TRANSPERINEAL ULTRASOUND

Pessary treatment and image analysis advancements

CLAUDIA MANZINI

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Transperineal ultrasound: pessary treatment and image analysis advancements
(with a summary in English and Dutch)
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(met een samenvatting in het Nederlands)

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Ai miei genitori

"Sempre e per sempre

Dalla stessa parte mi troverai"

F. De Gregori

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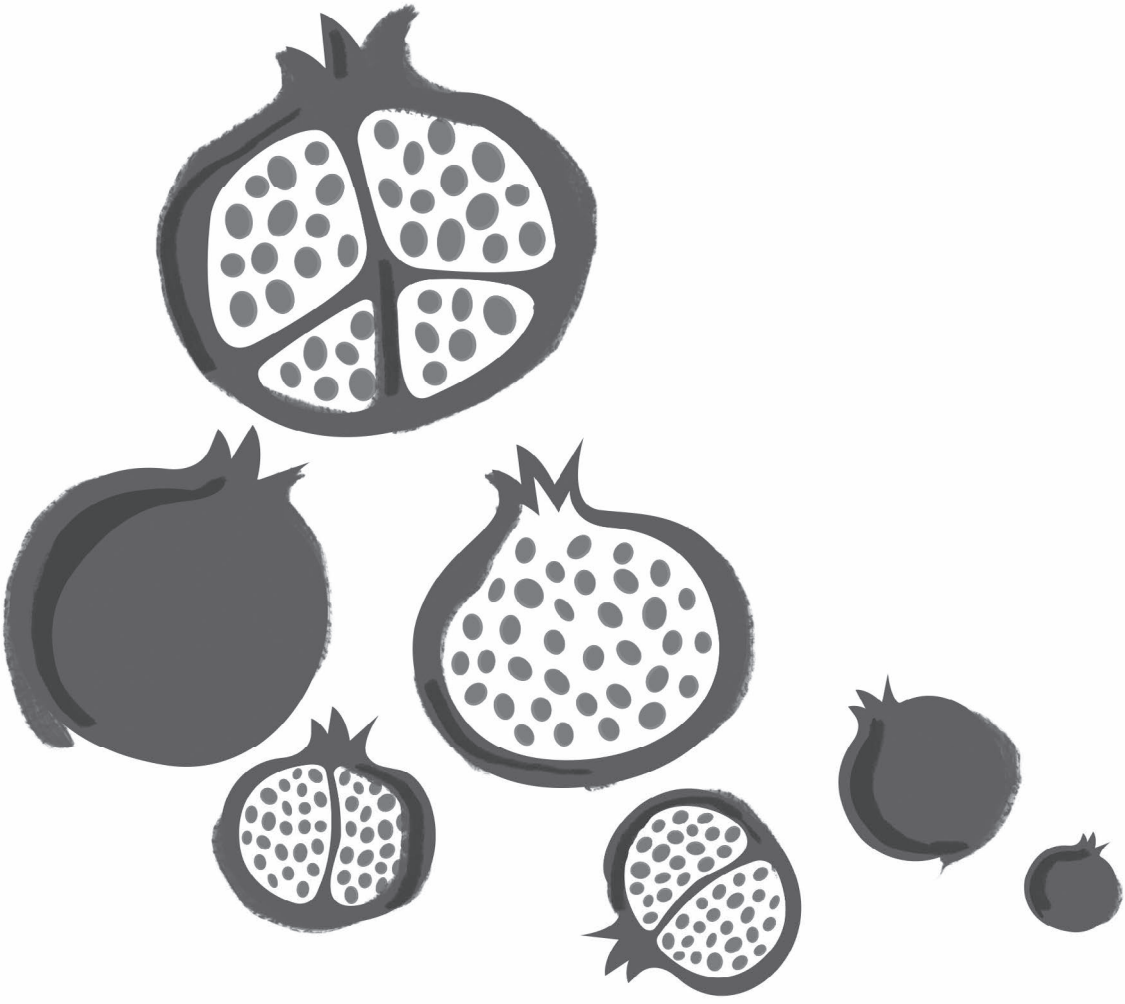


CHAPTER 1

General introduction

BACKGROUND

Pelvic organ prolapse

Pelvic organ prolapse (POP) is a pelvic floor disorder (PFD) characterized by the descent of pelvic organs from their normal position. It is classified based on the affected vaginal compartment: anterior compartment prolapse (cystocele and/or urethrocele), central or apical compartment prolapse (uterine prolapse or vaginal vault prolapse in case of prior hysterectomy), and posterior compartment prolapse (rectocele or enterocele).

Prevalence

The exact prevalence of POP is difficult to determine because different classification systems are used in the literature for the diagnosis. In addition, the exact percentage of women with POP who seek medical help is not known. Moreover, the prevalence of symptomatic and asymptomatic POP is very different [1]. With this respect, an overall prevalence of 3-6% in the general population was reported when POP was defined and graded based on POP symptoms, while an overall prevalence of 41-51% was reported when POP was defined and graded based on clinical examination [2]. In a Dutch study a prevalence rate of 8.7% of feeling vaginal bulging was reported in the general population based on a questionnaire [3]. A subgroup of the respondents also underwent clinical examination: only 25% of the women had no POP (stage 0), whereas 36.5% had a stage I POP, 33% a stage II POP, 5% a stage III POP, and 0.5% a stage IV POP.

The prevalence of PFD increases with age [4] and demographic changes include population ageing. This implies that the prevalence of PFD is expected to grow. Based on the population projections from the U.S. Census Bureau and published age-specific prevalence estimates for symptomatic PFD, Wu and co-workers predicted an increase in number of women with POP of 46% between 2010 and 2050 in the United States [4]. On the one hand, these growing numbers require farsighted planning strategies for the healthcare system to respond to the increasing request. On the other hand, they urge scientific effort to improve POP prevention and treatment with the aim of counteracting this growing numbers.

Risk factors

Parity is a major risk factor for POP [5,6]. The proposed mechanisms of damage leading to POP as a consequence of a vaginal delivery include: a) levator ani muscle (LAM) avulsion [7,8], i.e., disconnection of the most medial part of the LAM from its insertion on the inferior pubic ramus, and b) stretching of the LAM (with its most medial part being stretched up to 3.3 times [9]). The anatomical and functional consequences of these types of damage can be assessed with transperineal ultrasound (TPUS), as discussed later on.

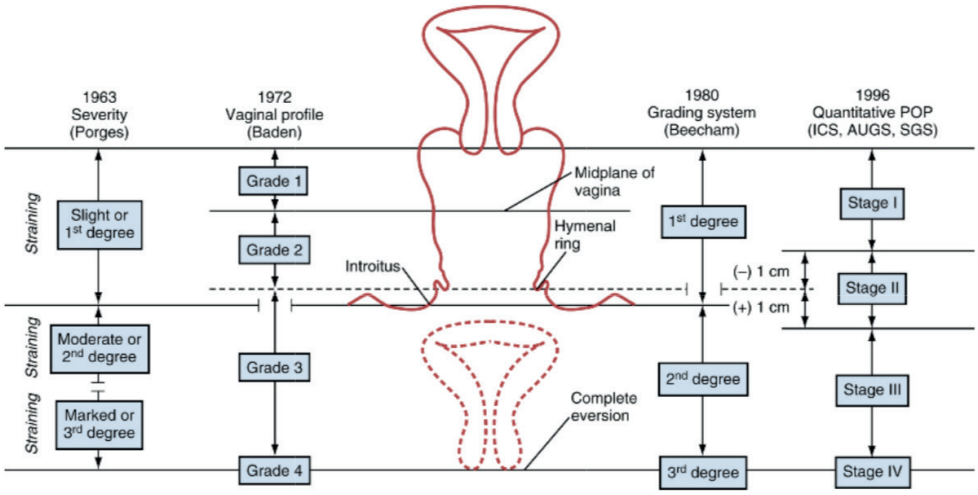
Additional risk factors include: older age [10], obesity [11], ethnicity (with Latina and white women having a four to five times higher risk of symptomatic POP compared to African American women [12]), increased intraabdominal pressure (e.g. due to chronic constipation [13] and heavy lifting [14]), collagen abnormalities [15], and family history [16].

Clinical manifestations

Sensation of a vaginal bulge or of something falling out of the vagina are typical POP symptoms with 81% positive predictive value and 76% negative predictive value for POP [17]. Other symptoms associated to POP include: low back and pelvic pain, urinary, defecatory and sexual dysfunction. A mild anterior compartment POP (Pelvic Organ Prolapse Quantification system stage I) can present with stress urinary incontinence (SUI), while advanced anterior compartment POP can cause urethral kinking and voiding difficulties; a uterine POP can cause lower back pain and sacral pain by placing tension on the uterosacral ligaments and accompanying nerves; a rectocele can be associated with incomplete evacuation and digital manipulation [18]. However, it must be noted that symptoms do not necessarily correlate with compartment-specific defects [19]: urinary and defecatory symptoms can be present in women with any type of POP. Moreover, lower back pain and sacral pain in a woman with POP are not necessarily due to POP. Lastly, POP can have a significant negative impact on sexual function [20]: compared to women without POP, women with POP can experience reduced satisfaction with sexual relationship, higher rate of urinary and fecal incontinence with sexual activity, higher rate of dyspareunia, and significantly higher rate of avoidance due to embarrassment.

Assessment

Different systems have been used in the past to quantify pelvic organ prolapse. In 1996 the International Continence Society (ICS) published a document aimed at standardizing the terminology of female POP and pelvic floor dysfunction [21]. In this document the Pelvic Organ Prolapse Quantification system (POPQ), i.e., a quantitative description of pelvic organs position, was proposed. The standardization of POP terminology has allowed the comparison of studies from different institutions and longitudinal evaluation of individual patients [21].



