Clinical evaluation and risk assessment of urogynecological pessaries to treat patients with genital organ prolapse (POP) or stress incontinence (SI) frequently due to preceding pregnancy/delivery and of cervical pessaries to prevent preterm birth in singleton and multiple pregnancy.

Dr. Arabin GmbH & Co KG, A. Herrhausen Str. 44 58455 Witten-Germany

We are certified according to ISO 13485-2016 including Design and Development (Chapter 7.3) Products which are now in a process of development (see § 7.3) are excluded from this evaluation because they are still not CE-registered or only used as customized samples.

This clinical evaluation must be repeated every year according to the E**uropean Guideline 93/42/EWG and the Revision 4 of GL MEDDEV 2.7/1** for clinical evaluation .

We already consider the Medical Device Regulation (**MDR), specifically** Annex XIV Part A.

The Medical Device Coordination Group (**MDCG)** published a new GL on 24th of April: **2020-5 MDCG 2020-5 "clinical evaluation on equivalence: A guide for manufacturers and notified bodies" and a GL 2020-6 "Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC".**

We acknowledge

- The increasing requirements for author qualification
- Whether there is evidence of comparable equivalence of medical products and studies
- A proof of a systematic search and selection strategy in international data base systems
- A proof of regular updates
- A critical judgement on the literature and the large experience of our company with post medical surveillance (PMS) and post medical clinical follow-up (PMCF)

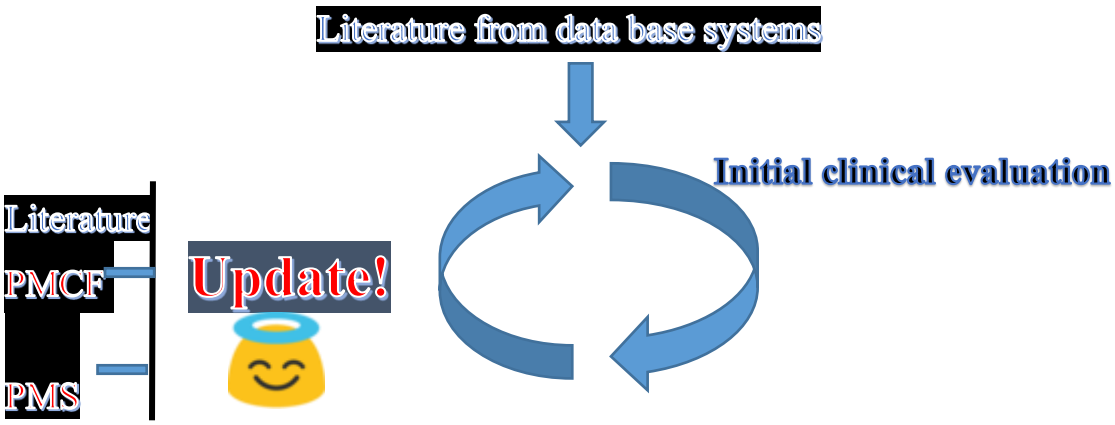


Fig. 1) Process of clinical evaluation according to ISO 13485-2016 / MDCG 2020-5 & 6: Continuous update of evaluation and instructions demanded,

We follow a strategy:

- **Goals**
- **Identification** of publications from data base systems and/or clinical studies
- **Selection criteria for evaluation**
- **Analysis in a summarized rating system**
- **Report** about the evaluation

Own definitions of device groups

A) Product Family 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 2-4 and/or stress incontinence

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

Product family A-c) Special devices with described purpose

10. Adjustment set of ring pessaries
11. Vaginal dilator

B) Product Family Obstetric Pessaries, CE certified

12. Cerclage Pessary (perforated and unperforated)

1.Responsibility

The clinical evaluation and risk assessments were based on MEDDEV 2.7.1Rev.4 & Directive 93/42/EEC, but now on the MDR Annex XIV Part A and guidelines of the **MDCG 2020-5 and -6: Clinical evaluation on equivalence: "A guide for manufacturers and notified bodies" and "Clinical evidence needed for medical devices previously CEmarked under Directives 93/42/EEC/ 90/385/EEC**".

2. Process description

2.1 History and short overview

Vaginal pessaries were already used by Hippocrates ("**primum non nocere**") and in ancient Egypt for the treatment of pelvic floor disease [1-5]. These pessaries were originally made of metal, glass, clay, porcelain, or rubber. **Cervical pessaries** have been used since around 50 years to treat cervical insufficiency during pregnancy, since the 1990s diagnosed by transvaginal sonography (TVS) [6, 7]. Our products are fabricated by high quality body-compatible silicones.

Vaginal pessaries have been used to treat symptomatic genital organ prolapse (POP) and stress incontinence (SI) avoiding risks of surgery or anesthesia. The Dr. Arabin GmbH &Co KG started in 1968 as a small manufacture to provide devices of pessaries for women's' needs by Dr. Hans and Dr. Gretel Arabin, mainly for their own patients. A summary of their experience was provided in a book chapter which was only published in 1990 after the death of Hans Arabin[8].

After transperineal sonography (TPS) and TVS were introduced to objectify the indication of pessaries in the field of gynecology and obstetrics, Birgit Arabin realized the clinical value in desperate patients with either genital prolapse or cervical insufficiency during pregnancy. Since no company wanted to continue with the manufacture she decided to found a small GmbH & Co KG on the campus of the PRIVATE UNIVERSITY WITTEN-HERDECKE and transferred the production to a center for handicapped workers in Zwolle-the Netherlands (WEZO/TIEM). With increasing

numbers of pessaries produced injection molding techniques were integrated. Work processes were standardized and CE-certified with the support of MDSS HANNOVER and MED CERT Hamburg. In 2012, a training center in Berlin was established and training courses expanded in cooperation with urogynecologists and specialists in MFM to stimulate studies and to develop new designs. The coordination of design, technical, biological and clinical science and the whole safety process is controlled by increasingly demanding European regulations.
To meet **"patients 'needs" devices have to be continuously improved or even new models have to be designed.** This was the motivation to get certified for ISO 13485-2016 including Annex II, which means the possibility to adapt previous devices, to develop new forms and to improve. **Similarly, the instructions must be continuously adapted according to post clinical surveillance and physician and patients should consider this material on our web site: www.dr-arabin.de.**
Experienced colleagues regularly conduct training courses mainly how to use urogynecological devices – but lately, it became clear that also the application, surveillance and removal of cervical pessaries also must be trained. There is still a huge discrepancy between the chances of pessary treatment within competent teams and the reality, where "anybody" tries to prescribe a pessary without any understanding of the technical, biological and clinical features, indications and contra-indications. Specialists are rarely trained and regard pessary treatment not as an equivalent therapy to surgical or pharmacological treatment. Pharmacological treatments are less time consuming to explain and surgical treatments offer a higher income for hospitals and physicians.
Last, but not least, nowadays' study and opinion leaders are rarely human clinicians, but rather use statistics of RCTs or meta-analyses for lectures or publications without being able to separate those without good clinical practice.
The risk-benefit ratio of pessary treatment is evaluated by cohort studies and randomized trials. **For all pessaries, the risks are relatively small. The benefits not only depend on the devices themselves but also on their handling (see below).** .

2.2 Description of physical/chemical properties

We have strived to summarize the most important features in a Tab. 1 (2 pages). Thereby, we comment the present most important groups and single models and their names, the classification according to contact times with vaginal mucosa, the sizes, the indications and contraindications and the origin of silicone.

Pessary type/classification	Sizes	Duration Therapy Without interruption	Indications	Contraindications	Silicon/Manufacturer
GYNECOLOGICAL PESSARIES	**UMDNS-13004 GMDN 34149**				
Thick Ring - IIa CE+ since 1970 	50-100 mm Each in 5 mm steps	< 30 days	Symptomatic prolapse grade I-II with or without stress incontinence	Prolapse grade III, no resistant pelvic floor	Neukasil networker and RTV25 WEZO-NL
Hodge Pessar-IIa CE+ with aluminum since 1968 	55-95 mm Each in 5 mm steps	<30 days	Rare situation that requires an adaptation of the shape, uterine retroflexion	Prolapse grade III, no resistant pelvic floor	Neukasil networker and RTV25 early tailor
Bowl and sieve bowl pessaries - IIa CE+ since 1968 	55-95 mm Each in 5 mm steps	< 30 days	Symptomatic prolapse grade I-II, Stress incontinence	Prolapse grade III, no resistant pelvic floor	Neukasil networker and RTV25 WEZO-NL
Urethral cup pessary - IIa with pressure point for Urethra **CE+** since 1968 	55-90 mm Each in 5 mm steps	< 30 days	Stress incontinence	Neurogenic incontinence Prolapse grade III, i.e. no load-bearing pelvic floor	Neukasil networker and RTV25 WEZO-NL
Urethra Pessary -IIa CE+ with steel spring core steel 4301/4310 and pressure point for urethra since 1968  **Without steel inlay** **Standardized compression Since 07-2019**	45-100 mm Each in 5 mm steps	< 30 days	Stress incontinence	Neurogenic Incontinence, Prolapse Grade III i.e. no load-bearing pelvic floor	Until 2019 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
Ring pessary - IIa CE+ with steel spring core Steel 4301/ 4310 since 1970  **Without steel inlay** **Standardized compression Since 07-2019**	50-100 mm Each in 5 mm steps	< 30 days	Prolapse grade I-II, stress incontinence only during exercise	Prolapse grade III	Until 2019 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

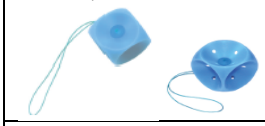
Cube Pessary –IIa CE+ Perforated/ unperforated with button and threat, since 1970 	25-100 mm (edge length) In 5 mm steps	Daily change by patient	Severe genital prolapse (Grade II-III)	Increase of incontinence, ulcers, limited capability for daily change	Elastosil R+4000 Color paste PT RAL5010 RILSAMID AMNOTLDPA12 (button)
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	Elastosil R+4000 Color paste PT RAL 5010 compelling
Club (Gelhorn) pessary -IIb CE+, since 1970, **IIa proposed** since 2020 	55-90 mm in 5 mm-steps	>28 days	Severe genital prolapses grade II-III when other devices do not help	Eventually atrophic sensitive vagina	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	Sexual dysfunction (e.g. after operations, aberrations)	First 2 weeks after an operation	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	Uncertainty of sizes **Validation for cleaning & sterilization**	None	Elastosil FL 6010/ Green color paste RAL v.Kempen-NL
OBSTETRIC PESSARIES	**UMDNS13004 GMDN 35260**				
Cerclage-Pessary - IIb CE+(Model 3) (un) perforated and compression adapted since 2020, 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	Silpuran8020 Color paste PT RAL5010 v.Kempen-NL until 2020 and DINO AG from 2020 onwards including compression adaptation

Table 1) Direct comparison and characterization of devices / Dr.Arabin GmbH &Co KG

Page 1: Product group A-a) Annular gynecological pessaries for genital prolapse I-II and/or stress incontinence
Page 2: Product group A-b) gynecological pessaries for genital prolapse II-IV and/or stress incontinence
Page 2: Product group A-c) Vaginal Stretchers/ADAPTION SETS/ Product group B) obstetric pessaries

2.3 Literature search, evaluation & rating, current knowledge of all products

The **search date** is the end of June 2020. For the **methodology of the literature search,** the general methods for the preparation of a systematic review are recommended and the following databases were searched using mesh terms (e.g. pessary, genital prolapse, preterm birth etc.)):

- The Cochrane Library, John Wiley & Sons update.
- PubMed database, up to date, if available EMBASE.
- Personal congress visits and correspondence
- The database "clinical trials" was searched for ongoing studies.
- Guidelines from various countries.

