, which are requested as special designs. Own experience with cerclage pessaries also exists and has been adequately published[17, 29]

Clinical data from the defined literature search (literature path)

A detailed description has already been given. It is therefore referred to here.
An overview of published and ongoing studies on the cerclage pessary can be found as Tables 3 and 4 in the Annex to the literature list.

2.5 Summary and assessment of clinical data

A) GENITAL PROLAPSE WHICH REDUCES LIFE QUALITY OF WOMEN MAINLY DUE TO PREVIOUS PREGNANCIES AND DELIVERIES WITH SYSTEMATIC OR ANATOMIC LESIONS OF THE PELVIC FLOOR LEADING TO PELICORGAN PROLAPSE (POP) OR STRESS INCONTINENCE (SI)

OUTCOME DATA REFER TO VALIDATED QUESTIONNAIRES

When searching clinical trials.gov with the search terms pelvic organ prolapse (POP) and vaginal pessary, no studies are found which unfortunately means that this problem limiting life quality of so many women who are frequently unnecessarily operated suffering from complications and recurrence rates of up to 50% is not in the focus of interest (yet).

The conservative treatment of **POP and/or SI** is **cheaper and less risky compared to** surgical procedures and has not only a short-term symptomatic but also a **long-term therapeutic effect**. The individual situation of the patient must be taken into account during the consultation. The side effects and recurrence rates of an operation should be mentioned during educational discussions. The decision can then only be made by the patient herself. The advantage of pessary treatment is that it can also be used by experienced auxiliary staff, which has proved its worth in developing countries and in the care of the elderly [8]. The physicians should have experience with different models.
At least 75% of women who receive a pessary due to prolapse then refuse surgical treatment, as a new study has shown [14] (EVIDENCE IA). In a RCT of the group of Thakar, the World president of urogynaecology, there was no difference in satisfaction of operative or conservative (pessary) treatment in the treatment of POP with specified pessary models [71] (EVIDENCE IA). Therefore, international guidelines recommend conservative treatment as a first choice for treatment of POP.

B) SECONDARY PREVENTION OF PRETERM BIRTH BY THE CERVICAL PESSARY TO REDUCE THE RATE OF EARLY AND LATE PRETERM BIRTH IN WOMEN WITH A SHORT CERVIX OR CHANGE OF THE CERVICAL ANGLE

OUTCOME DATA REFER TO RATES OF PRETERM BIRTH; PERINATAL AND NEONATAL MORTALITY; IMMEDIATE NEONATAL OUTCOME SUCH AS RDS-SPESIS-BPD-COMBINED NEONATAL OUTCOME AND IDEALLY LOING-TERM SEVERE HANDICAP IN SINGLETONS AND TWINS

When searching clinical trials.gov with the search terms preterm birth and cervical pessary 61 registered trials are indicated. Most of them were using the Arabin cerclage pessary, some studies are completed and others ongoing (Table 3-4).

According to current studies, the conservative treatment of **cervical insufficiency** with pessaries appears to be promising, but it also takes time until this may be accepted by established committees. **For singleton pregnancies**, there **are two positive RCTs** which prove the effectiveness of the cervical pessary in opposite to control cases with **expectant management** to prevent not only preterm birth but also neonatal morbidity (Goya et al. Lancet 2012 [18], Saccone et al. JAMA 2017 [42], (EVIDENCE IA).
For twin pregnancies, there are **two RCTs showing an effect of the cervical pessary versus expectant management to prevent preterm birth** (Goya et al, AJOG 2016 [31], Liem et al, Lancet