Visual representation of systems used to quantify pelvic organ prolapse. In the last column on the right the Pelvic Organ Prolapse Quantification system. Theofrastous JP, Swift SE. The clinical evaluation of pelvic floor dysfunction. Obstet Gynecol Clin North Am 1998;25:783–804. Lobo, R. A., Gershenson, D. M, Lentz, G. M., & Valea, F. A. Comprehensive gynecology. 7th edition. Philadelphia: Elsevier; 2017 [22a,22b]

The POPQ is now the standard method to assess and describe the extent of POP (i.e., POP stage). The definition of POP stage is based on the position of the most distal portion of the POP with respect to the hymen during maximal Valsalva maneuver.

- Stage O: No POP is demonstrated.
- Stage I: The most distal portion of the POP is > 1 cm above the level of the hymen.
- Stage II: The most distal portion of the POP is ≤ 1 cm above the level of the hymen.
- Stage III: The most distal portion of the POP is > 1 cm below the level of the hymen but protrudes no further than 2 cm less than the total vaginal length.
- Stage IV: The distal portion of the POP protrudes to or further than 2 cm less than the total vaginal length.

Management

Treatment is only indicated for women who have symptoms and treatment options include: expectant management, conservative management (i.e., PFMT, pelvic floor muscle treatment, and/or vaginal pessaries), and surgical management. Expectant management is reasonable for women who do not find their symptoms bothersome and prefer to avoid treatment. PFMT is generally advised to women with mild POP stage and current evidence indicate that it has a positive effect on POP symptoms and severity, but there is a lack of data on long-term outcomes [23]. Pessary treatment has proven effective in relieving POP symptoms [24–29] and because this is the treatment option investigated in the present thesis, it will be discussed more extensively later on. Surgical treatment is indicated in the case of unsuccessful conservative management or if the

woman declines conservative management, but it is not recommended for women who desire to have more children. There are various types of surgeries, including native tissue repairs or surgeries with graft materials which can be realised via a vaginal or abdominal approach [30]. The lifetime risk until the age of 80 of undergoing POP surgery has been estimated as high as 12.6% [31]. A Dutch study showed that the prevalence of POP surgery increases with age and observed a prevalence of 20% in the age group 76-85 years[32]. The success rate of POP surgery varies based on the definition of treatment success (i.e., lower for anatomical success and higher for symptomatic success) [30]. The short-term success rate can be considered high: symptomatic success (defined as reduction of vaginal bulge symptoms) ranges from 62.1% to 100% in the case of anterior colporrhaphy at one to three years follow-up [30]. However, the biggest limitation of POP surgery is the high recurrence rate, estimated between 27% and 42% after native tissue repair for anterior compartment POP [33].

Pessary treatment

Vaginal pessaries for POP are mechanical devices inserted in the vagina to physically support the vaginal walls and the pelvic organs behind them [24]. One of the earliest "pessaries" used in history consisted of half a pomegranate placed in the vagina, as described by the Greek physician Polybus [34]. Modern pessaries are made of inert silicone-coated rubber and are classified as support pessaries and space filling pessaries. Oliver and co-worker published a review on the different pessary types currently in use [34].

Support pessaries

Ring pessary with support. Robert M, Schulz JA, Harvey M-A. Technical update on pessary use. JOGC 2013;35:664–74. [35]

Ring pessaries are the pessary type most commonly used [36]. They are available in sizes 0 (44.5 mm) to 13 (127 mm) and are generally described as mostly effective for women with POP stage I and II. However, it is our clinical experience that they can be also effective for higher POP degrees, as also reported in the literature [37]. Advantages of the ring pessary are as follows: ease of insertion and removal, ability to continue penetrative intercourse and no need for daily removal. Disadvantage of the ring pessary without support is that the prolapse (uterine and posterior compartment POP, especially) can protrude thought the opening. In this case a ring pessary with support is generally more effective.

Space filling pessaries

From left to right: Gellhorn, Donut, and cube pessary. Robert M, Schulz JA, Harvey M-A. Technical update on pessary use. JOGC 2013;35:664–74. [35].

Space filling pessaries are more difficult to insert and remove compared to ring pessaries and they are not compatible with sexual intercourse. Therefore, they are generally tried only after failure of ring pessaries. Gellhorn pessaries are described as useful for higher grades of POP, as opposed to the ring pessaries (even if ring pessaries can also be successful for higher grades of POP, as previously discussed). Donut pessaries are described as effective for the treatment of more severe grades of POP when the perineal support is lax. Cube pessaries retain their position by suction of their surface to the vaginal walls. It is generally advised to remove them daily as the suction can lead to erosions and fistulas of the vaginal walls. However, new versions have holes for drainage and daily removal is in principle not necessary.

Pessary fitting

Pessary fitting is the process of finding a pessary that stays comfortably in place and relieves POP symptoms, taking into account the type of POP, sexual activity, ability of self-management and of attending follow-up visits alone or with a caregiver [34]. In this thesis, "initial fitting" refers to the first visit, which is considered successful if the woman leaves the clinic with a pessary that stays comfortably in place. "Pessary fitting" refers to the process from initial fitting until the last fitting trial and is considered successful if the last fitting trial is successful, i.e., the woman decides to continue pessary treatment. Pessary fitting is based on clinical examination and proceeds by trial and error [34]: a woman may have to undergo more than one fitting trial with different pessary types and sizes until a suitable pessary is found. It can also happen that a woman undergoes more fitting trials, and no suitable pessary is found. The most common reasons for pessary fitting failure are as follows: pessary dislodgment, failure to relieve POP symptoms, pain/discomfort, or urinary symptoms [38]. In these cases, a different treatment could be undertaken. The success rate of pessary fitting varies between studies [27,37,39–60]. In general, it is relatively limited with success rates reported as low as 41% at three weeks follow-up [49]. This prompted the work reported in the present thesis with the aim of better understanding the reasons for failure and of applying TPUS to make pessary fitting more efficient and effective.

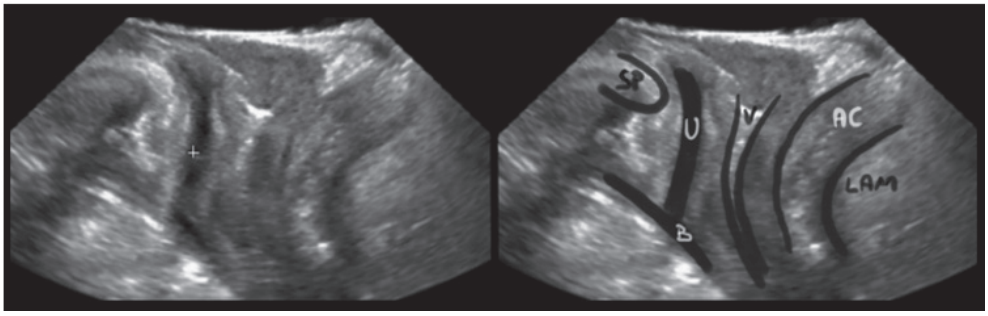
Compared to surgery, pessary treatment is non-invasive, reversable and with mild complications, i.e., bleeding, extrusion, vaginal discharge, pain/constipation or incontinence [61]. More serious complications, such as fistula formation and peritonitis, are very unusual and only related to neglected pessaries [34]. Considering all these aspects and that the superiority of surgery has not yet been demonstrated, the Dutch guidelines suggest to offer pessary treatment to all women with POP. In addition, more (scientific and clinical) effort should be put in trying to improve pessary fitting success rates.

Transperineal ultrasound (TPUS)

To reach this goal (i.e., improving pessary fitting success rate) imaging techniques, such as TPUS, can be used to get more insight into what a proper fit is. The first reports of the use of TPUS date back to the eighties of the 20th century. This technique was initially introduced to study anatomic defects of women with SUI [62]. Nowadays, it can be used to assess anterior, apical, posterior compartment, LAM, anal sphincter, and implant materials [63]. TPUS is used in the current thesis for LAM assessment. Therefore, LAM assessment will be described in further detail. In the literature the terms TPUS and translabial ultrasound are used interchangeably. In this thesis the term TPUS will be used.

Data acquisition

TPUS is performed in supine position after bladder emptying. The transducer is placed vertically against the symphysis pubis and the perineum [63]. If the transducer is correctly placed, the midsagittal plane shows from left to right: symphysis pubis, urethra and bladder, vagina, and anal canal. The woman is then instructed to perform maximal pelvic floor contraction and maximal Valsalva maneuver [64].



Midsagittal plane. SP= symphysis pubis, U=urethra, B= bladder, V=vagina, AC= anal canal, LAM= levator ani muscle.

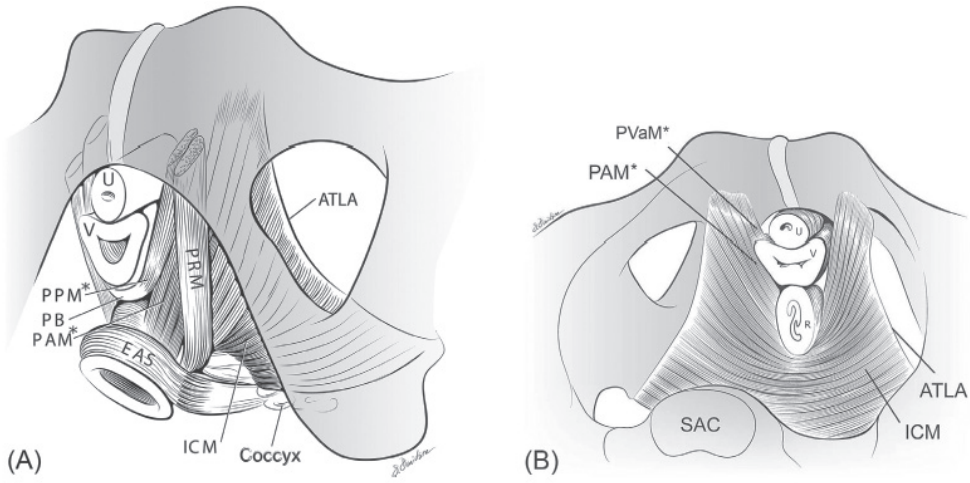
LAM assessment

It was previously mentioned that mechanisms of damage leading to POP as a consequence of a vaginal delivery include a) LAM avulsion [7,8], i.e., disconnection of the most medial part of the LAM from its insertion on the inferior pubic ramus, and b) stretching of the LAM (with

its most medial part being stretched up to 3.3 times [9]). TPUS allows clinicians to assess the anatomical and functional consequences of these types of damage. Before explaining the technique for LAM assessment with TPUS, the anatomy of the LAM will be shortly described.