The Regulation (EU) 2017/745 on medical devices **(MDR)** provides criteria to use clinical data related to an equivalent device required for a device under conformity assessment of a device for which equivalence to the device in question can be demonstrated or rejected. MEDDEV 2.7/1 rev. 4 is now replaced by the MDR Annex XIV Part A(3). In case of divergence between MEDDEV 2.7/1 rev.4 and MDR, **the MDR with the according guidelines of the MDCG has priority requiring that technical, biological and clinical characteristics are evaluated and rated.** A Gap analysis was performed according to differences in criteria (see below):

Tab. 2) Comparison of criteria for evaluation by the MDR as compared to MEDDEV 2.7/1rev.4

Technical characteristics

MDR, Annex XIV Part A (3)	MEDDEV 2.7/1 rev 4, Appendix A1
The device is of similar design; is **used under similar conditions of use**; has similar specifications and properties including physicochemical properties such as intensity of energy, tensile strength, viscosity, surface characteristics, wavelength and **software algorithms**; uses similar deployment methods, where relevant; has similar principles of operation and critical performance requirements.	- be of similar design, and - **used under the same conditions of use,** and - have similar specifications and properties (e.g. physicochemical properties such as type and intensity of energy, tensile strength, viscosity, surface characteristics, wavelength, surface texture, porosity, particle size, nanotechnology, specific mass, atomic inclusions such as nitrocarburising, oxidability), and - use similar deployment methods (if relevant), and - have similar principles of operation and critical

Biological characteristics

MDR, Annex XIV Part A (3)	MEDDEV 2.7/1 rev. 4, Appendix A1
The device uses the same materials or substances in contact with the same human tissues or body fluids **for a similar kind and duration of contact and similar release characteristics of substances, including degradation products and leachables**	Use the same materials or substances in contact with the same human tissues or body fluids. **Exceptions** can be foreseen for devices in contact with intact skin and minor components of devices; in these cases risk analysis results may allow the use of similar materials taking into account the role and nature of the similar material.

Clinical characteristics

MDR, Annex XIV Part A (3)	MEDDEV 2.7/1 rev. 4, Appendix A1
The device is used for the **same clinical condition or purpose**, including similar severity and stage of disease, at the same site in the body, in a similar population, including as regards age, anatomy and physiology; **has the same kind of user**; has similar relevant critical performance in view of the expected clinical effect for a specific intended purpose.	- used for the same clinical condition (including when applicable similar severity and stage of disease, **same medical indication**), and - used for the same intended purpose, and - used at the same site in the body, and - used in a similar population (this may relate to age, **gender**, anatomy, physiology, possibly other aspects), and - not foreseen to deliver significantly different performances (in the relevant critical performances such as the expected clinical effect, the specific intended purpose, the **duration of use**, etc.)

Demonstration of equivalence (E)

MDR, Annex XIV Part A (3)	MEDDEV 2.7/1 rev. 4, Appendix A1
The characteristics listed in the first paragraph shall be similar to the extent that there would be no clinically significant difference in the safety and clinical performance of the device. Considerations of equivalence **shall be based on proper scientific justification**.	For assuming equivalence, - all three characteristics (clinical, technical, biological) need to be fulfilled; - similar means that no clinically significant difference in the performance and safety of the device would be triggered by the differences between the device under evaluation and the device presumed to be equivalent.

PART A: Gynecological pessaries

Group Aa: Round pessaries for the treatment of pelvic organ prolapse (POP) I-II or [9]prolapse II-IV and/ or stress incontinence (SI)

Background of medical condition and introduction

Complains of pelvic organ prolapse (POP) and/or stress incontinence (SI) may already arise during pregnancy, e.g. "pregnancy is already a window for future health of mothers-to-be [10]". During vaginal delivery, a variety of risk factors may additionally change the structure and anatomic integrity of the connective tissue and ligaments with visible macro- or invisible microtrauma, may cause injuries and tears of muscles of the pelvic floor, specifically the levator ani ("avulsion") which can be diagnosed clinically and sonographically [9]. Injuries of the internal and external sphincter ani are frequently diagnosed after birth but can also be overlooked and cause later problems without proper treatment. In general, lesions may occur at different compartments (anterior/posterior/lateral) Consequently, around 1/3 of elderly women suffers from mild or severe POP and/or SI.
Imaging of the pelvic floor structures can be learned . Nevertheless, only a few obstetricians have a deep understanding how to prevent, diagnose and treat POP or SI and rather refer the patients at a late stage to urogynecologists.
Operations imply risks of surgery and irreversible complications, as described for Mash operations but also have recurrence risks depending on the surgeon and the technique. In patients who still plan to get pregnant or who have medical risks for surgery or just minor symptoms at stressful occasions (e.g. sports) pessary treatment is the first choice[11]. In symptomatic prolapse, pessary treatment may relieve symptoms immediately, during 6-12 months [12] or even lifelong.

Studies/reviews with non-equivalent/equivalent/ round pessaries as compared to our devices

Most studies published in the international literature used similar models whereby it is not always clear whether the material is "equivalent". The indication of gynecological pessary therapy depends on education and experience [13]. Care takers should primarily consider the individual situation and preferences of the patient after appropriate informed consent [14-16]. According to recommendations of international and national expert committees, conservative treatment should always be the first choice mainly for patients with genital prolapse before surgical therapy is recommended. The direct comparison of both methods is irrelevant for patients in whom surgery is contraindicated.
Typical complications of pessary therapy may depend on the material, on the shape of the pessary itself, but primarily on the adjustment, teaching and information of the patient, her handling and regular replacement. After the menopause, the use of additional creams can avoid lacerations and improve insertion and vascularization of the mucous tissue. German experts recommend to use 50g Oestrogynadion (2x/week), Vagisan-Dr. Wolff Cream (to re-establish the pH 5x/week) and Linova (a fat protection cream) (7x/week), but this should be adapted to the patients 'needs. Pessary treatment with ring pessaries was more frequently abandoned in patients with previous hysterectomy or stress incontinence and pelvic organ prolapse (POP) [17]. However, it is not sufficiently discussed that other models might have been more satisfying. Most gynecologists have limited education in pessary therapy and do not take enough effort to adapt the pessary or different models. Nevertheless, 75% of women with the most simple ring pessaries pessaries decided not to undergo surgery only after a standard therapy with ring pessaries [17].

Studies performed with our cube pessary

Our cube pessary was examined in a quality of life study. It turned out that in patients > 60 years the quality of life after therapy with this pessary increased significantly [18].

Guidelines/Cochrane reviews/Overviews

A Cochrane review on the use of mechanical devices for POP stated in 2013: There is no consensus on the use of different types of device, indications nor the pattern of replacement and follow-up care. There is an urgent need for RCTs to address the use of pessaries in comparison with no treatment, surgery or conservative measures [19]. Since then there is little progress.

The German S23-guideline refers to conservative treatment of genital prolapse. The final conclusions are: Vaginal pessaries can be combined with operations, long-time studies are missing whether this increases the success rates, but observations are discrepant (EVIDENCE III). Vaginal pessaries should be advised for genital prolapse, Unfortunately, the type of models which should be chosen was never investigated systematically (II) [20].

The **Canadian guidelines referring to gynecological devices recommends** [21] (S**tatements):**

1. Most women can be successfully fitted with a pessary when they present with prolapse. (II-2)
2. Complications are usually minor, vaginal discharge is the most common complaint. (II-3)
3. Vaginal erosions are treated with removal of pessaries optimizing estrogen supplementation. (II-2)
4. Satisfaction rates with pessary use are high. (II-2)

Recommendations: 1. **Pessaries should be considered in all women presenting with symptomatic prolapse and/or urinary stress incontinence. (II-1A) and the patients should be informed about these conservative therapy options before deciding for a more invasive and costly operation.**

The most recent overview in German language summarizes the state of the art in 2020 [22].

ANALYSIS OF SINGLE STUDIES

In Tab.3 we refer to a systematic literature search and try to rate the meaning for our devices considering the criteria of MDCG -2020-5.

TAB. 3) Literature search, stepwise rating of gynecological pessaries (acc. to MDCG 2020-5) E=Equivalence

Country/Design (Study/Device)	Reference	Study population	Technical criteria	Biological criteria	Clinical criteria (results)	Rating (agreement of 2 independent external auditors)
CHINA RCT/ RING pessary	Tam et al: The effect of time interval of vaginal ring pessary replacement for POP on complication and patient satisfaction. Maturitas. 019;128:29-35. Epub 2019	101 patients with POP stage I-IV, randomized for controls	E (?)	Longer treatment durations than our products, no different models	Patients satisfaction/ safety: overall complication rate in the 6-monthly group higher than that in 3-monthly group at third visit (9 [30%] vs.3[10.3%];OR 3.71; 95%CI 0.89-15.58)	Not valid for our products because a)indications and b)duration not similar justifies classification to IIa products
CHINA OBSERVATIONAL RETROSPECTIVE RING pessary CLUB pessary	Yang et al. Ring and Gelhorn pessaries used in patients with POP: a retrospective study of 8 years. Arch Gynecol Obstet.2018;298:623-9.	300 patients with POP Pelvic Floor Disability Index PFDI-20 and PFIQ-7, mean age 68y,n=249 (83%) successful fitting	E (?)	Longer duration, no different models	Patients satisfaction/safety: 79% (very) satisfied, Difficulty in inserting or removing (30%), erosions (22.8%) were the main factors, which affected the satisfaction.	Partly relevant for our products, but more models in case of no satisfaction should be offered (e.g. cube)
THAILAND OBSERVATIONAL RETROSPECTIVE RING pessary CLUB pessary	Yimphong et al. Discontinuation/ adverse events after 1 year of vaginal pessary use in women with pelvic organ prolapse. Int Urogynecol J. 2018 ; 29:1123-28.	140 patients, with POP, mean age 71 y., discontinuation rate after 1 year was 16.1%.	E (?)	Longer duration, no different models	Reason for discontinuing expulsion (26.3%), vag. discharge:17.1%. BMI and history of hysterectomy were additional risks (0.76 [0.62-0.93] and 15.89 [1.67-151.02]	Partly relevant for our products, since more models in case of no satisfaction (e.g. cube) should be offered
CANADA CASE REPORT(2) NO TREATMENT RING PESSARY	Liu et al. Unusual Perils of POP. J Obstet Gynaecol Can. 2017 ;39(11):1038-41. .	3 patients: a 64-y-old with grade 4 POP, an 81-y-old treated for 18 y, VV fistula, an 80-y-old with long-standing pessary stopped vag. estrogen 2 y before developing a fistula.	E (?)	Longer duration, no different models	SAFETY ISSUE, Fistula from an ulcerated area of the prolapse into the peritoneal cavity with longstanding pessary	Not valid for our series because inadequate model and duration of treatment.
USA RETROSPECTIVE COHORT	Jackson et al. Knowledge, perception and attitudes tow. POP and UI in Spanish-Speaking Latinas.	24 women/ 2 groups with POP/UI, 2 groups with POP symptoms, 1 group asymptomatic. 52y, concepts identified	E (?)	NA	Views of POP/UI as "abnormal conditions"; providers downplay/ ignore symptoms of POP/ UI; embarrassment; massage therapy effective	Confirms ignorance of physicians and poor health literacy towards options of pessary therapy