2013 [27]) and to reduce neonatal morbidity and mortality by the factor of 6 (3 versus 18 deaths) [27] (EVIDENCE IA).
Although RCTs have shown a positive effect of progesterone in singleton pregnancy on the rate of early preterm births and a reduction in premature birth-associated diseases [49-52], the results have also been questioned by the FDA report , the work of Prior et al. [53] and the Opptimum Trial[54]. The effect of progesterone in twin pregnancies or after an "episode of premature labor" is doubtful [55].
In singleton pregnancies, one RCT **compared the pessary versus vaginal progesterone** – there were **no significant differences** (Cruz-Melguizo et al. Obstet & Gynecol 2018 [44], EVIDENCE IA).
In twin pregnancies, one RCT **compared pessary versus vaginal progesterone** showing **clear benefit of the pessary versus vaginal progesterone** in the total group of twin pregnancies but more clearly in those where the CL was shortened < 25th centile in terms of **reduction of preterm birth and neonatal outcome** (Dang et al. Obstet Gynecol 2019 [43], EVIDENCE IA).
Two RCTs also show a favourable effect of cerclage pessaries after an episode of preterm labor in singleton and twin pregnancies (Pratcorona et al. AJOG 2016 [57], Merced et al. AJOG 2019 [32], EVIDENCE IA), **where no other method could show a meaningful effect** [57], **and even a demonstrable effect on the outcome of children after 3 years with a NTT (number to treat) of 1/6, in avoiding a childhood death or handicaps** [58] (EVIDENCE IIA).
The advantage is that pessary therapy can also be combined with pharmacological therapy.
We have shown **in a pilot study that progesterone had no further effect on the duration of pregnancy in single pregnancies as compared to pessary alone** (Stricker et al. AJOG 2016 [59], EVIDENCE IIIA).
Two RCTs both of the group of Nicolaides, who did not teach nor audit pessary treatment in multi-continental trials showed no benefit and no harm of the cervical pessary in either singleton (Nicolaides et al, NEJM 2017 [36, 37]) or twin pregnancies (Nicolaides et al. AJOG 2016[38] , EVIDENCE IA). **However, the authors themselves admitted that it was not controlled whether the pessary was placed the right way, similarly no teaching was performed what to do in specific situations.**
Recently, we have shown that the application of the pessary when it is placed upside down as falsely indicated even on the cover of the AJOG 2016, does not have the effect of pressure relief (Barbone et al. UOG 2019 [60], EVIDENCE IVB). This is why the European and German guideline demand some kind of teaching by courses, internet and instructions. It has been shown that there is also a learning curve and that the rate of successful treatments increase with increasing experience within one center (Franca et al. FMFM abstract 2015, EVIDENCE III B).
Three **underpowered** RCTs could not prove any benefit (Hui et al. 2013 [62], Dugoff et al. UOG 2017[61], Berghella et al UOG 2018 [63]). **However, these studies do not fulfil the basic quality requirements** (AMSTAR or ROBIS) for a RCT and did not used the Arabin pessary.
At this stage, there is a tsunami of RETROSPECTIVE meta-analyses about the treatment with cervical pessaries with doubtful quality and varying results. **These publications should be neglected and more serve the curriculum or ego of the authors than to find the truth**. The Cochrane board has refused any review at this stage, before further now ongoing RCTs are completed.
The NIH under the guidance of George Saade strives to perform a PROSPECTIVE meta-analysis which is less prone to bias and will allow more specified indication from individual data analysis of many patients (Table 4).

Analysis of clinical data, including summary of conformity assessment with safety requirement (93/42/EEC Annex I, Section I, point 1)
In contrast to the respective alternatives, pessary therapy is the least invasive and most controllable method for the patient.
Summary of conformity assessment in relation to the requirement for acceptability of risk-benefit balance (93/42/EEC Annex I, Section I, point 1)
Pessary therapy can be regarded as a therapy that, unlike the respective alternatives, can be regarded as having the best cost-benefit analysis.
Summary of conformity assessment with the performance requirement (93/42/EEC Annex I, Section I, point 3)
Pessary therapy can be regarded as a therapy that in many cases contributes to the satisfaction of the patients after indication of the medical findings.
Summary of conformity assessment in relation to the requirement for acceptability of adverse reactions (93/42/EEC Annex I, Section I, point 6)
Pessary therapy can be regarded as a therapy that, unlike the respective alternatives, can be regarded as having the best cost-benefit analysis.

Summary
All the above-mentioned risks of our pessaries - both for the treatment of pelvic organ prolapse and incontinence and also for the treatment of threatening premature birth - are acceptable and risks are assessed, provided that the patients or treating physicians follow the instructions. This risk assessment was adapted to the current literature in consultation with Prof. Dr. Arabin. Further important and continuously updated documents, such as the risk management report, which is prepared in cooperation with the management, QMB and safety officers, can be found in medical product files.

2.6 Date of the following clinical evaluation

The clinical evaluation is kept up to date by the management on an ongoing basis and is renewed and reviewed annually in its written form.