LAM anatomy

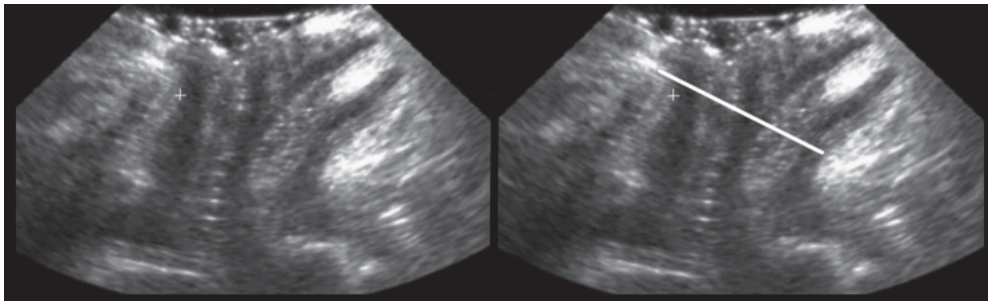
The LAM is the most important muscle of the pelvic floor and consists of the following subdivisions: pubovisceral (also known as pubococcygeal), iliococcygeal, and puborectal muscle (PRM). The pubovisceral muscle has three components: pubovaginal, puboperineal, and puboanal muscle. The PRM is the LAM subdivision surrounding the levator hiatus which can be assessed on TPUS, as discussed later on.



Panel A shows a schematic view of the levator ani muscle (LAM) from below. Panel B shows the LAM seen from above. ATLA=arcus tendineus levator ani; EAS=external anal sphincter; ICM= iliococcygeal muscle; PAM=puboanal muscle; PB= perineal body; PPM= puboperineal muscle; PRM= puborectal muscle; PVaM= pubovaginal muscle; R=rectum; SAC= sacral promontory; U= urethra; V= vagina. ©DeLancey. R. Kearney, R. Sawhney, J.O. DeLancey, Levator ani muscle anatomy evaluated by origin-insertion pairs, Obstet. Gynecol. 104 (1) (2004) 168-173.

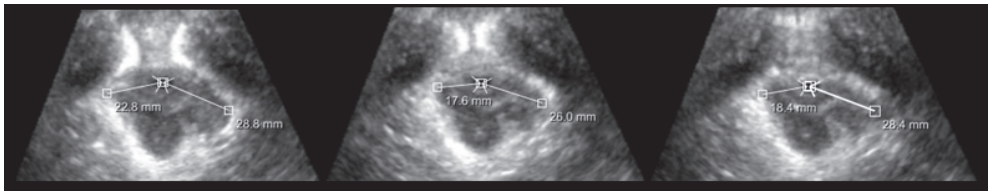
LAM avulsion

The anatomical status of the LAM is assessed on volume data acquired at maximal pelvic floor contraction, which allows for better tissue discrimination [63]. At first, the plane of minimal hiatal dimensions is obtained. For this purpose, a 3D/4D machine is needed. The plane of minimal hiatal dimensions is the plane identified by the shortest line that connects the dorsal aspect of the pubic symphysis, ventrally, and the ventral aspect of the anorectal angle, dorsally, on the midsagittal plane. To ascertain that the plane of minimal hiatal dimensions is correctly visualized, the pubic bone should appear symmetrical on the axial and coronal planes.



Identification of the plane of minimal hiatal dimensions.

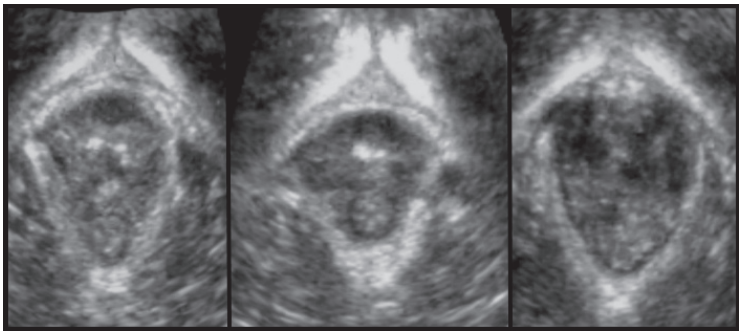
Having obtained the plane of minimal hiatal dimensions, tomographic ultrasound imaging (TUI) is used with a 2.5 mm interslice interval, according to the method described by Dietz [63]. The central slice is placed at the plane of minimal hiatal dimensions, showing the symphysis pubis closing medially. Afterwards, the levator–urethra gap (LUG) is measured in the three central slices. The LUG is the distance between mid-urethra and most medial margin of the LAM at its connection with the pubic bone, in the case the LAM is still connected to the pubic bone, or most medial and ventral margin of the LAM, in the case of loss of connection. Complete LAM avulsion is defined as levator–urethra gap ≥ 25mm on the three central slices on the right side, on the left side (unilateral) or both sides (bilateral). Complete LAM avulsion is associated with enlarged levator hiatal area (HA) [65], anterior and apical compartment POP [66] and reduced pelvic floor muscle function [65,67].



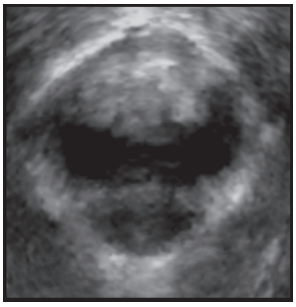
Transperineal ultrasound of a woman with complete unilateral avulsion showing the three central slices. On one side the levator–urethra gap is < 25 mm (i.e., intact), while on the other side it is ≥25 mm (i.e., complete avulsion).

Levator hiatus

The levator hiatus is the opening encircled by the pubic bone ventrally, and the PRM laterally and dorsally. The levator hiatus is described as the largest potential hernial portal in the human body. With this respect, another definition of POP is the herniation of the pelvic organs through the hiatus [64]. This means that an enlarged levator hiatus can impair pelvic organ support, thus leading to POP. On TPUS the levator HA, which is the area encircled by pubic bone and puborectalis muscle, can be measured at the plane of minimal hiatal dimensions. Enlarged levator HA is associated with symptoms and signs of POP, and abnormal distensibility of the levator HA, or "ballooning", is defined as a levator HA on maximum Valsalva ≥ 25 cm^2 [68]. Levator HA measurements have been proven highly repeatable [69,70].



From left to right: levator HA at rest, maximum contraction, and maximum Valsalva with a normal distensibility of the hiatus (i.e., levator HA on maximum Valsalva of 18.69 cm^2)



Abnormal distensibility of the hiatus (i.e., levator HA on maximum Valsalva of 29.77 cm^2)

RATIONALE OF THE THESIS

What is (if any) the added value of TPUS in pessary treatment for symptomatic POP? This is the main research question of the present thesis, which was prompted by the following consideration.

As aforementioned, the prevalence of pelvic floor disorders (PFD) is expected to grow [4]. In addition, POP treatment has some limitations (i.e., relatively low pessary fitting success rate and relatively high recurrence rate after surgery). The combination of these two factors implies that a non-negligible number of women being left without an appropriate treatment can be anticipated in the coming years. Thus, our idea was to use TPUS to get more insight into the reasons why pessary fitting is successful in some women and unsuccessful in others. Moreover, we wanted to investigate the added value of TPUS in pessary fitting process with the ultimate goal of increasing pessary fitting success rate, which would reduce the need of POP surgery and, as a consequence, the absolute number of recurrences. To achieve this goal, advancements in LAM assessment are needed. Therefore, we also set out to improve the anatomical and functional assessment of the LAM using TPUS.

AIMS OF THE THESIS

In Chapter 2 we present a systematic review and meta-analysis aimed at clarifying which parameters are associated with unsuccessful pessary fitting up to three months follow-up.

In Chapter 3 we set out to identify which parameters are associated with a specific reason for pessary fitting failure. The reasons for pessary fitting failure are diverse: pessary dislodgment, pain/discomfort, failure to relieve POP symptoms, and urinary symptoms [38]. The aim of this study is to test the hypothesis that different reasons for pessary fitting failure are associated with different predictive parameters.

In Chapter 4 we assess the added value of TPUS in identifying the ring pessary size that properly fits a woman without causing pain/discomfort and without being dislodged or failing to relieve POP symptoms.

In Chapter 5 we assess the functional changes of the PRM assessed with TPUS three months after successful pessary fitting.

In Chapter 6 we set out to automatically identify the plane of minimal hiatal dimensions and to automatically segment levator HA and levator diameters, which would make TPUS analyses faster and reduce the interobserver variability of the measurements.

Currently, TPUS images are mostly analyzed in 2D. Since TPUS can capture muscle movement in 3D, in Chapter 7 we set out to identify and describe the separate appearance of LAM subdivisions on 3D TPUS, which would allow for in vivo 3D biomechanical analysis of the pelvic floor function.