NEPAL PROSPECTIVE COHORT STUDY RING PESSARY	Robert et al. Feasibility of using pessaries for treatment of pelvic organ prolapse in rural Nepal. Int J Gynaecol Obstet 2017;136:325-30	411 women, 142 with symptomatic POP, initial fitting for 134 (94.4%) After 1y 130 (97.0%) evaluated, 72 (55.4%) still using pessary.	E (Partly)		First reason for discontinuation was falling out a)(35/58, 60.3%). Other complication. erosion (18/130,13%)only in PM women, PM . status was a predictor of con. use (OR 3.12, 1.45-6.72; P=0.004).	Not valid because of a)inadequate model and b) inadequate uncontrolled duration.of therapy
HONG KONG RCT RING PESSARIES	Cheung et al. Vaginal Pessary in women with symptomatic POP A RCT. Obstet Gynecol. 2016 Jul;128(1):73-80.	276 randomized as follows: 137 controls, 139 pessary group.	E (Partly)	Longer duration, no different models	POP Inventory & Impact Questionnaire decreased in pessary group (POPDI: -29.7 compared with -4.7, P<.01; POPIQ: -29.0 vs. 3.5, P<.01). Complication rates were similar.	Shows that pessary better works than expectant management even when only ring pessaries are used.
The NETHERLANDS SURVEY ALL SORT OF PESSARIES	Velzel et al. A nation-wide survey concerning practices in pessary use for POP. Int Urogynecol J. 2015;26:1453-8. Velzel	Nationwide survey. Response rate 59 %. 13 % of women had a written protocol for pessary treatment, as proposed by 69 % ..	E (?	Longer duration, no different models	Side effects: discharge., blood loss, Follow-up after placement by 69 % of respondents at 2/6 weeks, by 2 % at 8 weeks, and by 29 % at 12 weeks.	The study confirms that there is no guideline/ no basic knowledge about indications for different devices.
CANADA LITERATURE SURVEY 1942-2014 PASSARY INSUFFICIENTLY DESCRIBED	Abdulaziz: An integra-tive review and severity classification of complications related to pessary use in the treatment of female POP. Can Urol Assoc J. 2015;9:E400-6.	61articles: discharge, erosion, bleeding related to pessary shape, material, duration in situ, serious complications adjacent organ fistula and death.	E (?)	Longer duration, no different models described	Few reports about complications/ estimated frequency of pessary use worldwide. Prosp. studies with complications by shape, material, size, & objective classifying severity are required.	Different models, short uninterrupted treatment period Development of PMS & PMCF guidelines for long-term users justified.
USA SURVEY PESSARY NOT DESCRIBED	Tenfelde et al. Quality of life in women who use pessaries for longer than 12 months Female Pelvic Med Reconstr Surg. 2015;21:146-9. .	56 women, 74.4 y, completed the survey. Duration pessary use was 4.5 (1-15) y. 31 women (55.4%) went to the clinic for pessary care every 3 months.	E (?)	Longer duration, no different models described	PFDI-20 in women performing self-care vs follow-up. 29% reported vaginal erosion. 41% considered surgical repair Pessaries can be used to control POP for extended periods.	Shows that self-care (what we recommend) is equivalent.
THAILAND PREFERABLY RING OR RING WITH SUPPORT PESSARIES	Lekskulchai et al. Factors Affecting Successfulness of Vaginal Pessary Use for the Treatment of POP. Med Assoc Thai. 2015; 98 Suppl 3:115-20.	252 women with POP, 67(29-92 y). 78.2%, had severe POP (stage 3-4). 194 women had vaginal pessary. 83.5% used continuously more than 3 months.	E (Partly)	Longer duration, no different models described	The ring is was mostly used with fewer complications followed by ring with support. Short vag. length and post. defects impair pessary use, duration > 3 months!	Not valid because most patients used pessaries longer than 3 months without interruption
USA PATIENTS AFTER MESH EXCISION 1 PESSARY USER, NOT SPECIFIED	George et al. Recurrence of prolapse after transvaginal mesh excision. Female Pelvic Med Reconstr Surg. 2013,-19:202-5.	71 patients with partial or complete (63%) mesh excision.	-E (Partly)	-?	At 1 year postoperatively, patients with total excision were better. No patients required a second surgery, and one patient was treated with a pessary.	Only shows serious complications with mesh surgery.which was now forbidden by the FDA, these patients would have been better treated with a pessary
USA MEDICARE SURVEY UNSPECIFIED MODELS	Alperin et al. Patterns of pessary care and outcomes for medicare beneficiaries with POP. Female Pelvic Med Reconstr Surg. 2013 19(3):142-7.	Of 34,782 women with POP, 4019 women (11.6%)were treated with a pessary., 40% underwent a follow-up visit with the provider who had placed the pessary, through 9 years after the initial fitting,	E (Partly)	Unacceptable care, this means too long duration of unchanged mucosa contact	3% vesico-vaginal/ rectovaginal fistulas, 5% mechanical genitourinary device complication, 12% had surgery for POP by 1 year; 24% by 9 years. A low percentage of Medicare beneficiaries undergo pessary fitting. Lack of continuity of care associated with fistulas.	Justifies our concept **"Dare to care"**
HONG KONG RETROSPECTIVE COHORT	Chan et al. Symptoms, quality of life, and factors affecting women 's treatment decisions Regarding POP. Int Urogynecol J. 2012;23:1 027-33.	308 women with POP assessed by Pelvic Floor Distress Inven-toryPFDI, Pelvic Floor Impact Questionnaire PFIQ Short Form-36, POP Quantification	E	Longer duration without care, no different models described	Complication, urody-namic stress incontinence (USI), stage of prolapse, and Pelvic Organ Prolapse Distress Inventory scoring were factors for choosing surgery	Difficult to interpret because care and pessary models not specified.

AUSTRALIA RETROSPECTIVE CHART REVIEW RING PESSARY	Sarma et al. Long-term vaginal ring pessary use: discontinuation rates and adverse events. BJOG. 2009;116: 1715-21.	273 women fitted with a ring pessary, 167 successfully using it at 4 weeks.	E	Different biological material (polyester)	93 (56%) experienced complications (bleeding, discharge,pain, constipation. Only 23/167 (14%) continued with pessary at the study endpoint	Not valid because polyester rings were used not equivalent with our series of products nor our care concepts.
THAILAND PROSPECTIVE COHORT	Sitavarin et al. The characteristics and satisfaction using vaginal pessaries. J Med Assoc Thai. 2009;92:744-7.	40 subjects, age 70y. Reasons for choosing a pessary included risks and reluctance to undergo surgery.	E	Unclear biological comparison	The complications from using a pessary were vaginal erosion, 1 case. 37 (92.5%) were satisfied and continued to use pessaries.	Confirm our experience.
UK NATIONWIDE SURVEY UNSPECIFIED MODELS; MOSTLY RING PESSARIES	Gorti et al. Evaluation of vaginal pessary management: a UK-based survey J Obstet Gynaecol. 2009 29(2):129-31.	640/1,173(54.6%) clinicians returned questionnaires 555 (87%)used pessaries. 23% used to change pessaries every 3-6 months; 67% every 6 months	E	LONGER DURATION	Complication rates of 40%, 35%/ 18% by controls 12 monthly, 6-monthly and 3-monthly intervals. Discontinuation after expulsion in 54%, discomfort in 27% vaginal bleeding/ infection 7.8%, dislike change:10%.	Not valid because difficult to compare with our series of many different devices and a stepwise approach
USA CASE REPORT	Kaaki et al. Vesicovaginal fistula resulting from a well-cared-for pessary. Int Urogynecol J Pelvic Floor Dysfunct. 2007 18:971-3.	A84-year-old woman presented with a vesicovaginal fistula after appropriate use of a Gehrung pessary for 12 y.for stage III POP.	Not equivalent	Not equivalent	The patient reported strict adherence to removing her pessary nightly and replacing it in the morning.	Not valid because a)his model is not in our series, b)unusual duration
USA PROSPECTIVE STUDY DEVICE NOT SPECIFIED	Clemons et al. Patient satisfactionand changes in prolapse and urinary symptoms. Am J Obstet Gynecol. 2004 190: 1025 -9.	100 women with symptomatic POP fitted with a pessary, 73 had a successful 2-week fitting trial.	E	Unclear duration without change,	POP symptoms resolved in 2 months, pressure (49% to 3%; P<.001), discharge (12% to 0%; P=.003),UI improved in 45%,urge incontinence in 46%, voiding difficulty in 53%, de novo UI occurred in 21%, At 2 months, 92% of women were satisfied with pessary., 6 (8%) dissatisfied/ occult SI	Shows that pessary therapy is justified and low risk.
THE NETHERLANDS RCT MOSTLY USED RING PESSARY	Coolen et al., Primary treatment of POP: pessary use versus prolapse surgery. Int Urogynecol J, 2018. 29(1): p. 99-107.	113 women (74 with pessary, 39 with surgery). After 12 months, the POP domain score was 0 (10^{th}-90th centile 0-33) with P vs. 0 (10^{th}- 90th centile 0-0) with surgery ($p < 0.01$).	E	Unclear duration of treatment	In women with POP stage II or higher undergoing surgery, POP symptoms were less severe than in patients with a pessary, but 72% of women with a pessary did not opt for surgery.	Shows that pessary treatment makes sense, devices should be specified and when a ring is not helpful another device should be used before surgery.
UK PROSPECTIVE COHORT RING AND CUBE PESSARY	Fernando et al. Effect of Vaginal Pessaries on Symptoms Associated With POP. Obstet Gynecol2006;108:93-9.	203 women fitted with pessary, 153 (75%) successfully retained the pessary at 2 weeks, and 97 completed ques-tionnaires at 4 months. Failure to retain a pessary was associated with parity (OR 1.52,1.14-2.02,), hyste-rectomy (OR 4.57, 1.71-12.25, P = .002).	E	E Professional use, equivalent to our recommended procedures	At 4 months voiding was improved in 39 women in (40%, P = .001), in urge urinary incontinence by 28 (29%, P = .015), in bowel evacuation by 27 (28%, P = .045), in urge fecal incontinence by 19 (20%, P = .027)16 (17%, P =001) reported increase in sexual activity, and 11 (11%, P = .041) improved satisfaction.	In professional hands, pessary use improves all complaints of POP.
UK PROSPECTIVE COHORT STUDY RING AND CUBE PESSARIES	Lone et al. A 5-year Prospective Study of Vaginal Pessary Use for Pelvic Organ Prolapse Int J Gynaecol Obstet 2011;114(1):56-9.	Of the 151 women, 21 (13.9%) discontinued use at some point after 4 weeks, whereas 130 (86.1%) used the pessary successfully over 5 years.	E	E Professional use, equivalent to our recommended procedures	12.1% of women experienced complications (6.9% pain or discomfort, 3.2% bleeding, and 2.0% constipation within 4 weeks of insertion. After cessation of pessary use, 70 (28.5%) of the 246 women chose surgery and 10 (4.1%) chose no further treatment.	In professional hands, pessary use improves all complaints of POP

UK PROSPECTIVE COMPARATATIVE STUDY RING & CUBE PESSARY SAUDI ARABIA SYSTEMATIC REVIEW DIFFERENT MODELS USED	Lone et al. One-year prospect. comparison of vaginal pessaries and surgery for POP using the validated question-naires. Int Urogynecol J. 2015;26:1305-12. Al-Shaikh et al. Pessary Use in Stress Urinary Incontinence: A Review of Advantages, Complications, Patient Satisfaction, and Quality of Life Int J Womens Health 2018, 17;10:195-201.	287 women with symptomatic POP were recruited. 269 women completed a question-naire at baseline and 183 at 1 year. PubMed and Cochrane databases searches from 2000-2016 and published guidelines of Am. Urolog. Association, Canadian Urological Association, American Urogyn. Society, NIH and NICE were searched: A total of 192 original research papers, review articles, and clinical trials were identified.	E E	Professional use, equivalent to our recommended procedures Unclear	Overall improvement in vaginal, sex, QOL and urinary symptom scores in both groups. No significant difference noted between surgery and pessary groups. The reviewed studies document that vaginal pessaries provide an adequate control of SUI if they are fit properly and managed by frequent replacements and regular checkups. They should be considered among the first line of treatment for SUI associated with exercise and increased intra-abdominal pressure.	In professional hands, pessary use improves all complaints of POP Confirms our recommendations

Conclusion from clinical studies:

a) Technical aspects: Older studies analyzed pessary treatment made from polyester or rubber, present studies use silicone devices with a similar design as our devices. But many health care providers only use one model and have no experience with the diversity of different devices. Unfortunately, the material is insufficiently described in many studies which makes equivalent rating difficult.
b) Biological aspects: The contact time with the mucosa varies widely with recommendations of leaving the pessaries up to 6-12 months before a control is advised. In our instructions, we recommend a check-up 1 week after placement and then again after 4 weeks. We also advise self-control as much as it is possible, e.g. frequent changes to avoid overdistension, any erosions and to avoid fistulas.
c) Clinical aspects: Success of pessary use to treat POP or SI highly depends on instructions of patients, frequent change and choice of appropriate devices. Patients with POP and posterior defects and/or hysterectomy have more treatment failures or should have different models.
A stepwise use of models might further improve the success rates. Thereby, good studies are missing.