2.7 Date and signature

Witten, 30.8. 2019

Prof. Dr. med. Dr.h.c. Birgit Arabin

2.8 Author's qualification/curriculum

Universities	1971-75	Albert Ludwig University Freiburg
	1975-78	Free University of Berlin
Medical Curriculum	1978-79	Research Assistant Free University of Brussels and Berlin
	1979-85	Specialist training OBGYN Ruprecht Karl University Heidelberg
	1985-88	Assistant Professor at the Institute for Perinatal Medicine Berlin
	1988-93	Assistant Professorship Freie Universität Berlin
	1992-93	Parallel education School of Public Health Hannover
	1993-08	Prenatal High Risk Perinatal Centre Zwolle - NL
	2000-18	Faculty Private University Witten-Herdecke/Humboldt University Berlin
	2008-18	Head of Prenatal/High Risk PregnancyAcademic Perinatal Board Philipps University Marburg-Germany
	2019-?	Guest Researcher/Professor Charite Humboldt University of Berlin
Sabbatical	1988	Harris Birthright Center London/ Prof. Nicolaides
	1991	Department of Prenatal Medicine Bonn/ Prof. Hansmann
	2008	Centre for Prenatal Therapy Poissy-Paris/ Prof. Ville
Organizations		Member/Board Societies of Perinatal Medicine such as WAPM, SMFM, ISUOG, IAPM, NVOG, DGGG, DGPM, DGPPM Reviewer BMBF and numerous international journals.
Publication		Approx. 50 books/book articles, >150 peer reviewed publications, >500 international lectures
Med. Interests		Prevention of preterm birth, fetal growth, fetal programming, prenatal diagnosis, multiple pregnancy, public health concepts, national/international education, future aspects of health.
Awards	1988	Staude Pfannestiel Prize
	2005	Ambroise Pare Medal Int. Academy Perinatal Medicine
	2008	Award World Association Perinatal Medicine
	2009	Hackert Price Prenatal Medicine
	2010	Level III DEGUM
	2013	Pschyrembel Medal
	2014-19	TOP Medical Female Focus
	2014-20	German Ambassador Society of Maternal Fetal Medicine USA
	2015	Dexeus Medal Barcelona
	2016	Honorable Membership Society of Obstetrics & Gynecology Cuba
	2016	Dr . honoris causa Sorbonne-Paris
	2018	Prof. honoris causa Moscow University, Nat. Medical Research Centre
Varia	1997	Founder Clara Angela Foundation http://.clara-angela.info and the Dr. Arabin GmbH & Co KG Witten/Berlin (Head) www.dr-arabin.de
Languages		German, English, Dutch, French, Italian, Spanish
Other interests		Music, literature, art and poetry, integration of humane concepts into halth policy, Organizing creative meetings, encouraging artists & scientists to cooperate, caring for young people on concepts for mothers and children before, during & after pregnancy (affects all of us),

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Table 3) Overview of some essential published studies on the Arabin cerclage pessary with evidence level

Country	Author	Study population		Methods	Evidence	Reference
NL	Arabin et al.	Singletons and twins		Case control	C Per pessary	Arabin et al. J Perinat Med. 2003; 31:122-33
SPA	Goya et al.			Methods US		Goya et al. UOG 2011; 38: 205-9.
SPA	Goya et al.	Singletons, CL< 25 mm		RCT	A	Goya et al. Lancet. 2012 12;379(9828):18
SPA	Carreras	Twins +Laser, CL< 25 mm		Case control	C	Carreras et al. Prenat Diagn. 2012;32:1181-5
HK	Hui et al.	singletons		RCT	B	Hui et al. On J Perinatol. 2013;30:283-8
HK	Ting et al.	singletons		observational	C	Ting et al. JMFNM. 2012;25:269,3-5
GB	Alfirevic et al.	Singletons at risk		Cohort study	C Per pessary	Alfirevic et al. UOG 2013;41:146-51
GER/GB	Arabin & Alfirevic	review		review	D (review)	Arabin Alfirevic UOG 2013;42:390-9
BELG	Cannie et al.	MRI		MRI	D	Cannie et al. UOG 2013;42:426-33
NL	Liem et al.	review		review		Liem et al. Obstet Gynecol 2013: 576723
NL	Liem et al.	twins		RCT	A	Liem et al. Lancet. 2013 Oct 19;382 (9901) :1341-9
NL	Liem et al.	twins		Cost effectiveness	B	Liem et al. UOG 2014; 44(3): 338-45
GER	Kyvernitaks et al.	Patients after conisation		Cohort study	C Per pessary	Kyvernitakis I, et al. GebFra. 2014;74:1003-8
GER	Stricker et al.	singletons		Historical cohort study	B	Stricker et al. AJOG 2016 2016; ;214(6): 739.e1-739.e10
ITAL	Di Tommaso et al.	Twin pregnancies with CL< 25 mm		Retrospective case control		J Obstet Gynaecol. 2016 Aug;36(6):715-718
SPA	Goya et al.	Twins, CL< 25 mm 20-24 SSW		RCT	A	A J O G. 2016 214(2):145-52
ITAL	Saccone et al.	singletons CL<25 mm		RCT	A	JAMA. 2017 19;318 (23): 2317-24
Global	Nicolaides et al.	Twins and singletons, NO TEACHING, NO AUDIT		RCT RCT	A A	A J O G 2016 ;214(1):3.e1-9. N Engl J Med. 2016 Mar 17;374(11):1044-52.
USA	Fox et al.	twin pregnancies		Retrospective study	C	Obstet Gynecol. 2016 Apr;127(4):625-30
NL	Van't Hoofd et al.	twin pregnancies 3 year follow-up		RCT, follow-up until 3 years	A	Ultrasound Obstet Gynecol. 2018 Feb 22
SPA	Pratcorona, , et al.,	Cervical pessary to reduce preterm birth before 34 weeks of gestation after an episode of preterm labor and a short cervix:		RCT	A	Am J Obstet Gynecol, 2018.
SPA	Merced, C., et al.,	Cervical pessary for preventing preterm birth in twin pregnancies with maternal short cervix after an episode of threatened preterm labor:		RCT	A	Am J Obstet Gynecol, 2019. 221(1): p. 55 e1-55 e14.
Vietnam	Dang et al.	twin pregnancies Comparison with vag. PG		RCT	A	Obstet Gynecol. 2019;133; 459-67