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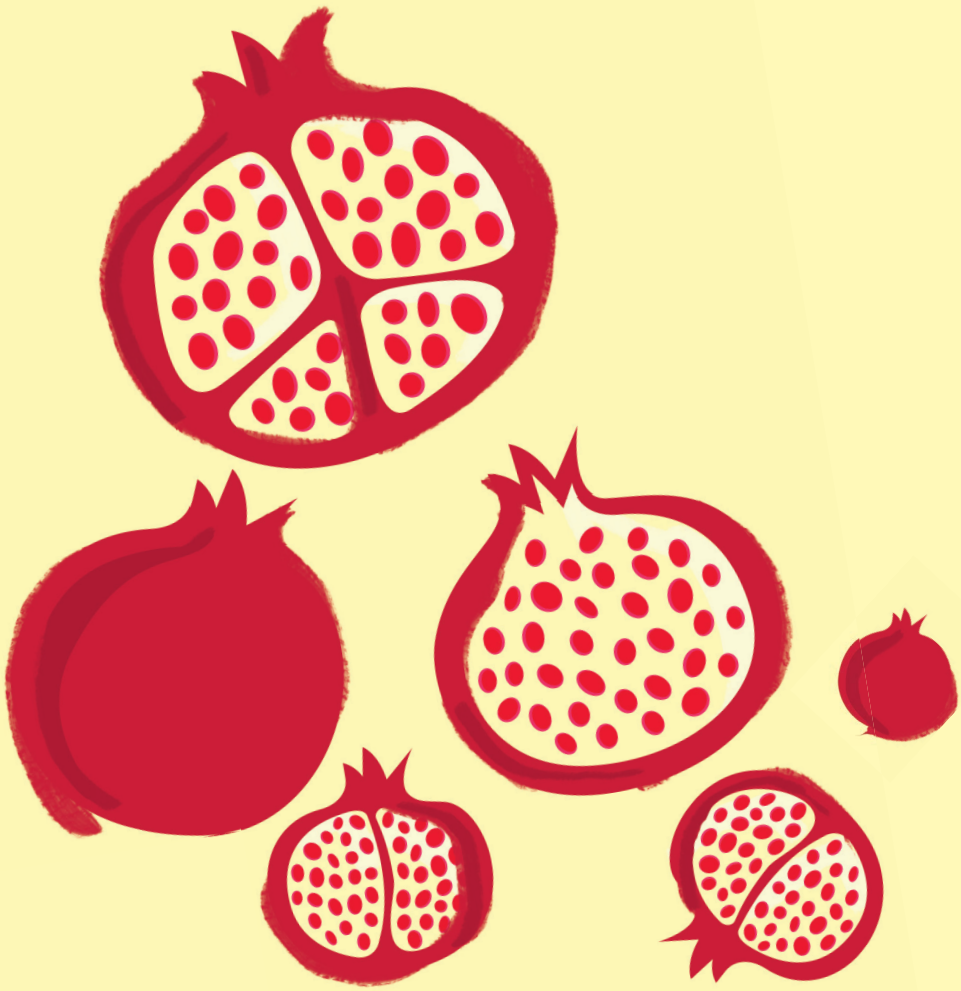
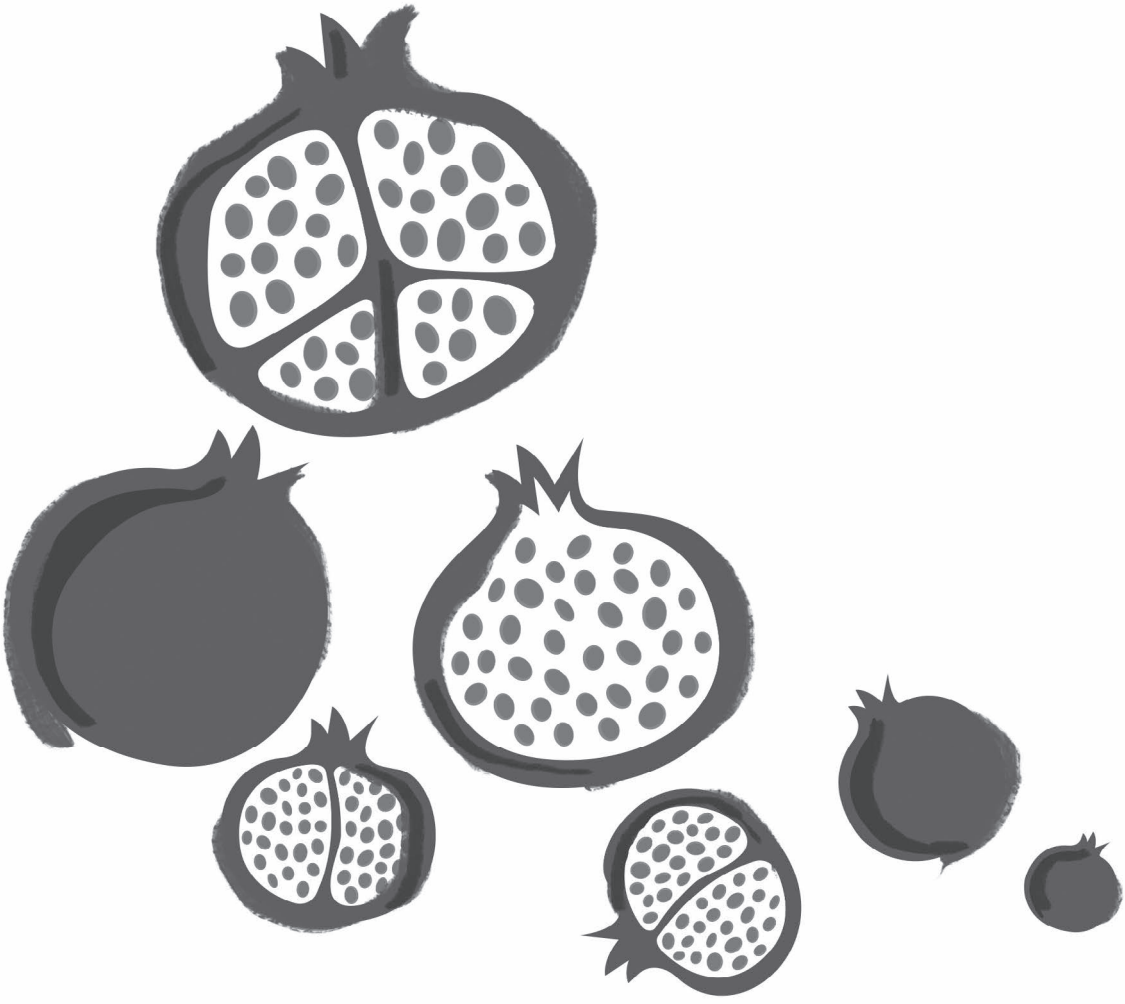


PESSARY TREATMENT



CHAPTER 2

Parameters associated with unsuccessful pessary fitting for pelvic organ prolapse up to three months follow-up: a systematic review and meta-analysis

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Abstract

Objectives: To clarify which parameters are associated with unsuccessful pessary fitting for pelvic organ prolapse (POP) up to three months follow-up.

Methods: Embase, PubMed and Cochrane CENTRAL library were searched in May 2020. Inclusion criteria were: (1) pessary fitting attempted in women with symptomatic POP, (2) pessary fitting success among the study outcomes with a follow-up of maximal three months, (3) baseline parameters compared between successful and unsuccessful group. A meta-analysis was performed using the random effects model.

Main results: Twenty-four studies were included in the meta-analysis. Parameters associated with unsuccessful pessary fitting were: age (OR 0.70, 95% CI 0.56-0.86); BMI (OR 1.35, 95% CI 1.08-1.70); menopause (OR 0.65 95% CI 0.47-0.88); de novo stress urinary incontinence (OR 5.59, 95% CI 2.24-13.99); prior surgery, i.e., hysterectomy (OR 1.88, 95% CI 1.48-2.40), POP surgery (OR 2.13, 95% CI 1.34-3.38), pelvic surgery (OR 1.81, 05% CI 1.01-3.26), and incontinence surgery (OR 1.87, 95% CI 1.08-3.25); Colorectal-Anal Distress Inventory-8 scores (OR 1.92, 95% CI 1.22-3.02); solitary predominant posterior compartment POP (OR 1.59, 95% CI 1.08-2.35); total vaginal length (OR 0.56, 95% CI 0.32-0.97); wide introitus (OR 4.85, 95% CI 1.60-14.68); levator ani avulsion (OR 2.47, 95% CI 1.35-4.53) and hiatal area on maximum Valsalva (OR 1.89, 95% CI 1.27-2.80).

Conclusion: During counselling for pessary treatment a higher risk of failure due to the aforementioned parameters should be discussed and modifiable parameters should be addressed. More research is needed on the association between anatomical parameters and specific reasons for unsuccessful pessary fitting.

List of abbreviations

BMI: Body Mass Index

CRADI-8: Colorectal-Anal Distress Inventory-8

GH: Genital Hiatus

HRT: Hormone Replacement Therapy

POP: Pelvic Organ Prolapse

SUI: Stress Urinary Incontinence

TPUS: TransPerineal UltraSound

TVL: Total Vaginal Length

Introduction

Vaginal pessaries are widely used as a conservative treatment option in the management of pelvic organ prolapse (POP) [1,2] and have proven effective in relieving POP symptoms [3–5]. However, multiple attempts with different pessaries are sometimes required before obtaining an adequate fit [6]. Additionally, pessary fitting is reported as unsuccessful in up to 59% of the women [7], the most common reasons being pessary dislodgment, discomfort/pain, de novo urinary symptoms, and failure to relieve POP symptoms [8]. Many studies have been published on the factors associated with (un)successful pessary fitting for POP [7-39]. Among other potential predictors, age, body mass index (BMI), prior surgeries, predominant POP compartments, and advanced POP have been assessed, but results differ across studies. It is thus necessary to clarify which parameters are associated with unsuccessful pessary fitting. This knowledge could improve the clinical practice of physicians dealing with POP: the counselling for pessary treatment would be more effective and more targeted, and potential parameters associated with failure would be known and discussed with the patient. In addition, modifiable factors could be addressed to increase the probability of success.