Final conclusion from PMS:

Pessaries from Silpuran/Elastosil silicone (injection technique)
In the various reports from our TD we could detect that our devices are well accepted, in general it is appreciated that the **ring and urethra** pessaries which were developed using compression values are now fabricated without metal inside. Some older patients, however, still prefer the older models because they were thinner and the pelota rounder.
Cube pessaries still have a small chance that a threat might dislocate in spite of all our efforts to improve the button with threat. Otherwise these are the best accepted and mostly used devices
Pessaries from Neukasil (manually produced)
Feed-back about other gynecological pessaries demonstrate low rates of complaints, the club pessary, which is indicated in severe genital prolapse, is quite stiff – when the devices are compressed this can be objectified in Newton. Nevertheless, this is a reason why we now start research in verification and validation to change the models to thinner ones so that patients can handle them more easily.

Final conclusions from PMCF

No serious reports, no indication for further inquiries.
For each device, we have extensive descriptions related to risk-analysis and reports in each technical documentation.

Group A-c) Vaginal dilators

Background of medical condition and introduction

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 [23] and Edmonds [24], 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 vaginal reconstruction is a first line approach in most patients". Patel et al. described use of vaginal stretchers in case of vaginal agenesis; > 50% of users reported success by regular sexual intercourse. Complications were only discomfort/pain during therapy. One Cochrane review reports on the use of vaginal dilators during radiotherapy concluding that "there is no evidence that routine vaginal dilation during radiotherapy prevents stenosis or improves quality of life. More studies are needed" [25].

Final conclusion from clinical studies:
a) Technical aspects: The sizes might be adapted in a future change procedure.
b) Biological aspects: The material determining the biological properties of vaginal expanders is Neukasil. Biocompatibility should be similar to our tests with the same material (urethra pessary).
c) Clinical aspects: There are rare indications for vaginal expanders, safety issues are not relevant since patients have always control of their therapy and it is timely.

Final conclusion from PMS:
Air filled expanders are appreciated. The sizes might be adapted. Under some circumstances. Stiffer models are desired.

Final conclusions from PMCF:
No serious reports, no indication for further inquiries

Customized pessaries

Together with a team of experts (Team "input"), we have tested modifications of our devices in the treatment of POP and SI including early prevention after vaginal delivery and/or operations (under research conditions). However, the co-operation of specialized urogynecologists is not always easy. We are also prepared to fabricate completely different models by customized procedures according to patients' needs. For the order, fabrication and evaluation we have special document process.
This work has to be followed in the future, but since directly printed models are not yet allowed as class II products with a longer stay with human mucosa, it has to be awaited whether customized models might be useful for some patients in a directly printed form (3D).

PART B: Obstetric pessaries

Cervical pessaries of our team in different sizes and resistance

Background of medical condition and introduction

Preterm birth is defined as any delivery before completed 37 gestational weeks and is associated with suffering for families. In spite of many efforts, its frequency has not decreased because secondary prevention by physicians can change little in comparison to primary prevention – which needs political efforts. Therefore, iatrogenic and spontaneous preterm birth still challenges health care providers and health care politicians. It is the leading cause of perinatal and neonatal mortality and of death among children up to 5 years worldwide, accounting for approximately 35% of deaths among newborns. In 2014, it affected 10.6% of livebirths globally (14.84 million live born preterm neonates) [26]. Survivors experience short-term impairments such as respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), sepsis, and (decreasing rates of) retinopathy, .have lower cognitive, motor, and intellectual scores, are more likely to have cerebral palsy, visual and hearing impairments, attention deficit hyperactivity disorder, behavioral problems and are associated with a higher risk of developing chronic metabolic and cardiovascular diseases in adulthood (also summarized in [27]).

Already in 1981 we have summarized in a German book chapter a **"pyramid" of etiologic factors"** whereby precocious cervical ripening (Figure 2 a) is only the tip of the iceberg and the **interrelationships of pathophysiological processes in a circular model** (Figure 2 b). Basic etiologic risk factors are socioeconomic environments, decreased stress resilience, gynecological diseases and actual pregnancy complications such as breakdown of maternal-fetal tolerance, vascular disorders, risks for infection/inflammation, uterine overdistention leading to anatomical changes in the myometrium and the cervical collagen structure. Biochemically, a decline in placental progesterone action and increased secretion of prostaglandins and interleukins may also be interrelated. Thus, cervical pessary may only postpone some actions of this process. **Nevertheless, in this book chapter from 1981 Model 1 of the cervical pessary was demonstrated for the first time which was then rarely used only by a few German specialists [28].**

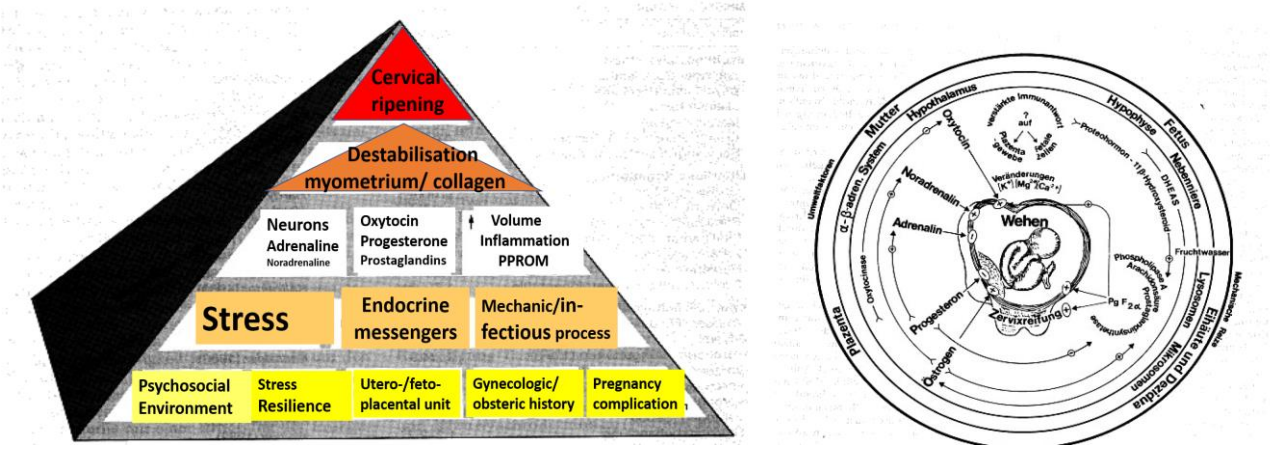


Fig. 2) Pyramid of etiologic factors (a) and pathophysiological processes (b) associated with preterm birth (designed by B.Arabin 40 years ago).

Only when transvaginal sonography (TVS) was introduced after 1990 and B.Arabin was confronted with desperate patients in a preterm birth clinic in the Netherlands, she tried to integrate the model into clinical care and evaluated the effect in a pilot case-control study [29].
Preterm birth had been also declared to be a “syndrome” with many causes [30]. More specific animal and human research could detect the role of “transgenerational and actual stress” (summary in [31]) and that toxins from the vaginal microbiome may directly affect the cervical tissue without necessarily ascending to the amniotic cavity [32] . Not only preterm birth, but also cervical shortening as diagnosed by TVS [33] are only one sign of precocious cervical ripening. Although the sensitivity of cervical length (CL) measured by TVS is relatively poor, the detection of the CL has become a pragmatic tool to diagnose asymptomatic threatening preterm birth. Given the complex etiology, pessary treatment cannot be the only solution to solve a process which has already been started. Nevertheless, studies taken before and after treatment by NMRI have shown that a pessary can direct the cervix towards the sacrum, can non-invasively change the utero-cervical angle and “restore” funneling and cervical shortening [34].

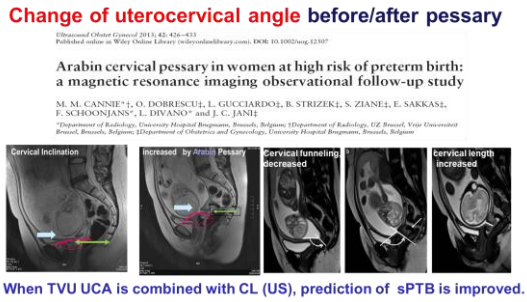


Fig. 3) NMR imaging of cervices before and after pessary application according to Cannie et al. 2013.

After the first pilot publication in single and twin pregnancies [29] it took 10 years until randomized controlled trials (RCTs) were published: In April 2012, the first RCT with the indication "Prevention of premature birth in single-gravidity and short cervix" appeared in the Lancet [35] with a corresponding comment [36]. In this cohort only qualified and audited Spanish clinicians, preferably from Barcelona were involved, who inserted, followed and removed the devices. It was could be proven that the pessary not only postponed preterm birth, but also reduced the incidence of neonatal morbidity. Other publications such as a retrospective cohort study of Alfirevic, comparing the treatment of pessaries, cerclage and progesterone [37], a pilot study of Carreras et al. in twin pregnancies with twin-to twin transfusion syndrome and laser therapy[38], the Protwin trial from the Netherlands, which also suggested that pessaries may postpone early delivery and its combined consequences in pre-defined subgroups of patients with singleton and twin pregnancies at risk [39, 40]. An analysis of costs versus benefits of twin pregnancy was published after the PROTWIN study [41]. Team Hebron published another RCT in twin pregnancies with short CL between 20 and 24 weeks for pessary versus no treatment [42]. Births before 34 weeks were significantly reduced. When 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 weeks [43]. A Cochrane analysis carried out in 2013 concluded that there were still insufficient data for final conclusions [44]. Retrospective meta-analyses carry risks of selection bias, only one meta-analysis tried to use only pre-registered RCTs and showed a significant advantage of the pessary over no treatment in singleton pregnancies [45].
Since 2014 there have also been efforts to plan a prospective meta-analysis: ”Prospective Individual Patient Data Meta-Analysis of Pessary Trials” supported by the Global Obstetrics Network (GONet), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the Maternal-Fetal Medicine Units (MFMU) Network. The group had defined a unified OUTCOME through a Delphi survey of patients, midwives and physicians. Unfortunately, there seems to be no progress of this initiative.

In 2016, 2 RCTs were published by the group of Nicolaides et al. on the effect of the cervical pessary in twin pregnancies [46] and in singleton pregnancies [47] . Although Nicolaides once declared **"Care givers should be trained, and their results should be subjected to external quality assurance**"[48], only 10 years later, he distributed pessary within different continents admitting that he had not carried out any teaching nor audit related to cervical pessary application, follow-up and removal [49]. A lack of supervision and training is reflected by the high rate of early removal but also by the high rate of antibiotics for discharge [47, 50, 51]. Secondary analyses of the Pro-Twin study had shown that good teaching and compliance to protocols improved the results [52, 53]. In singleton pregnancies, Saccone et al. found a significant effect of the pessary when added to vaginal progesterone [54]. Convincing results in favor of pessary treatment in twin pregnancies are those of an RCT comparing vaginal progesterone and pessary in twin pregnancies – the secret was a continuity of care [55]. Another study compared pessaries with progesterone in singleton pregnancies finding no significant difference in preterm birth rates [56]. **A significant effect of reducing bleeding and prolonging gestation was described in pregnant women with placenta previa** [57].

The **European guideline on Preterm Birth** recommended teaching and audit [58]. The summary reads as follows: "Although promising due to 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, the Workgroup on Preterm Birth of the German Society for Gynecology and Obstetrics included an **addendum on the use of pessaries as part of the guideline on preterm birth** designed in accordance with medical device regulations (MDR) and instructions. Despite encouraging results obstetric pessaries have also been used **without good clinical practice**. Mixing these data in meta-analyses implies a bias. The Cochrane criteria were primarily established for pharmacological studies but not for medical devices or clinical management which cannot be blinded. Nevertheless, **according to the European Medical Device Regulation (MDR)** instructions for medical devices of providers must be followed to avoid claiming of patients. Features of the cervical pessary of our team have also changed which might have some impact on the technical and biological features of the device:: Up to 2014, darker blue models were made from Neukasil in a perforated and non-perforated version. From 2014-2020 cervical pessaries were delivered with less color concentration (approved by the FDA for research), now made from Silpuran (best testing rates of biocompatibility, toxicity, genotoxicity, irritation). Perforations were produced secondarily. From 2020 onwards, we directly produce the perforated cervical pessary and adapt compression tests according to the indication and the approximate weight of the uterus and the size of the vagina.