Table 4) Overview of registered ongoing studies on the Arabin cerclage pessary (most of them still recruiting)

Country	Coordinator	Content	Design
USA/NIH GLOBAL INTEGRATION	Saade	CROWN OUTCOME	prospective meta-analysis
USA	Hoffman MFM network	Pessary vs. PG in singletons	RCT
USA	Biggio MFM network	CL< 30 mm v PG, vs.exp (3 A) in twins	RCT (3 armed)
USA	Weiner et al.	Patients with pessary and PG vs. PG alone,	RCT
GB	Shennan et al. NH network	Pessary vs. PG/ Cerclage	RCT (3 armed)
GB	J. Norman NH network	Pessary vs. wait and see	RCT
GB	Alfirevic	Pessary vs. PG	RCT
ES	Carreras	Pessary vs. expectant in MC twins with laser	RCT
Vietnam	Dong et al.	Pessary vs. Cerclage in twin pregnancies	RCT
Belgium	Lewi et al. UV Leuven	RCT of Arabin pessary to prevent PTB in twin pregnancy	RCT
F	Vayssiere et al. Toulouse	Pessary vs. expectant policy in twins	RCT
F	Chu St. Etienne	Prevention of PTB in singletons using pessary after reso-lutive threatened PTB	RCT
GREECE	Antsaklis	Pessary vs. expec-tant management in twins	RCT
BRAZIL	Brizot et al. University of Sao Paolo	Pessary vs. PG in twin pregnancies	RCT
BRAZIL	University of Sao Paolo	Comparison of PG and Pessary for the Prevention of PTB	RCT
NL	Pajkrt et al. 5P study	Pessary vs. PG	RCT, Intention to treat
NL	APOSTEL IV study group Amsterdam	Pessary versus cerclage in singleton risk pregnancies	RCT

ITALY	University of Naples Federico II	Arabin pessary vs. Exp. Management in singleton pregnancies with arrested labor	RCT
ITALY	University of Naples	Pessary as Adjunctive Therapy+ Cerclage for the Prevention of PTB	RCT
ITALY	Saccone et al.	Does Cervical Pessary prevent PTB in Twin Pregnancies with short CL	RCT
GB	Koullali et al. CP study	Pessary vs. PG	RCT
Australia	Mol et al.	Pessary vs. PG	RCT
CANADA	Canadian obstetric network	Canadian Study on the association of Arabin pessary w PG	RCT
CANADA	Barret et al.	Arabin pessary vs exp. management in twins	RCT
GER	Kyvernitakis et al. IMPETUS trial	Twin pregnancies Arabin pessary vs. Expectant management	RCT NCT03418311
GER	Kyvernitakis et al. PROMETHEUS trial	Singleton pessary vs. PG	RCT NCT03418012
TURKEY	Zeynep Kamil Maternity and Children's Hospital	Zeynep Kamil Maternity and Children's Hospital Istanbul, Turkey	RCT

Registration of products (see representatives www.dr-arabin.de)

All European countries
Russia and countries from the former Soviet Union (e.g. Kazakhstan, Ukraine, Georgia, etc.)
Latin American countries (Brazil, Chile, Argentina, Peru, Bolivia, etc…
North Africa (Tunisia, Marroquin)
Japan
Malaysia
Thailand
Indonesia
South Korea
USA/Canada (for research, ongoing clinical trials for evaluation)

Ongoing registrations
Pakistan
Mexico
India