The aim of the current review and meta-analysis is to clarify which clinical, demographical, and anatomical (assessed by clinical examination or imaging techniques) parameters are associated with unsuccessful pessary fitting for POP up to 3 months follow-up. A maximum of 3 months follow-up was chosen to focus on pessary fitting process instead of long-term pessary use.

Methods

Sources

The first author searched Emtree/MeSH terms and keywords related to prolapse, pessary, and the exposures (i.e., parameters associated with unsuccessful pessary fitting) through Embase, PubMed and the Cochrane CENTRAL library. The outcome, e.g., unsuccessful pessary fitting, was not included in the search to avoid the risk of missing relevant records. The terms searched through Embase are reported in Table 1 (the same search strategy was translated to PubMed and Cochrane CENTRAL library). The final search was made on the 8th of May 2020. No time restrictions were applied, while restrictions were used for language (i.e., English). All results were exported to RefWorks (Legacy version), and duplicates were removed. If an abstract and a paper reporting the same data were retrieved, the abstract was considered a duplicate and removed.

Table 1. Embase search strategy. BMI= body mass index; TVL = Total Vaginal Length; GH = Genital Hiatus

Emtree terms	Prolapse	Pessary	Exposure(s)
	'pelvic organ prolapse' 'pelvic floor prolapse'	'vagina pessary'	parameters 'prediction and forecasting' 'morphological trait' 'groups by age' 'body mass' 'body weight' 'gynecologic surgery'
Keywords	prolapse(s) cystocele 'anterior vaginal wall prolapse' 'anterior compartment prolapse' 'uterus prolapse' 'uterine prolapse' 'descensus uteri' 'vault prolapse' 'apical prolapse' 'apical compartment prolapse' rectocele enterocele 'posterior vaginal wall prolapse' 'posterior compartment prolapse'	pessar*	predictor(s) factor(s) characteristic(s) parameter(s) age BMI weight surger(y,ies) hysterectom(y,ies) compartment(s) stage(s) TVL GH

Eligibility criteria

Studies were included in which (1) pessary fitting was attempted in women with symptomatic POP (at least 80% of the study population had to have symptomatic POP), (2) one of the assessed outcomes was the success of "initial fitting" and/or "fitting process" with a follow-up of maximal three months (in the case of a longer follow-up, at least 80% of the unsuccessful group had to have discontinued the pessary within three months from the initial fitting), and (3) baseline parameters (i.e., clinical, demographical, and anatomical parameters) were compared between successful and unsuccessful group. Study design was not a selection criterion and studies reported only in conference abstracts were not excluded. In the following, "initial fitting" will refer to the first visit, which is considered successful if the patient leaves the clinic with a pessary that stays comfortably in place. "Fitting process" will refer to pessary use from initial fitting until a defined follow-up time. It is considered successful if the patient is still using the pessary at follow-up. "Pessary fitting" will refer to both initial fitting and fitting process, if no distinction between the two is needed.

Study selection

To select records eligible for full text assessment, title and abstract were screened by first and second author, independently from each other. Any disagreement was resolved by discussion and the opinion of a third party (last author). The full text of the selected records was independently assessed by the same two authors. Disagreements were again resolved by discussion and the opinion of a third party (last author). The authors of a record were contacted if the full text of their paper was not accessible neither online nor at our institutional library, and if some relevant parts of the records were unclear [e.g., definition of pessary fitting (un)success, time to follow-up, statistical significance of the observed differences or incorrect numbers].

Data extraction

A standardized data extraction form was created to retrieve the information relevant to the research question. The following data were extracted: reference (first author, year, journal citation), study design type, study setting, inclusion and exclusion criteria, sample size, prolapse assessment (i.e., Pelvic Organ Prolapse Quantification system or Baden–Walker), pessary types used, assessment of initial fitting and/or fitting process, definition of successful fitting, success rate, time to follow-up, parameters compared between successful and unsuccessful group, significant parameters on univariate analysis, and significant parameters on multivariate analysis (if performed). In case a record reported follow-ups beyond 3 months, only the parameters relating to the follow-ups of the first 3 months were extracted.

Assessment of risk of bias

The Newcastle-Ottawa Scale (NOS) for case-control studies was used to assess the risk of bias of the included full-text articles [40]. Records only available as abstracts (i.e., no full-text available) were not assessed, because of the limited amount of information they can provide. The NOS is specifically designed for non-randomized studies. It consists of three domains: Selection, Comparability, and Exposure. The maximum total score is nine (four for the Selection domain, two for the Comparability domain, and three for the Exposure domain). The first item assessed in the Selection domain is the adequacy of case definition and requires an independent validation. Since the success of pessary fitting is mostly patient self-reported, and no independent validation is applicable, no points could be given to this item. Therefore, the maximum score for the Selection domain was three. A standard criterion for what constitutes a high-quality study base on the NOS has not yet been established. Generally, a study scoring ≥7 is considered high quality [41]. However, since no studies could get the maximum score on the Selection domain, we used a score of ≥6 as definition of high-quality studies.

Data Synthesis

To produce a qualitative synthesis of the results, all parameters assessed on their association with unsuccessful pessary fitting were clustered in a limited number of domains. For each domain one table was produced enumerating all studies in which a specific parameter was assessed on univariate and/or multivariate analysis.

To assess pessary fitting success rate, the weighted success rate at different times to follow-up was calculated. Sub-analyses were made for those studies which excluded and included women with unsuccessful initial fitting.

A meta-analysis of the parameters compared between successful and unsuccessful group in at least two records was performed. All available studies were combined without making any distinction based on the time to follow-up. A study was not included in the meta-analysis if the necessary input data were not reported, and if, after having contacted the authors, they did not provide the requested data. In case of overlap between study populations of two records, the record with the largest sample size reporting the parameter of interest was included in the analysis. The meta-analysis was done with the Comprehensive Meta-analysis (CMA) version 3 software. Input data for dichotomous variables were number of exposed (i.e., number of patients with a specific parameter, e.g., prior hysterectomy) and sample size of unsuccessful and successful group, when available, or odds ratio (OR) and confidence intervals. In the last case, unadjusted OR were used in the meta-analysis. For continuous variable input data were mean, standard deviation (SD), and sample size of unsuccessful and successful group or, if a t-test was run to compare the two groups, p-value and sample size of the two groups. If the data were reported as median and range (minimum-maximum) or interquartile range (IQR), the authors were contacted and asked for mean and SD. In case of no response, mean and SD would have to be imputed to include the study in the meta-analysis. At first, the meta-analysis was run excluding the studies that required data imputation. To test if the imputed data would have influenced the results, the meta-analysis was also run after data imputation. If the data were reported as median and range, the mean was imputed using the method described by Hozo et al [42], and the SD was imputed using the method described by Wan et al [43]. If the data were reported as median and IQR, mean and SD were derived using Wan's method. Authors were also contacted if they reported a parameter as significant or not significant without providing quantitative data. A random effect model was applied for the analysis. The summary measure used was OR. Heterogeneity was assessed with Q test and I-squared. For the significant parameters the risk of publication bias was assessed with the Trim and Fill procedure [44]. The meta-analysis without data imputation is presented in the result section, while the meta-analysis with data imputation is reported in Appendix E.

The review was conducted in adherence to the PRISMA and MOOSE guidelines. The protocol of the review was not registered before implementation.

Results

Study selection

Using the search strategy described, 1084 unique records were identified. The screening of title and abstract left 151 records. Of these, 119 were excluded after full text assessment and are reported in Appendix A. Thirty-two records (27 papers and five conference abstracts) were included in the qualitative synthesis, and 24 in the meta-analysis (Figure 1).

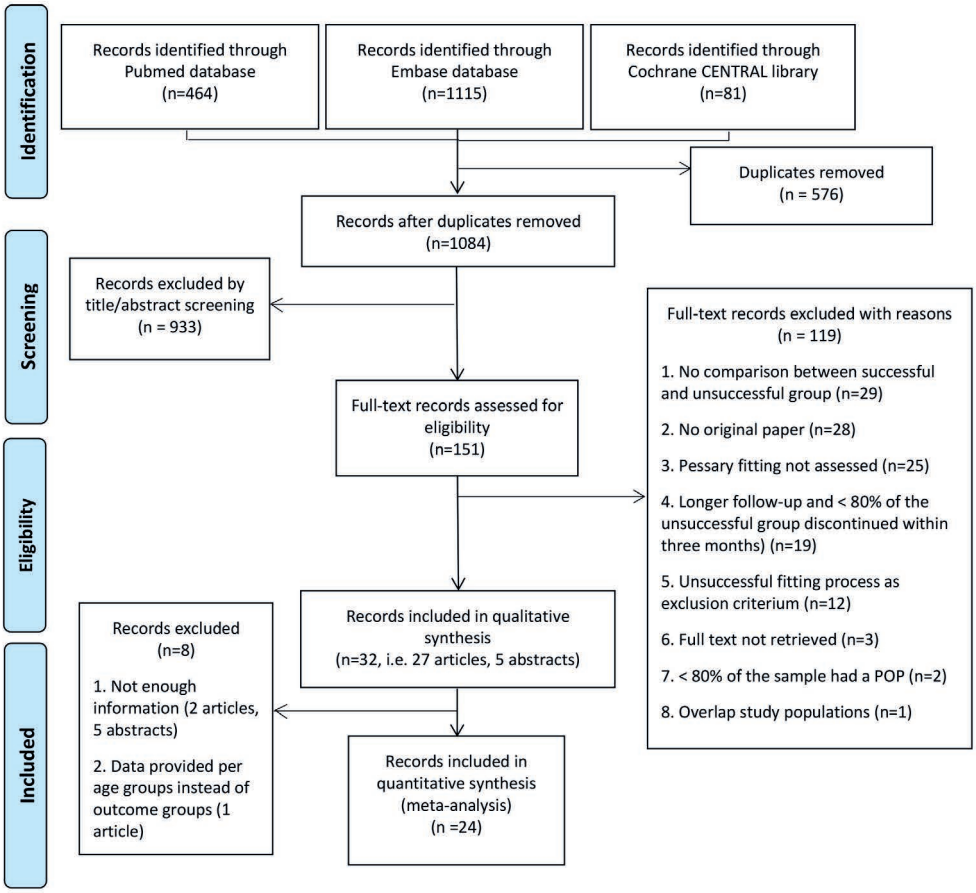

Figure 1. Records identification, inclusions and exclusions with reasons.