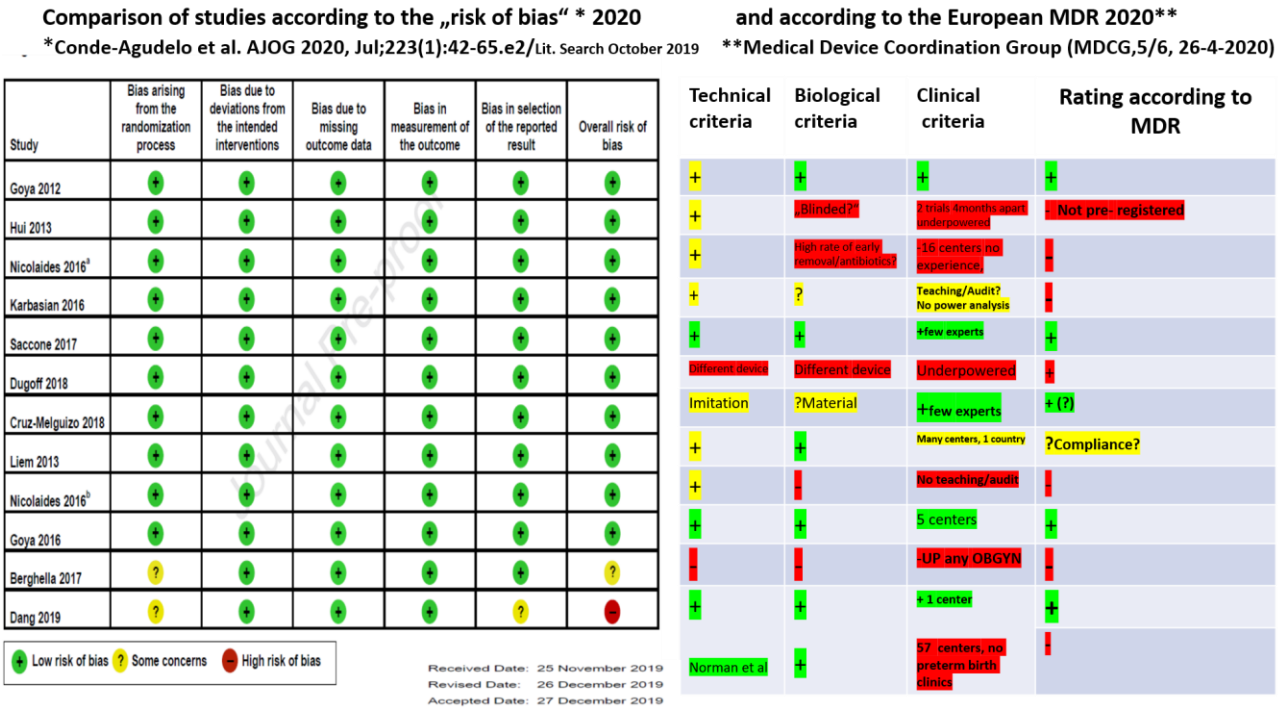
Different devices which are not even registered for the indication of preventing preterm birth cannot be regarded as equivalent.

Retrospective observational studies were mostly performed by clinicians **with experience** as opposed to **prospective trials where first authors "distributed**" the devices **frequently without clinical experience themselves**. Meanwhile, there are more retrospective meta-analyses (up to 17 published until July 2020 and several more registered in PROSPERO) than good clinical observational or prospective trials on pessary use. Unfortunately, all RCTs and meta-analysis are only based on the cervical length measurement which by itself has a poor prediction given the fact that preterm birth is a syndrome with many causes and different background risks [59]. Optimal antenatal care is prerequisite to alleviate pregnancy-associated complications and a reduction of preterm birth [60]. Unfortunately, intensified care is not necessarily performed and surely not evaluated in RCTs

In the most recent meta-analysis on the use of pessary in singleton and twin pregnancies the authors state that 414 records with mesh-terms "pessary" and "preterm birth" were found, 393 records were excluded based on title and/or abstract, 21 full-text articles assessed for eligibility, finally 12 studies (14 articles) were included in a qualitative synthesis. **Appropriate clinical use was no criterion [27]**. Two independent auditors have additionally investigated whether the devices within each study were equivalent according to the European MDR guidelines and used conform the instructions which must

be based on trials, post market surveillance (PMS) and post marketing clinical follow-up (PMCF) (Fig. 1 & 4) according to MDCG 5-8. **In Tab.4 we limit more detailed descriptions of the European MDR rating to RCTs as selected by the latest meta-analyses [27].** This meta-analysis was registered in PROSPERO, the criteria of Amstar or Robis to improve the quality were not considered or discussed. In this clinical evaluation we are obliged to follow the criteria of the European MDR/MDCG device guidelines and to rate (opposite of statisticians) whether technical, biological and clinical aspects were considered in RCTs. In Fig.4 the subjectively rated Cochrane categories of the publication in the AJOG [61] are opposed to the rating of two independent external reviewers of our notified body (MedCert) according to the MDR criteria. The authors of the meta-analysis have no or little clinical experience in inserting and surveillance of patients and did not analyze whether pessaries were inserted within a specified outpatient unit ("preterm birth clinic"). This is easily demonstrated on the cover of the AJOG where the corresponding author of the publication who is simultaneously the Editor of the same Journal demonstrated **a pregnant uterus with twins and a pessary placed upside down** (Fig. 5). There was no erratum. In 2020, a team of bioengineers demonstrated that wrong placement of the pessary cannot support or rotate the cervix and therefore does more harm [62]. This is only one explanation, why non-audited studies carry risks of clinical bias even when they appear statistically perfect. There is a wide range of indications, cut-off values of the cervical length. Given the fact that this is not a sensitive marker for preterm birth, it is surprising that even by authors who publish on preterm birth as a syndrome, on background risks and the importance of audits these characteristics (e.g. history or ART or preterm birth, socioeconomic factors), additional therapy, re-assurance by experienced vs. non-experienced care, antibiotics with impact on the vaginal microbiome (up to > 40% for discharge[47] were debated or analyzed. It is doubtful, whether counting all these different patients contributes to improved care (**Fig. 4).**

Fig. 4) Comparison of a subjective study classification of authors of a recent meta-analysis[61] (left) with the classification according to European Device regulation (MDR) approved by two independent reviewers (right), showing large differences with respect to validity. Useless to say, that a letter to the Editor who is also the corresponding author of this paper makes no sense.



Tab.4) Systematic literature search and detailed rating of RCTs cervical pessaries (MDCG 2020-5/6)

Singleton pregnancies (n=7), twin pregnancies (n=6),underpowered or not preregistered studies carry a risk of p-hacking [63]

Country/ Design (Study/Device)	Reference	Study population, outcome	Technical criteria	Biological criteria	Clinical criteria (results)	Rating (agreement of 2 independent external auditors)
BARCELONA/SPAIN Multicenter RCT with teaching of the team, Continuous clinical surveillance PESSARY Dr. Arabin GmbH &CoKG, **Model 1 perfortaed**	Goya et al. Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomized controlled trial. Lancet 2012; 379:1800-6.	Women with a singleton gestation:/ CL ≤25 mm -Arabin pessary (n=190) -No pessary (n=190) 20-23; weeks mean, 22.3 Pessary group/ No pessary group: Spont. PTB <34 weeks	E	E	Significant differences in primary outcome (PTB> 34 weeks) and in poor combined outcome in favor of patients with pessaries	Clin.Trials.gov NCT00706264 Well-designed, pre-registered, continuous surveillance according to instructions, Pre-start courses on how to use and to follow patients with pessaries within preterm birth clinics.
HONG KONG Underpowered RCT, No experience PESSARY Dr. Arabin GmbH &CoKG, **Model 1 perforatedf**	Hui et al. Cerclage pessary for preventing preterm birth in women with a singleton pregnancy and a short cervix at 20 to 24 weeks: a RCT. Am J Perinat 2013;30:283-8.	Women with a singleton gestation and a cervical length <25 mm -Arabin pessary (n=53) -No pessary (n=55)	E	E	No significant difference in outcome	Clin.Trials.gov: Not registered Not valid because a)RCT not pre-registered, b)patients were "blinded" for pessary (unethical, hurts protocol of instructions) and c)the same center published a second trial in the same year with separated high risk patients d) underpowered, No compliance to instructions
MULTI-CONTINENTAL Multicenter RCT, no clinical teaching, no audit, no continuity of care PESSARY Dr. Arabin GmbH &CoKG, **Model 1 unperforated**	Nicolaides KH, et al. A Randomized Trial of a Cervical Pessary to Prevent Preterm Singleton Birth. N Engl J Med 2016;374:1044-52.	Arabin pessary (n = 465) No pessary (n = 467) PTB <34 weeks	E	Too early removed in many cases, >40% antibiotics	No significant differences No safety issues 16 centers, all beginners, number of clinicians involved unclear	Clin.Trials.gov NCT00735137 Questionably valid because a) the treatment was delegated by a beginner without teaching to beginners in different continents (25 centers), b)no audit of TVS, insertion, follow-up, removal c) Antibiotics for discharge in >40% in the pessary group (effect microbiome?), No compliance to instructions
IRAN RCT, no clear power analysis, no teaching PESSARY Dr. Arabin GmbH &CoKG, **Model 1 Not shown perforated or unperforatedc**	Karbasian et al. Combined treatment with cervical pessary & vaginal progeste-rone for prevention of preterm birth: A randomized clinical trial. J Obstet Gynaecol Res 2016;42:1673-9.	Arabin pessary plus vag. progesterone 400 mg/d (n=71) Vaginal progesterone 400 mg/d (N=73) PTB <37 weeks	E	E	No significant differences Small sample, no described power analysis	Clin.Trials.gov: negative Not valid because a)not pre-registered, b)no data on clinical teaching, it is only described who randomized, any obstetrician inserted a device, c) no described power analysis. d) no audit of TVS/No compliance with instructions .
ITALY RCT unicentered, continuous care PESSARY Dr. Arabin GmbH &CoKG, **Model 2 perforated**	Saccone et al. Italian Preterm Birth Prevention (IPP) Working Group. Effect of cervical pessary on spont. PTB in women with singleton pregnancies and short cervical length: a RCTl. JAMA 2017;318:2317-24.	-Arabin pessary (n=150) -No pessary (n=150) Spontaneous PTB <34 weeks	E	E	Among women without prior spontaneous preterm birth who had asymptomatic singleton pregnancies and short CL, use of a cervical pessary, compared with no pessary , resulted in a lower rate of spontaneous preterm birth at less than 34 weeks of gestation.	Clin.Trials.govNCT02716909 The conclusions of the authors that "results of this single-center study require confirmation in multicenter trials" only make sense when these centers have the same skills/ training within an organized preterm birth clinic. .
USA Underpowered, no teaching BIOTEC DEVICE	Dugoff et al. Prevention of preterm birth with pessary in singletons (PoPPS): RCT trial. Ultrasound Obstet Gynecol2018; 51: 573-9.	-Bioteque cup pessary (n=60 vs -No pessary (n=58) PTB <34 weeks	Not equivalent	Too early removed	No significant differences	Clin.Trials.govNCT02056652 Not valid because the study a) used a device not registered for the prevention of PTB b) underpowered. c) audit of TVS/teaching not described. No compliance with instructions
MADRID/SPAIN MULTICENTER (27) RCT, continuous care	Cruz-Melguizo et al. Cervical Pessary Compared with vaginal Progesterone for preventing early	-Cervical pessary (n=125) -Vaginal progesterone 200 mg/d (n=118	Probably equivalent	Contact with mucosa probably similar	A cervical pessary was not non inferior to vaginal progesterone for preventing spontaneous birth before 34 weeks of	Clin.Trials.gov NCT01643980 Imitated pessaries with the same sizes were used, probably equivalent