Study characteristics

The characteristics of the 32 included records are enumerated in Table 2. In the following, the included records will be referred to according to the numbers reported in Table 2 and a superscript number will be used in the text. It has to be noted that there is an overlap between the study populations of Cheung et al. (2017) and Cheung et al. (2018) and Manchana (2011) and Manchana et al. (2012). In Appendix B the list of the authors contacted during the review process is reported.

Table 2 Characteristics of the included records

Journal Papers: Authors, Year	Journal	Inclusion criteria	Exclusion criteria	N*	Pessary types
1) Cheung et al, 2017	UOG	- Symptomatic POP - No prior POP treatment - Double ring pessary allowed - Max 3 re-fittings	- POP surgery or pessary removal within 1st year - No documented 1-year follow-up	255	Ring (double allowed)
2) Cheung et al, 2018	Maturitas	- Symptomatic POP - No prior POP treatment - Double ring pessary allowed - Max 3 re-fittings	- POP surgery or pessary removal within 1st year - No documented 1-year follow-up	528	Ring (double allowed)
3) Clemons et al, 2004	AJOG	Symptomatic POP stage ≥ 2	-	100	Ring with diaphragm, Gellhorn, donut, double pessary
4) Cundiff et al, 2007	AJOG	- Symptomatic POP stage ≥ 2 - Interest in non-surgical treatment	- Pregnancy - Prior pessary use - Vaginal narrowing or agglutination	134	Ring with support, Gellhorn
5) Ding et al, 2015	IUJ	- Symptomatic POP stage 3-4 - Willingness to try a pessary	Unsuccessful initially fitting with a ring with support pessary	81	Ring with support
6) Fernando et al, 2006	Obstet Gynecol	- Symptomatic POP - Willingness to try a pessary	- Willingness to undergo surgery - Non–English speaking, learning difficulties, dementia	203	Ring, cube, Gellhorn, donut
7) Geoffrion et al, 2013	Female Pelvic Med. Reconstr. Surg.	Symptomatic POP	-	101	Ring with/ without support (with/without knob), Gellhorn, oval, donut, Gehrung
8) Jones et al, 2008	Obstet Gynecol	- Symptomatic POP - Willingness to non-surgical treatment	- Current pessary use - Pessary contraindications (active infection vagina or pelvis, undiagnosed vaginal bleeding, erosions, severe dementia)	90	Ring with support, Gellhorn, incontinence ring with knob, oval pessary
9) Ko et al, 2011	J Minim Invas Gyn	- Symptomatic POP stage ≥ 2 - Successful initial fitting with a Gellhorn	Gynecologic malignancy	46	Gellhorn
10) Lekskulchai et al, 2015	J Med Assoc Thai	Women with POP treated with a pessary	Lost to follow-up before 3 months	194	Ring with/ without support, donut, Gellhorn, pingpong ball
11) Maito et al, 2006	J Midwifery Womens Health	- POP and/or urinary incontinence (87% POP or both) - Willingness to try a pessary	-	120	Most common: ring with support

Study design	Set-ting[*2]	Initial fitting/ fitting process	Definition of success	Follow-up[*3]		Success rate fitting	
				Study	Review	Initial	Process
prospective observational	A	Fitting process	No pessary expulsion within 1 year (96% expulsion within 2 weeks)	1 year	2 weeks	-	59
prospective observational	A	Fitting process	No pessary dislodgement within 1st year (94% dislodgment within 2 weeks)	1 year	2 weeks	-	69
prospective observational	A	Both combined	Pessary use 1 week after initial fitting / re-fitting (vs discontinuation within 2 weeks)	2 weeks		94	73
randomized crossover trial	B	Both combined	Pessary use for 3 months	3 months		92	59 ¤
prospective observational	C	Fitting process	Continued pessary use for over 3 months from the initial fitting	3 months		-	67
prospective observational	A	Both combined	Reduction of POP without discomfort at the 2-weeks follow up	2 weeks		-	75
retrospective	A	Both combined	Pessary use after 4 weeks from initial fitting	4 weeks		78	74
Prospective, observational, cohort	A	Both combined	Successfully continued pessary use at the 3-month visit	3 months		-	47
retrospective	A	Fitting process	Pessary use for longer than 2 months	1 year	2 months	-	80
retrospective chart review	A	Fitting process	Pessary use for longer than 3 months	3 months		-	84
retrospective chart review	E	Both combined	Comfortable pessary retained on Valsalva and void at the time of fitting/ re-fitting (max 3 times)	17 months	Initial visit/ refitting	90	86

Journal Papers: Authors, Year	Journal	Inclusion criteria	Exclusion criteria	N*	Pessary types
12) Manchana, 2011	Arch Gynecol Obstet	- Symptomatic POP - Willingness to try a pessary	-	100	Ring
13) Manchana et al, 2012	IUJ	- Symptomatic POP - Willingness to try a pessary	-	126	Ring
14) Mao et al, 2018	BJOG	- Symptomatic POP (stage ≥ 2) - Willingness to try a pessary (i.e. mainly contraindication/ unwilling to surgery, possible future pregnancy or >60 years old)	-	343	Ring with support/ Gellhorn
15) Markle et al, 2011	Female Pelvic Med. Reconstr. Surg.	Symptomatic POP with/ without urinary incontinence	Missing data	158	Gellhorn, Shaatz, incontinence dish or ring, ring (with/without support), cube, donut, Gehrung, Inflatoball, Regula, Smith-Hodge
16) Mokrzycki et al, 2001	J Low Genit Tract Di	- Symptomatic POP - Willingness to try a pessary	- Suspicion of gynecological malignancy - Unexplained vaginal bleeding - Prior pessary use	42	Ring with support, cube, Gellhorn, Smith-Hodge, donut
17) Mutone et al, 2005	AJOG	- Symptomatic POP - Trial of pessary management	Lost to follow-up (n=23)	384	Ring with support, Gellhorn, cube, donut, Marland, Gehrung, Shaatz, Hodge, continence dish, regula, inflatoball
18) Nemeth et al, 2013	IUJ	- Symptomatic POP stage ≥ 2 - Willingness to try a cube pessary as first line treatment	- Undiagnosed vaginal bleeding - Vaginal erosions - Active vaginal infections - Dementia - Restricted mobility - lost to follow-up (n=6)	78	Cube
19) Nemeth et al, 2017	IUJ	- Symptomatic POP stage ≥ 2 - Women intended to be treated with a vaginal pessary	- Active infections of the pelvis or vagina - Inability to remove and reinsert the pessary - Unlikely to follow-up	629	Cube, ring with/ without support, ring with support and knob
20) Nguyen et al, 2005	J WOCN	- Pelvic floor relaxation - Preference for nonsurgical management	-	130	Ring (with/ without support), ring incont, Gellhorn, continence dish, Gehrung, cube, donut, regula

Study design	Set-ting[*2]	Initial fitting/ fitting process	Definition of success	Follow-up[*3]		Success rate fitting	
				Study	Review	Initial	Process
retrospective chart review	F	Both combined	Pessary use for longer than 2 weeks after initial fitting/ re-fitting	13 months	2 weeks	77	62
retrospective chart review	F	Both combined	Pessary use for longer than 2 weeks after initial fitting/ re-fitting	1 year	2 weeks	-	61
prospective observational	C	Both combined	Pessary use for longer than 2 weeks after initial fitting/ re-fitting	2 weeks		92	88
retrospective observational	C	Both combined	Pessary comfortably retained, and plan to continue its use at 1-week follow-up	1 week		-	59
retrospective chart review	A	Fitting process	Ability and desire to continue pessary use at 3 months follow-up	3 months		-	57
retrospective chart review	A	Both separate	1. Successful initial fitting 2. Patient still using the pessary at the 3 weeks follow-up and willing to continue	3 weeks		71	41
prospective cohort	A	Fitting process	Pessary use at 1-year follow-up (vs discontinuation 2-4 weeks after initial visit)	1 year	2-4 weeks	97	71
prospective cohort	A	Initial fitting	Successful initial fitting (vs failure to insert a pessary of appropriate size or loss/ displacement during Valsalva)	initial visit		96	-
retrospective chart review	C	Initial fitting	Successful initial fitting (vs inability to comfortably retain any pessary)	initial visit		63	-