IMITATED Cervical pessaries Medesign	Preterm Birth: An RCT Obstet Gynecol 2018;132:907-15.				gestation in pregnant women with short cervixes.	
THE NETHERLNDS MULTICENTER RCT PESSARY Dr. Arabin GmbH &CoKG, **Model 1 perforated**	Liem et al. Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN) a multicentre,open-label RCT Lancet 2013;382: 1341-9.	-Arabin pessary (n=401) -No pessary (n=407) Composite adverse perinatal outcome	E	E	No significant difference in total group but a 6-fold reduction of neonatal mortality in pessary group in patients with a CL< 38 mm between 16 and 20 weeks	Clin.Trials.gov:Not registered Questionably valid because a)not pre-registered, many centers with different clinical care not always compliant to instructions and protocol, however a secondary analysis tried to select cases with good clinical care, results improved
BARCELONA/SPAIN MULTICENTER RCT PESSARY Dr. Arabin GmbH &CoKG, **Model 2 perforated**	Goya, M., et al., Cervical pessary to prevent preterm birth in women with twin gestation and sono-graphic short cervix: a multicenter RCT (PECEP-Twins). Am J Obstet Gynecol, 2016. 214(2): p. 145-152.	-Arabin pessary (n=68) -No pessary (n=66) Spontaneous PTB <34 weeks	E	E	Significant reduction of preterm birth < 34 weeks	Clin.Trials.gov NCT01242410 Good training and continuity of care
MULTICONTINENTAL RCT PESSARY Dr. Arabin GmbH &CoKG, **Model 1 Not perforated**	Nicolaides KH, Syngelaki A, Poon LC, et al. Cervical pessary placement for prevention of preterm birth in unselected twin pregnancies: a RCT. Am J Obstet Gynecol 2016;214:3.e1-9.	-Arabin pessary (n=588) -No pessary (n=589) Spontaneous PTB <34 weeks	E	Too early removed in many cases	No significant differences of pessary versus expectant management.	Clin.Trials.gov: Not registered Not valid because a) not pre-registered, b) beginner distributed pessaries to beginners in different continents (25 centers), c) author admitted in a letter poor audit and poor teaching. No compliance with instructions
USA UNDERPOWERED RCT BIOTEC DEVICE	Berghella et al. Prevention of preterm birth with pessary in twins (PoPPT): a randomized controlled trial. Ultrasound Obstet Gynecol 2017;49:567-72.	-Bioteque cup pessary (n=23) -No pessary (n=23) Spontaneous PTB <34 weeks	Not equivalent	E	No significant differences between pessary and expectant management	Clin.Trials.gov NCT02056639 Not valid because a)The device not registered for preterm birth prevention and not equivalent b) underpowered, -in the end only 10(167 planned) cases useful for statistics. No compliance with instructions
VIETNAM RCT PESSARY Dr. Arabin GmbH &CoKG, **Model 2 Perforated**	Dang et al. Pessary compared with vaginal Progesterone for the prevention of preterm birth in women with twin pregnancies and CL less than 38 mm: a RCT. Obstet Gynecol 2019; 133:459-67.	Pessary (n=148) vs. -Vaginal progesterone 400 mg/d (n=149) 16-22, Spontaneous preterm Birth <34 weeks	E	E	Preterm birth < 34 weeks 24 (16%) cases with pessary/33 (22%) in the PG group ([RR] 0.73, 0.46-1.18). The pessary reduced poor outcomes(19% vs 27%: RR 0.70, 95% CI 0.43-0.93). In women with CL <28 mm, pessary reduced PTB <34 wks from 46% (16 35) to 21% (10/47) (RR 0.47, 95% CI 0.24-0.90) and improved composite poor perinatal outcome.	Clin.Trials.gov NCT02623881 Experienced team, continuity of care.
GB RCT PESSARY Dr. Arabin GmbH &CoKG, **Model 2 Perforated**	Norman et al. Randomized controlled trial: Arabin pessary to prevent preterm birthin twin pregnancies with short cervix. Supplement Am J Obstet Gynecol LB1S756 Jan.2020	2228 women screened 230 received pessary vs. expect. management Women < 35 mm CL randomized between 18 & 20+6 gest. weeks, Spont. PTB < 34 weeks, comp. neonatal outcome . Results: No significant difference	E	E? rates of pain or discomfort not conform other studies	56 UK /1 Belgium center involved, less than 4 per center	Clin.Trials.gov NCT02235181 Not valid because a) a beginner taught beginners, b)no audit of TVS and surveillance, c)spread of care between radiographers, midwifes, practitioners, too little experience (on average 4/center), d)pessary treatment allowed in control group after 21 weeks. No compliance with instructions

Figure 5) Cover of AJOG 2/2016 (Editor R. Romero) with conflicting publications of Goya et al. and Nicolaides et al. related to pessary in twins. Nicolaides et al. at least committed that the audit of pessary treatment was insufficient. Neither him nor the Editor recognized that on the title page the pessary is placed upside down. Although both were instructed about the error, no erratum was performed.

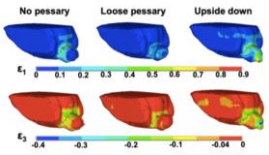


Figure 6) Mechanical engineering model demonstrating that in wrongly placed pessaries there is no pressure relief and the pessary does more harm than good [62].

The first RCT comparing vaginal pessaries with vaginal progesterone in twin pregnancies showed a positive impact of pessary use on the rate of preterm birth, but more importantly, on neonatal outcome, mainly in patients with a shorter CL (Tab. 5, [55]). The compliance to progesterone intake and pessary treatment was high, only experienced physicians followed these patients. **It is hard to understand why this extensive study of the patients was rated as "high risk of bias"(red) whereas an underpowered blinded RCT where all pathological cases had been excluded was rated as low risk of bias (green) in the meta-analysis [27] and leaves it open, in how far these classifications are of any importance or open for personal opinions.**

Tab. 5) Direct comparison of vaginal progesterone and cerclage pessary in twin pregnancy[55]

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)**

Final conclusion from clinical studies in 2020:

For this clinical evaluation which is prerequisite for MDR certification and all our technical documentation, our devices must be rated according to the guidelines MDCG 5-8 which overrule previous guidelines of the European Union (Tab.1). These criteria should also be applied to results of RCTs and retrospective meta-analyses. "Counting what is countable" should not overrule more subtle clinical and statistical analyses. The most recent meta-analysis is characterized by

- A large variety of entry categories for RCTs
- Not differentiating between devices with different biological/technical/clinical properties
- Not analyzing background risks of populations and their impact on the PTB rates
- Not analyzing the experience of the investigators or the treatments /center
- Not mentioning whether the diagnosis and therapy up to removal were audited
- Not mentioning data from post-clinical surveillance/post medical clinical follow-up
- Not mentioning long-term outcome and cost-effectiveness.

Therefore, this meta-analysis will be repeated introducing European device regulations.

a) Technical aspects: Most retrospective studies and prospective trials used different models of our cervical pessary which has changed in material and stiffness meanwhile 2 times: Models 1(dark blue, not transparent) was manually produced until 2014, model 2 (light blue transparent) until 2020, model 3 (light blue, transparent with objectified compression tests from 2020 onwards). We think that the most recently produced cervical pessaries are more probable to meet the demands of withholding the pressure and rotate the cervix adapted to the clinical situation. The differences can be investigated by verification tests under "in-vitro" conditions but whether this translates into "in vivo" results is still unknown.

Two underpowered studies of the recent meta-analysis [61] used a Biotec device which is not equivalent in demanded features. One study partly used imitations.

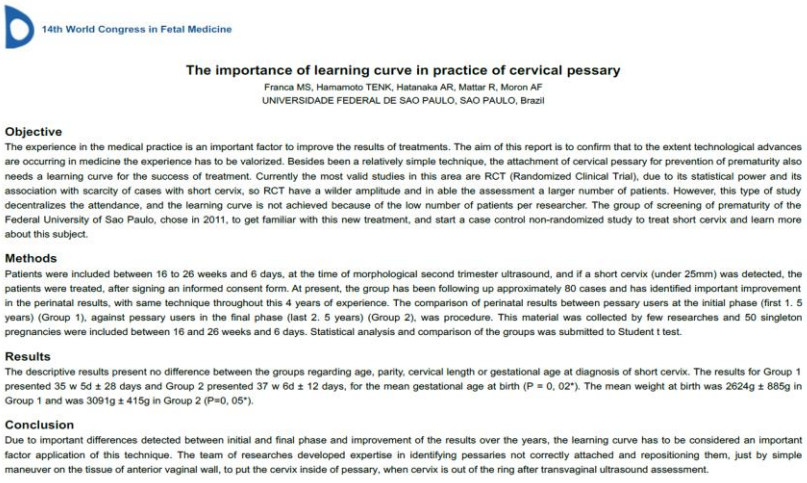
b) Biological aspects: The material and biological properties of different models of our team varied. Whether this had also biological effects is not probably because no complications of mucosa irritation or discharge rate has been reported up to now.

In the studies of Nicolaides et al. in singleton and twin pregnancies the group distributed pessaries to centers without experience before, it was not prespecified who followed the patients. The rate of preterm removal was high which could have affected the results. Even worse, in the study published in the NEJM the authors state : "Pathogens in the vaginal swabs, most commonly Candida albicans, group B streptococcus, or Gardnerella vaginalis, were found in a similar percentage of participants in the pessary group and the control group both at recruitment (28.6% and 25.8%, respectively; P = 0.39) and at any follow-up visit (31.4% and 30.0%, respectively; P = 0.75)"[51]. Nevertheless, the lack of experience led to a rate of antibiotic treatment (> 40%) in the pessary group which can impact the microbiome of the cervico-vaginal space and the preterm birth rate within the pessary group.

Imitated pessaries of Model 1 were used in a Spanish study, but we do not know the kind of material they were made of [56]. The Biotec pessaries differ from our pessary in material and compression values and are only registered for the treatment of pelvic organ prolapse.

In many studies the pessary was removed too early or inserted wrongly without strict control how the pessary was placed or whether it was dislocated. In the most recent RCT by Norman et al. presented during the SMFM pessaries were distributed to 57 centers without any clinical experience with the device [64]. The high number of so-called discomfort and pain can only be explained by substandard clinical care and differs widely from other studies. In June 2020, the paper has not yet been published but the conclusions not to treat patients with cervical pessaries can only hold true when high-risk patients are followed by low-educated staff (including radiologists, midwifes or physicians without any experience) within the British National Health care system instead of ONE team of experts within preterm birth clinics.

c) Clinical aspects: Within the meta-analysis by Conde-Agudelo et al. [61] there were large discrepancies in how the pessary was used, audited and whether there was continuity of care.
In most studies it was not clear who followed the patients after insertion of the pessary and whether the staff was familiar with the instructions or at least instructed by study leaders. As in other medical procedures there is a learning curve and trials should comment on the skills and experience of those who use and control the devices/maneuvers (Fig.7).



14th World Congress in Fetal Medicine

The importance of learning curve in practice of cervical pessary

Franca MS, Hamamoto TENK, Hatanaka AR, Mattar R, Moron AF
UNIVERSIDADE FEDERAL DE SAO PAULO, SAO PAULO, Brazil

Objective
The experience in the medical practice is an important factor to improve the results of treatments. The aim of this report is to confirm that to the extent technological advances are occurring in medicine the experience has to be valorized. Besides been a relatively simple technique, the attachment of cervical pessary for prevention of prematurity also needs a learning curve for the success of treatment. Currently the most valid studies in this area are RCT (Randomized Clinical Trial), due to its statistical power and its association with scarcity of cases with short cervix, so RCT have a wilder amplitude and in able the assessment a larger number of patients. However, this type of study decentralizes the attendance, and the learning curve is not achieved because of the low number of patients per researcher. The group of screening of prematurity of the Federal University of Sao Paulo, chose in 2011, to get familiar with this new treatment, and start a case control non-randomized study to treat short cervix and learn more about this subject.