Journal Papers: Authors, Year	Journal	Inclusion criteria	Exclusion criteria	N*	Pessary types
21) Panman et al, 2017	IUJ	- Age ≥55 years - Symptomatic POP stage 2-3 - Women randomized to pessary (secondary analysis of a RCT)	- POP treatment in previous year - Current treatment for urogynecological disorders - Pelvic organ malignancy - Impaired mobility - Severe or terminal illness - Cognitive impairment - Insufficient Dutch language	78	Ring without/ with support, Shaatz, Gellhorn
22) Paterson et al, 2018	S Afr J Obstet Gynaecol	Symptomatic POP	-	73	Ring with support
23) Ramsay et al, 2016	IUJ	- Symptomatic POP - ≥ 65 years, - Willingness to try a pessary	- Allergic to silicone - unwilling to conservative treatment - incomplete medial record (n=6)	304	Ring with support without/ with knob, regula, donut, Shaatz, oval, Gehrung, Marland with support
24) Turel et al, 2020	Aust N Z J Obstet Gynaecol	- Symptomatic POP - Willingness to try a pessary	- Obvious pessary contraindication - Incomplete dataset - Lost to follow-up	84	ring
25) Wu et al, 1997	Obstet Gynecol	- Symptomatic POP - Willingness to try a pessary	-	110	Ring with/ without support, cube
26) Yamada et al, 2011	J Obstet Gynaecol	- Uterine POP - Ring pessary treatment	-	69	Wallace ring pessary
27) Yang et al, 2018	Arch Gynecol Obstet	Symptomatic POP	- Abnormal cervical cytology - Inflammation in the genital organs - Allergy to silicon	300	Ring with support, Gellhorn

Study design	Set-ting[*2]	Initial fitting/ fitting process	Definition of success	Follow-up[*3]		Success rate fitting	
				Study	Review	Initial	Process
cross-sectional	G	Both combined	Ability to wear the pessary for 2 weeks without any discomfort, regardless of the number of pessary trials	2 weeks		-	58
retrospective cross-sectional	A	Both combined	Pessary use for 6 month-1 year (vs ≤ 1 month)	1 year	1 month	-	-
retrospective cohort	A	Both separate	1-month pessary use with subjective improvement POP symptoms and no significant complications	12 years	1 month	-	63
retrospective	A	Both combined	Pessary still in situ without complications at three-month follow-up	3 months	-	50	
prospective	C	Initial fitting	Successful initial fitting (i.e. pessary not expelled, patient could not feel the pessary, pessary did not descend to the introitus during testing)	4.5 years	initial visit	74	-
prospective	C	Fitting process	Pessary in situ for 4 weeks after the initial fitting (vs pessary expulsion)	1 month		-	77
retrospective	F	Both combined	Retaining the pessary for 1 week without discomfort	8 years	1 week	-	83

Conference abstracts: Authors, Year	Journal	Inclusion criteria	Exclusion criteria	N*	Pessary types
A) Cho et al, 2015	Female Pelvic Med. Reconstr. Surg.	Pessary fitting for symptomatic POP	- Current pessary use without prior POPQ assessment - Pessary for SUI only - Prior pelvic radiation - Pregnant at pessary fitting - No documented 6 months follow-up	254	Support/space occupying
B) Hooper et al, 2018	Female Pelvic Med. Reconstr. Surg.	- Symptomatic POP - Successful initial fitting with a cube pessary	-	25	Cube
C)Umachanger et al, 2018	IUJ	Symptomatic POP	-	130	Not specified
D) Triepels et al, 2019	Female Pelvic Med. Reconstr. Surg.	- POP stage ≥ 2 - Successful initial fitting	-	15	Not specified
E) Zhu et al, 2011	IUJ	- Symptomatic POP - ring pessary	-	66	Ring without support

***** N = number of patients included in the analysis

*[2] Setting = A: tertiary center, B: multicenter, C: gynecology department, D: urology department, E: nurse-midwifery pessary clinic, F: gynaecology clinic G: general practice

*[3] Follow-up: Study = longest time to follow-up assessed in the study; Review = time to follow-up considered for the current review

¤ 59 % = mean of the 2 trials of the randomized crossover trial

Abbreviations: POP = pelvic organ prolapse, SUI = stress urinary incontinence

Study design	Set-ting*	Initial fitting/ fitting process	Definition of success	Follow-up◊		Success rate fitting	
				Study	Review	Initial	Process
retrospective cohort	A	Fitting process	Pessary continuation ≥ 4 weeks after initial fitting	4 weeks		-	65
prospective observational	D	Fitting process	Ability to retain the pessary for up to 1 week	1 week		-	No report
retrospective chart review	C	Fitting process	Pessary use for longer than 3 months	3 months		-	67
pilot	A	Fitting process	No pessary expulsion	< 3 months		-	-
prospective	C	Fitting process	Satisfactory pessary fitting	1 month and 3 months		-	73 and 65

Risk of bias

In Table 3 the Newcastle-Ottawa Scale scores for the three domains and the total scores are reported. Mean total score was 6.

Table 3 Newcastle-Ottawa Scale scores

Papers	Selection max 4	Comparability max 2	Exposure max 3	Total score max 9
Cheung et al, 2017	2	2	3	7
Cheung et al, 2018	2	2	3	7
Clemons et al, 2004	3	0	3	6
Cundiff et al, 2007	3	0	3	6
Ding et al, 2015	3	0	3	6
Fernando et al, 2006	3	2	3	8
Geoffrion et al, 2013	2	2	2	6
Jones et al, 2008	3	2	3	8
Ko et al, 2011	2	0	2	4
Lekskulchai et al, 2015	3	0	2	5
Maito et al, 2006	3	2	2	7
Manchana, 2011	3	0	1	4
Manchana et al, 2012	3	0	1	4
Mao et al, 2018	3	2	3	8
Markle et al, 2011	3	1	2	7
Mokrzycki et al, 2001	2	0	2	4
Mutone et al, 2005	3	0	2	5
Nemeth et al, 2013	3	0	3	6
Nemeth et al, 2017	3	2	3	8
Nguyen et al, 2005	3	1	2	6
Panman et al, 2017	3	2	3	8
Paterson et al, 2018	2	0	2	4
Ramsay et al, 2016	3	0	2	5
Wu et al, 1997	3	0	3	6
Yamada et al, 2011	3	0	3	6
Yang et al, 2018	3	0	2	5
Turel et al, 2020	3	2	2	7

Synthesis of results: Success rate

Pessary fitting success rate ranged from 41%[17] to 96%[19]. In Table 4 the weighted means at different times to follow-up are shown. Sub-analyses were made for those studies which excluded and included women with unsuccessful initial fitting. When the unsuccessful initial fitting was included, the success rates were overall lower (data at 3-4 weeks and 3 months). No sub-analysis was run for studies assessing fitting process success rate at 1-2 weeks, because only one study excluded women with unsuccessful initial fitting[2].

Table 4 Weighted mean of pessary fitting success rate at different times to follow-up. Study reference refers to Table 2.

Time to follow-up	Success rate - weighted mean			Study reference
Initial fitting	86% (95% CI 78%-92%)			3, 4, 7, 11, 12, 14, 17-20, 25
1-2 weeks	72% (95% CI 64%-79%)			2, 3, 6, 13-15, 21, 27
3-4 weeks	65% (95% CI 53%-76%)	Unsuccessful initial fitting excluded	70% (95% CI 62%-76%)	18, 26, A
		Unsuccessful initial fitting included	60% (95% CI 40%-76%)	7, 17, 23
2 months	80% (95% CI 66%-89%)			9
3 months	63% (95% CI 53%-72%)	Unsuccessful initial fitting excluded	69% (95% CI 59%-78%)	5, 10, 16, C, E
		Unsuccessful initial fitting included	53% (95% CI 45%-66%)	4, 8, 24

Synthesis of results: Parameters

The parameters assessed on their association with unsuccessful pessary fitting by different authors were clustered into nine domains: a) Demographics, b) Obstetric history, c) (Uro)gynecological symptoms and medications, d) Prior surgeries, e) General history, f) Questionnaires, g) POP and pelvic floor assessment, h) Pessary, and i) Imaging. Appendix C shows the domain tables enumerating all studies in which a specific parameter was assessed on univariate and/or multivariate analysis. The results of the meta-analysis excluding imputed data are shown in Table 5 and the corresponding Forest plots in Figure 2 (significant parameters) and Appendix D (non-significant parameters).

Table 5 Results of the meta-analysis (imputed data excluded)

Parameter	OR (95% CI)	z-value	p-value	Heterogeneity				Trim and Fill		Study number
				Q value	df (Q)	p-value	I-squared	OR (95% CI)	Q value	
Demographics										
Age	0.70 (0.56-0.86)	-3.31	**0.00**	20.14	14	0.13	30.49	0.70 (0.56-0.86)	20.14	2, 3, 4, 5, 7, 8, 13, 14, 15, 16, 19, 20, 24, 26, 27
BMI	1.35 (1.08-1.70)	2.63	**0.01**	8.30	7	0.31	15.70	1.31 (1.05-1.63)	9.49	2, 7, 13, 14, 15, 19, 24, 27
Menopause	0.65 (0.47-0.88)	-2.74	**0.01**	5.66	8	0.69	0.00	0.65 (0.47-0.88)	5.66	2, 7, 8, 9, 13, 15, 18, 20, 24
White ethnicity	0.96 (0.29-3.23)	-0.07	0.95	10.19	3	0.02	70.56	-	-	3, 4, 6, 7
Obstetric history										
N. pregnancies	0.71 (0.45-1.12)	-1.48	0.14	0.02	1	0.89	0.00	-	-	7, 27
N. deliveries	1.02 (0.62-1.67)	0.06	0.95	19.35	5	0.00	74.16	-	-	3, 6, 7, 19, 26, 27
N. vaginal deliveries	1.13 (0.73-1.74)	0.55	0.58	1.01	2	0.60	0.00	-	-	7, 15, 16
Largest baby[o]	1.65 (0.43-6.25)	0.73	0.46	6.99	2	0.03	71.39	-	-	5, 7, 14
(Uro)gynecological symptoms and medications										
Stress urinary incontinence	2.06 (1.15-3.66)	2.45	**0.01**	22.33	8	0.00	64.18	1.88 (1.03-3.43)	26.28	3, 5, 7, 9, 13, 14, 16, 20, 14
Sexually active	1.27 (0.81-2.00)	1.04	0.30	9.46	5	0.09	47.17	-	-	2, 3, 7, 13, 15, 21
HRT	0.83 (0.51-1.35)	-0.75	0.45	9.25	5	0.10	45.94	-	-	3, 7, 8, 15, 20, 25
Prior surgeries										
Prior hysterectomy	1.88 (1.48-2.40)	5.09	**0.00**	17.99	15	0.26	16.63	1.88 (1.48-2.40)	17.99	2, 3, 6, 7, 8, 13, 14, 15, 17, 19, 20, 21, 24, 25, 26, 27
Prior POP surgery	2.13 (1.34-3.38)	3.21	**0.00**	27.30	10	0.00	63.37	2.13 (1.34-3.38)	27.30	3, 6, 7, 8, 14, 15, 17, 19, 20, 24, 25
Prior pelvic surgery	1.81 (1.01-3.26)	1.98	**0.05**	0.10	2	0.61	0.00	1.81 (1.01-3.26)	0.10	16, 21, 25
Incontinence surgery	1.87 (1.08-3.25)	2.24	**0.03**	1.01	3	0.80	0.00	1.87 (1.08-3.25)	1.01	7, 15, 20, 25
General history										
Smoking	1.65 (0.97-2.81)	1.85	0.64	3.16	4	0.53	0.00	-	-	5, 7, 20, 21, 24