Methods
Patients were included between 16 to 26 weeks and 6 days, at the time of morphological second trimester ultrasound, and if a short cervix (under 25mm) was detected, the patients were treated, after signing an informed consent form. At present, the group has been following up approximately 80 cases and has identified important improvement in the perinatal results, with same technique throughout this 4 years of experience. The comparison of perinatal results between pessary users at the initial phase (first 1. 5 years) (Group 1), against pessary users in the final phase (last 2. 5 years) (Group 2), was procedure. This material was collected by few researches and 50 singleton pregnancies were included between 16 and 26 weeks and 6 days. Statistical analysis and comparison of the groups was submitted to Student t test.

Results
The descriptive results present no difference between the groups regarding age, parity, cervical length or gestational age at diagnosis of short cervix. The results for Group 1 presented 35 w 5d ± 28 days and Group 2 presented 37 w 6d ± 12 days, for the mean gestational age at birth (P = 0, 02*). The mean weight at birth was 2624g ± 885g in Group 1 and was 3091g ± 415g in Group 2 (P=0, 05*).

Conclusion
Due to important differences detected between initial and final phase and improvement of the results over the years, the learning curve has to be considered an important factor application of this technique. The team of researches developed expertise in identifying pessaries not correctly attached and repositioning them, just by simple maneuver on the tissue of anterior vaginal wall, to put the cervix inside of pessary, when cervix is out of the ring after transvaginal ultrasound assessment.

Fig. 7) Abstract from the 14th World Congress in Fetal Medicine demonstrating the value of a learning curve for pessary treatment – as shown for other treatments.

Final conclusion from PMS:
Cervical pessaries have a high safety if appropriately used. The only complications, e.g. a cervical lesion occurred when a pessary was removed too late during active contractions or even forgotten during vaginal delivery. Up to now, we know about 6 cases :2 in the Netherlands, 1 in Spain, 1 in Germany, 1 in Poland (not surely our device because not announced to our company) 1 in Canada with cervical lesions which could all be surgical corrected without anatomical problems. Nevertheless, it might be challenging to remove the pessary at very early gestational age at the border of viability. The patient who demonstrated with a kind of conization during delivery because it was forgotten to remove the pessary during labor, a subsequent pregnancy was successfully treated with a cerclage. In all patients who demonstrate with active labor the cervix should be inspected after birth. In 1 case in Japan a vaginal lesion was reported which was sutured. We now overlook approximately 1 million of treated patients. The incidence is therefore relatively small. Even within RCTs which showed no effect to prevent preterm birth, there were no severe safety issues apart from discharge or when pain when the device was removed with violence instead of cut.
Final conclusions from PMCF
No serious reports in data collections, one published case report of a sepsis in a patient with a pessary, but it is not possible to discriminate whether this high-risk patient would have had a sepsis without a pessary or whether the clinicians removed the device too late.

2.4 Presentation of comparability, safety and benefit/risk ratio, performance, acceptance of undesired side effects of all devices

In general, the risk/benefit assessment of vaginal pessaries is favorable as compared to pharmaceutical and surgical procedures and mainly depends on training of indication, insertion, and follow-up. Accordingly, the acceptance of side effects (e.g. discharge) is good.

Product group annular gynecological pessaries genital prolapse I-II / stress incontinence
The conservative treatment is **less invasive and less expensive than** surgical procedures. The therapy may even have a **long-term therapeutic effect**. After indication, nurses or physiotherapists may be involved in care and teaching [65]. Health literacy of patients respecting her individual perspective are essential. The side effects of an operation as well as recurrence rates of POP and side effects of

surgical interventions should be mentioned during informed consent. Pessary treatment can be educated. The advantage is that it can also be transferred by experienced nurse practitioners (e.g. in developing countries and in care of the elderly) [11]. Around 75% of women who receive a pessary as a result of prolapse refrain from surgical treatment [17]. In a prospective study of the experienced group of Thakar et al. there was no difference in patient satisfaction between operative or conservative treatment of genital prolapse [66].

Product group gynecological pessaries genital prolapse II-IV / stress incontinence

The most reported clinical "complication" of patients with a pessary is increased discharge. This should never be confused with "infection" but can irritate patients without medical risks.

The most frequent complains about pessary devices of patients in our team are related to dislocated threats of the **cube pessary**, which mostly happens during cleaning and not during use. Therefore, the medical risk is small, and we replace the device. By fixing the threat in the cubes by a central button and a rigidly fixed nylon thread from 2018 onwards, and the by fixing the thread and button semi-automatically from 2019-2020 onwards, the number of complaints were reduced. Despite all efforts, daily handling might always carry a small final risk that the threat or the button dislocate.

With the **club pessaries,** the thick wall leads to a good function to treat (hold) severe grades of genital prolapse, but the pessaries are more difficult to change due to their stiffness. This could be objectified by compression tests. Therefore, we have started a process of change/development manufacturing these pessaries with the help of a controlled procedure by a team of highly qualified experts.

We tried to balance whether thinner walls and a central whole for handling and passage of discharge would still hold the prolapse but would also be easier for physicians and patients to insert and remove the pessary. According to a modern trial 75% of women who receive a ring pessary as a result of prolapse withdraw from surgery [17]. When cube pessaries were added, in a trial of the experienced team of Prof. Ranee Thakar (President of International Urogynecological Association -IUGA- 2019 -2020), no difference in satisfaction between patients with operative or conservative treatment was observed [66]. This shows that the risk/benefit ratio is also determined by the knowledge of the team of different pessary models, adapting the right size and instructing their patients.

Our ring and urethra pessaries are now fabricated without steel but slightly thicker walls. It still happens that some older ladies who are used to the older models of the urethra pessary still wish to use them. Although we pro-actively have performed compression tests this shows that subjective experience cannot be completely compensated by objective data.

Otherwise, we do not know of any serious risk which happened by using our gynecological pessaries. This is also due to the care and instructions of our leaflets and associated gynecologists who are quite well trained in seeing patients and controlling them: "Dare to care".

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.

Product Group Obstetric Pessaries

The most frequent complains during treatment with cervical pessaries are also vaginal discharge.

The conservative treatment of **cervical insufficiency** with pessaries is non-invasive, the cost-effectiveness has been tested after two trials and shows a cost-reducing effect. and a number of positive RCTs show beneficial effects when the physicians or trialists considered the instructions [67]
.

For singleton pregnancies, there are two positive trials which prove the effectiveness of the cervical pessary in opposite to control cases with expectant management to prevent preterm birth and neonatal morbidity [35, 54].
For twin pregnancies, there are two RCTs showing an effect of the cervical pessary versus expectant management to prevent preterm birth [35] [40]) and to reduce neonatal morbidity and mortality by the factor of 6 in a pre-defined group (3 versus 18 cases with perinatal death) [40]).
Vaginal progesterone
Although several 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 [68-71], the results of the study of the group of Romero have been questioned by the FDA report because within the study population only 2/44 hospitals outside the US had positive results: (https://ripetomato2uk.files.wordpress.com/2012/10/progesterone-fda-background-doc.pdf.
In addition, there was no effect proven on long-term outcome.
Prior et al. [63] stated that the paper of Fonseca et al. of the group of Nicolaides was not pre-registered and therefore prone to bias, he called this "p-hacking". When only pre-registered trials were considered, vaginal progesterone did not work. There is no paper showing a beneficial effect on long-term outcome and no paper which shows changes of the cervix after the application of vaginal progesterone. The Opptimum Trial [72] questioned the results as well but its value remains doubtful since patients had a poor compliance (< 70%). The effect of vaginal progesterone after an "episode of premature labor" is still doutful [73]. Conflicting meta-analyses exist also on the value of vaginal progesterone in twin gestations [73-75], see final considerations.

Comparison of cervical pessaries and progesterone to prevent preterm birth
In singleton pregnancies, one RCT compared the **pessary versus vaginal progesterone** – there were no significant differences [56]). First results of a pilot study with our Model 2 showed that vaginal progesterone had no further effect on the duration of pregnancy in single pregnancies [76] . In another retrospective analysis comparing a management of vaginal progesterone with a cervical pessary, the effects were similar with a history of PTB but progesterone better reduced PTB< 34 weeks in patients who had PPROM in a previous pregnancy [77]. The same group investigated whether an RCT would be feasible to compare the efficacy in preterm birth clinics.
Of 417 women screened between October 2015 and 2016, 25 (6%) were eligible for trial inclusion, of whom 18 (72%) agreed to participate at the rate 0.75 participants/site/month. Adherence to protocol was 100% in pessary and cerclage arms and 80% in the progesterone arm (95% CI 24-100%). No participants were lost to follow up [78]**.** At this stage, a three-armed RCT is running in GB**.**
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 [55].

Cervical pessary after an episode of preterm contractions
Two RCTs show a favorable effect of cerclage pessaries **after an episode of preterm labor in singleton** [79], **and twin pregnancies** [80]. However, this highly depends which patients might have been included into the trials – this also depends on the clinical experience not to include patients with suspicious inflammation or already in labor. This might have been the reason why another trial was negative [81].

Long-term effects
There was 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 [67].
Two RCTs of the group of Nicolaides et al., 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 [47]) or twin pregnancies [46]).However, the authors 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.
We have shown that the application of the pessary when it is placed upside down as falsely indicated on the cover of the AJOG 2016, does not have the effect of cervical pressure relief [82] (Fig. 5).
Therefore, the European and German guideline demand teaching by courses, internet and instructions**.**
It has been shown that there is a learning curve and that the rate of successful treatments increase with increasing experience within one center (Fig. 7).Three underpowered RCTs similarly showed no benefit [83-85]. However, these studies were underpowered, one was blinded and 2 did not use our pessary but a not-certified device designed for cystoceles.

Analysis of technical, biological and clinical data and associated risks

As stated in international guidelines, the risks of pessary therapy in gynecology are negligible. Systematic serious hazards are not known, but individual case reports reflect unintended complications when instructions were not considered. However, increased discharge is common.
Gynecological pessaries, the must be changed at certain intervals, additional cremes can increase the comfort and effect; in case of ineffective therapy, other models should be chosen. There are exceptional complications, (e.g. a ring pessary has been left for 16 years and forgotten without any complications [86]. However, such errors also led to rectovaginal and vesicovaginal fistulae [87-92].
Risks of obstetric pessaries arise when removed too early (no effect) or too late (cervical lesions). . It may be a difficult decision to remove a pessary at early gestion. We adjusted our instructions accordingly also with the aspect of continuity of care. The risk of vaginal mucosa lesions cannot be completely excluded, these are not necessarily caused by the material and shape of the pessary but by rare anatomical conditions. More serious complications were described when a pessary was forgotten.
Tested **materials should consider that monomer residues cannot be completely ruled out.**
After tempering and vulcanization is performed. The Shore hardness tested for each batch. Form July 2019 onwards, we apply compression tests for ring, urethra and cerclage pessaries.
Regarding the **life span 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. Meanwhile, we try to objectify the empirical recommendations by **specific aging tests**.
Primarily exposed **inserts** are excluded by the optical inspection of the pessaries. If they are not noticed, theoretically irritations of the vaginal mucosa may occur. No further risk of injury is to be expected. The remaining aluminum in (rarely indicated) Hodge pessaries has no toxic effects. The expected corrosion products of aluminum are harmless. Steel inlays have been removed to reduce the risks of exposure – also during MRT.
Pessaries are regularly tested for bioburden after a tempering process which leaves them clean but are not sterilized. We do not recommend the use of disinfectants that can irritate the mucous tissue.
Cerclage pessaries are classified as **PRODUCTS FOR SINGLE USE ONLY,** primarily as a precaution, since in case of a re-insertion additional infections cannot be excluded.
Bacteriological swabs were taken from untreated and treated patients before and after pessary use. The rate of bacterial colonization between the groups with and without pessary were comparable[47].
Women treated with pessaries did not experience an increased rate of chorioamnionitis or premature rupture of membranes [35].

2.5 Summary of clinical data (repetitions cannot be excluded)

A) GENITAL PROLAPSE WITH ANATOMIC LESIONS OF THE PELVIC FLOOR LEADING TO PELVIC ORGAN PROLAPSE (POP) OR STRESS INCONTINENCE (SI)
OUTCOME DATA ONLY REFER TO VALIDATED QUESTIONNAIRES OF POP/SI.

When searching at clinical trials.gov with terms POP and/or SI and vaginal pessary, no results are indicated. It means that a conservative treatment of POP and SI which reduce the life quality of women or even suffer from recurrence rates of up to 50% is not in the focus of interest (yet).

The conservative treatment of POP and/or SI is cost-effective and less risky as compared to surgical procedures. Pessaries may even have long-term therapeutic effects. The individual situation of the patient must be considered during informed consent and patients can also decide in a stepwise approach. The decision can then only be made by the patient herself. The advantage of pessary treatment is that it can also be applied by experienced auxiliary staff (e.g. in developing countries and in elderly patients)[11]. Nevertheless, physicians should have experience with different models.

At least 75% of women who receive a simple ring pessary due to POP then refuse surgical treatment [17]. In a RCT of the group of Thakar, there was no difference in satisfaction of operative or conservative (pessary) treatment in the treatment of POP with specified pessary models [93]. Thus, international guidelines recommend conservative treatment as a first choice for treatment of POP.

B) SECONDARY PREVENTION OF PRETERM BIRTH BY THE CERVICAL PESSARY IN WOMEN WITH A SHORT CERVIX OR CHANGE OF THE CERVICAL ANGLE
THE INCLUSION AND EXCLUSION CRITERIA FOR PESSARY TREATMENT WERE FREQUENTLY ONLY BASED ON NON-AUDITED SCANS OF THE CERVICAL LENGTH

When searching clinical trials.gov with the search terms preterm birth and cervical pessary in 2020, 69 registered trials are indicated which not all investigate cervical pessaries. Most of them were using the cerclage pessary of our company , some studies are completed, others ongoing. Unfortunately, clinical expertise and compliance to instructions and the MDR criteria have never been debated. Thus, the results do not necessarily comply with European device legislation.

Pessary versus expectant management: According to studies with experienced teams a pessary treatment of cervical insufficiency due to cervical "stretching" appeared to be promising. After exaggerated use by unexperienced clinicians, there are also negative data. There has rarely been an honest debate about the importance of preterm birth clinics. The mix of data should rather be summarized in a narrative way instead of summing-up these data in meta-analyses.
For singleton pregnancies, there are two positive RCTs proving the effectiveness of the cervical pessary versus controls with expectant management to prevent not only preterm birth but also neonatal morbidity [35] [54].
For twin pregnancies, there are two RCTs showing an effect of the cervical pessary versus expectant management to prevent preterm birth [40] [42], one trial suggested a reduction of neonatal morbidity and of perinatal mortality by the factor of 6 (3 versus 18 deaths [40]). Nevertheless, the study had included cases without compliance to the protocol (e.g. preterm removal, cerclage instead of pessary), --the authors performed a secondary analysis excluding these cases which improved the results [52].
Pessary versus vaginal progesterone: Although some 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 [68-71], the results were questioned by the FDA (https://ripetomato2uk.files.wordpress.com/2012/10/progesterone-fda-background-doc.pdf), the work of Prior et al. related to "p-hacking" [63] and the OPPTIMUM Trial [72]. The effect of progesterone in twin pregnancies or after an "episode of premature labor" is doubtful [73], although

a meta-analysis specified on risk pregnancies showed some benefit [75] but without integrating more recent results [55] [72] .

In singleton pregnancies, one RCT compared a cervical pessary versus vaginal progesterone: – there were no significant differences [56].

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 [55]).

Pessary after an episode of preterm contractions: Two RCTs also show a favorable effect of cerclage pessaries after an episode of preterm labor **in singleton** [80] **and twin pregnancies** [43], where no other method could show a meaningful effect [80]. A study conducted in the Netherlands showed no benefit in singleton pregnancies whereby the patients included might have differed [81].

Pessary and long-term outcome: Only one study followed children after pessary treatment 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 [67].

Combination of cervical pessary and other treatments: Pessary therapy can also be combined with either medication or cerclage. We have shown in a retrospective study that progesterone had no further effect on the duration of pregnancy in single pregnancies as compared to pessary alone [76].

Negative trials of pessary versus expectant management or vaginal progesterone: Two RCTs of Nicolaides et al., in multi-continental trials; showed no benefit and no harm of the cervical pessary in singleton [47, 51]) or twin pregnancies [46]. 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 and the rate of antibiotics was > 40% in the pessary group although not indicated by vaginal swabs. The application of the pessary when it is placed upside down as falsely indicated even on the cover of the AJOG 2016, MIGHT EVEN HAVE HARMFUL EFFECTS [82]). Therefore, the European and German guideline demand teaching by courses, internet and instructions and basic practical experience. 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, Fig. 7). The recent **STOPPIT -II** trial in twin pregnancies in Great Britain by Norman et al. could also not find significant differences between patients with a pessary and expectant management. However, the pessaries were distributed between 57 centers and not within specified preterm birth clinics. Expertise or continuity of care as recommended in the instructions could not be provided which is reflected by an unusual rate of discomfort or even pain in the treatment group.

When authors never see patients, only find negative results due to a network of trial participants (see a compliance of 60% in the **OPPTIMUM** trial) this is **NOT OPTIMAL** and should be **STOPPED:** Three **underpowered** RCTs could not prove any benefit (Hui et al. 2013 [84], Dugoff et al. UOG 2017 [83], Berghella et al UOG 2018 [85]). Two used a non-equivalent device and on postulated that the study was **blinded** (unethical, see instructions) and separated all severe cases for another publication from the same center with contradictory results [94].

Meta-analyses: At this stage, there is a tsunami of RETROSPECTIVE meta-analyses about clinical management of preterm birth with a high heterogeneity and little clinical understanding. Important risk factors such as the history, socioeconomic risks or maternal stress levels were not evaluated. The Cochrane board has not yet considered a review, but PROSPERO shows further registrations.

The NIH under the leadership of George Saade and NIH epidemiologists in Washington originally strived to perform a PROSPECTIVE meta-analysis which is less prone to bias and might allow to adapt data files and indications from individual data analysis. However, since recruitment can be a long-lasting process and this even , studies might have been terminated due to poor enrollment. When randomization procedures last too long studies should better terminated because the results cannot be interpreted similarly to trials from preterm birth centers with a high frequency of treatments.

FINAL CONSIDERATIONS OF THE AUTHOR

In 2018, the journal Nature has analyzed medical authors" who publish a paper every 5 days" [95].

Fig. 7) "Hyperprolific authors proliferate"

https://www.nature.com/articles/d41586-018-06185-8

Among the names within the appendix there are three specialists (BWM, KHN, RR) of maternal-fetal medicine. Together, these three have published >200 retrospective meta-analyses, many on secondary prevention of preterm birth with partly controversial results or just echoing each other. Were they not aware of the independent Cochrane board? It is not surprising that these authors do not have the time to follow patients themselves or at least to consult experienced clinicians. "Count what is countable and if it is not countable make it countable". This citation of Galileo Galilei originally applied to improve astrology should **not** be a standard for human science, because counting is taught at primary schools. What matters in medicine is a deep multi-dimensional understanding of basic and social sciences, not to forget excellent medical care and human empathy as stated by the president of the NIH Diana Bianchi [96]. Last but not least to count does not demand any creativity and according to one of the most brilliant brains within science (AE) "Imagination is more important than knowledge". In ancient times, Hippocrates introduced scientific views into medicine, whereas Sextus Empiricus only believed what he did himself. The father of evidence-based medicine, David Sackett, had hoped that both views get together, but it seems that this is an illusion. Retrospective meta-analyses mix results from different populations, individuals with different background risks, health care systems, compliance and sometimes fake data which is more difficult to recognize without clinical knowledge or when you have to publish a paper every 5 days. A recent RCT from a private practice in Egypt about vaginal progesterone in twin pregnancies which was neither pre-registered nor placebo-controlled but showed an unusually large cohort with extraordinary results [97] was chosen to convert negative results from traditional centres into amazingly positive results within a retrospective meta-analysis [74]. Green, yellow and red criteria for selection are prone to personal views although they suggest objectivity. During the 2nd World Congress of Maternal-Fetal-Neonatal Medicine in London in 2019, this was debated. Clinicians who carry responsibility for high-risk patients and their sorrows are increasingly irritated not only by conflicting data but also by the way how debates are conducted and/or suppressed. This development could be reversed by more decency, humour, and humbleness. **500 years ago**., famous artists had already a vision of pelvic floor disease or cervical insufficiency Therefore, I would prefer, if our gynaecological pessaries would be called ***Leonardo da Vinci*** devices and the obstetric pessaries ***Hieronymus Bosch*** devices. The picture of Leonardo (Fig.8) can be seen at Windsor Library. the picture of Bosch (Fig. 9) in Venice, Gallerie dell' Accademia in Venice.

Fig 8)Da Vinci:"Female pelic floor after birth"

Fig.9)Bosch:"Visions of the Beyond" (resembling a cervical pessary)

In the future, we should follow the advice of Donald Berwick- the former director of the US Institute for health improvement-specifically his Triple Aim (Fig. 10). It reminds us to decide whether we can improve the individual satisfaction, the health of the population and still to remain cost-effective[98].

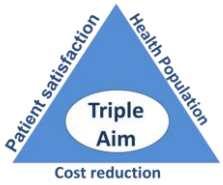


Fig.10) Triple aim according to D. Berwick [99].

Summary

In general, vaginal, and cervical pessaries carry minor clinical risks, as analyzed by extensive risk analyses in the technical documentation of each device. During the past year no "incidents" were reported to our team . The risk/benefit assessment may vary based on experience and training of health care providers, social and educational background of patients, severity and progression of diseases, additional actual risk factors, simultaneous interventions, and alternative treatment options. Unfortunately, many studies of unidimensional brains do not consider the multidimensional factors causing a high heterogeneity in results. In the end, patients should be satisfied, and goals be achieved. It is prerequisite that our medical instructions are permanently revised based on the feed-back from PMS, PMCF and the literature (Fig.1). According to European device regulations (MDR), instructions must be followed by health care providers and patients (to whom they must be explained). Individual claims will be investigated whether complications are due to violating the instructions or purely caused by the device. Up to now, the latter has not happened. Trials which do not consider the instructions and the indication and care by experienced staff after training are not regarded as valid.

Date of the following clinical evaluation

The clinical evaluation is continuously followed and evaluated considering new publications, PMS, and PMCF and will be re-written within one year.

2.6 Date and signature

Witten, 30th of June 2020

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

This review was approved to be conform EU MDR/guidelines 2020 by two representatives of the notified body MedCert

2.8 Author's qualification/curriculum 1(Birgit Arabin)

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 Pregnancy Academic Perinatal Board Philipps University Marburg-Germany
	2019/20	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, arts in medicine.
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 (CEO) www.dr-arabin.de
Languages		German, English, Dutch, French, Italian, Spanish
Other interests		Music, literature, art and poetry, integration of humane concepts into health policy, Organizing creative meetings, encouraging artists & scientists to cooperate, caring for young researchers on concepts for mothers and children before, during & after pregnancy (affects all of us).

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

Established registrations
All European countries
Australia
Russia and all countries from the former Soviet Union (e.g. Kazakhstan, Ukraine, Georgia, etc.)
South America (Brazil, Chile, Argentina, Peru, Bolivia, etc…
North Africa (Tunisia, Marroquin)
Japan
Malaysia
Thailand
Indonesia
South Korea
USA/Canada (for ongoing clinical trials)
Pakistan/India

Ongoing registrations
India
China
Mexico
New Zealand
Egypt, Kameron, Nigeria and African countries