Parameter	OR (95% CI)	z-value	p-value	Heterogeneity				Trim and Fill		Study number
				Q value	df (Q)	p-value	I-squared	OR (95% CI)	Q value	
Questionnaires										
CRADI-8	1.92 (1.22-3.02)	2.80	**0.01**	0.42	1	0.52	0.00	nm	nm	7, 27
POP and pelvic floor assessment										
Predominant anterior compartment POP*	0.69 (0.40-1.19)	-1.34	0.19	24.21	7	0.00	71.09	-	-	2, 5, 8, 14, 16, 17, 21, 26
Predominant apical compartment POP*	1.31 (0.60-2.15)	0.38	0.71	16.14	5	0.01	69.02	-	-	2, 5, 8, 14, 17, 21
Predominant posterior compartment POP*	1.78 (0.98-3.24)	1.88	0.06	13.85	6	0.03	56.68	-	-	2, 8, 14, 16, 17, 21, 26
POPQ stadium 3-4	1.20 (0.62-2.31)	0.54	0.59	32.1	7	0.00	78.19	-	-	2, 3, 8, 9, 13, 14, 16, 17
TVL	0.56 (0.32-0.97)	-2.07	**0.04**	21.01	5	0.00	76.20	0.56 (0.32-0.97)	21.01	2, 5, 8, 10, 15, 24
GH	0.66 (1.25-2.39)	0.68	0.50	19.26	4	0.00	79.24	-	-	2, 5, 8, 15, 24
Perineal body	1.37 (0.83-2.28)	1.23	0.22	9.10	3	0.03	67.04	-	-	2, 8, 15, 24
Wide introitus**	4.85 (1.60-14.68)	2.80	**0.01**	0.45	1	0.50	0.00	nm	nm	3, 12
GH/TVL	1.87 (0.86-4.05)	1.58	0.12	4.86	2	0.09	58.85	-	-	5, 7, 15
Pelvic floor strength	0.88 (0.50-1.54)	-0.45	0.65	0.22	1	0.64	0.00	-	-	7,24
Imaging										
Levator ani avulsion	2.47 (1.35-4.53)	2.93	**0.00**	1.56	1	0.21	36.00	nm	nm	1, 24
Hiatal area Valsalva	1.89 (1.27-2.80)	3.18	**0.00**	0.98	1	0.32	0.00	nm	nm	1, 24

Bold = Statistically significant; °Largest baby > 8 lbs (studies 5, 7) or 4 kg (study 14); *In case of predominant multiple compartments (e.g. maximum POP stadium in the anterior and apical compartment), the patient was included in all relevant groups (e.g. predominant anterior compartment POP and predominant apical compartment POP); **Wide introitus ≥ 4 fingerbreadths; nm = not measurable (to run a publication bias procedure at least three studies must be included); HRT= hormone replacement therapy; POP = pelvic organ prolapse; CRADI-8 = Colorectal-Anal Distress Inventory-8. The study number refers to Table 2.

Figure 2 Forestplots of the significant parameters (imputed data excluded)

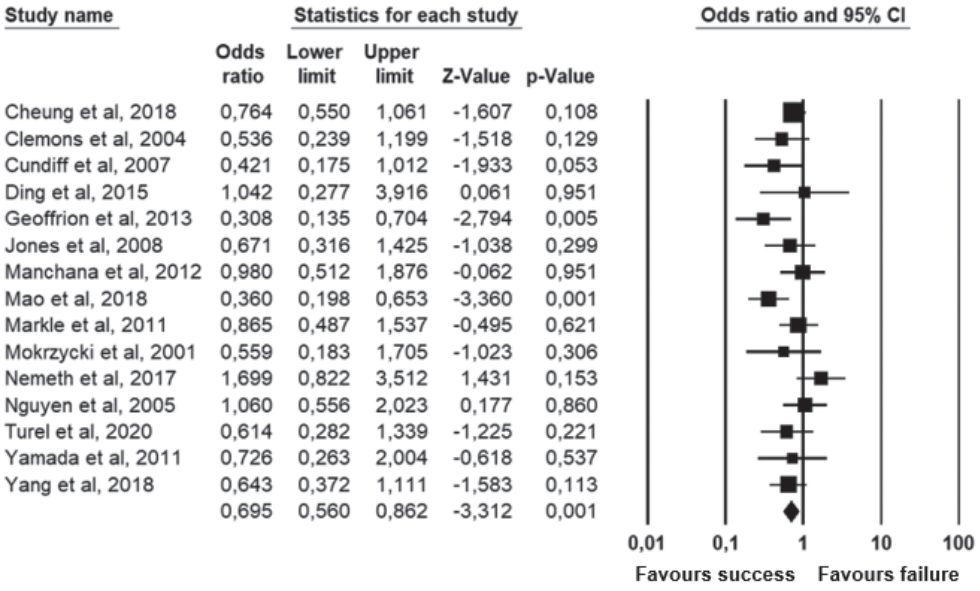

Figure 2.1. Forestplot for the association of **age** with successful pessary fitting up to three months follow-up (N= 2901).

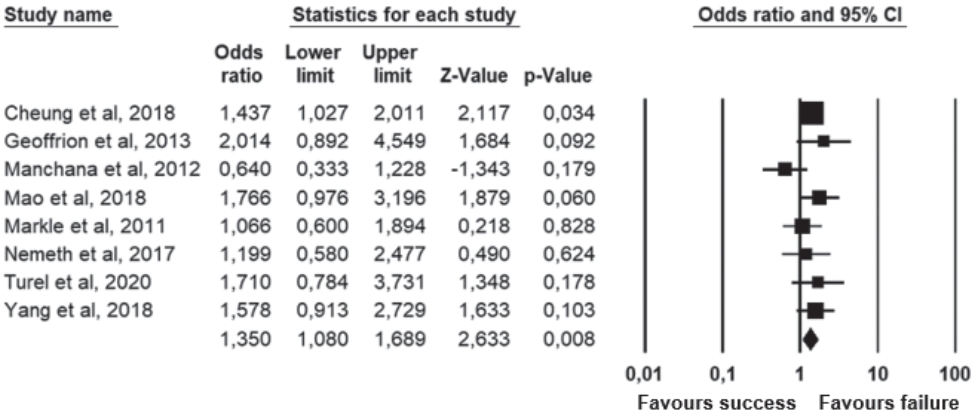

Figure 2.2. Forestplot for the association of **BMI** with unsuccessful pessary fitting up to three months follow-up (N=2244).

Study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Cheung et al, 2018	0,700	0,421	1,163	-1,376	0,169
Geoffrion et al, 2013	0,489	0,166	1,439	-1,298	0,194
Jones et al, 2008	0,946	0,267	3,356	-0,086	0,931
Ko et al, 2011	0,781	0,029	20,735	-0,148	0,882
Manchana et al, 2012	0,781	0,199	3,064	-0,354	0,723
Markle et al, 2011	0,998	0,359	2,775	-0,003	0,997
Nemeth et al, 2013	1,857	0,374	9,224	0,757	0,449
Nguyen et al, 2005	0,464	0,223	0,966	-2,053	0,040
Turel et al, 2020	0,325	0,117	0,904	-2,153	0,031
	0,645	0,471	0,883	-2,738	0,006

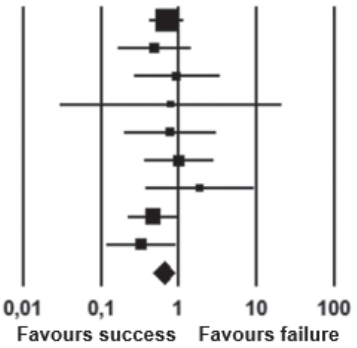

Figure 2.3. Forest plot for the association of **menopausal status** with successful pessary fitting up to three months follow-up (N=1338).

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Clemons et al, 2004	0,757	0,267	2,148	-0,523	0,601
Ding et al, 2015	3,722	0,612	22,634	1,427	0,154
Geoffrion et al, 2013	0,636	0,221	1,833	-0,837	0,402
Ko et al, 2011	40,385	1,860	876,924	2,355	0,019
Manchana et al, 2012	1,356	0,657	2,802	0,824	0,410
Mao et al, 2018	1,404	0,729	2,707	1,014	0,311
Mokrzycki et al, 2001	6,314	1,627	24,502	2,664	0,008
Nguyen et al, 2005	5,016	2,321	10,838	4,103	0,000
Wu et al, 1997	2,301	0,916	5,780	1,773	0,076
	2,056	1,154	3,660	2,448	0,014

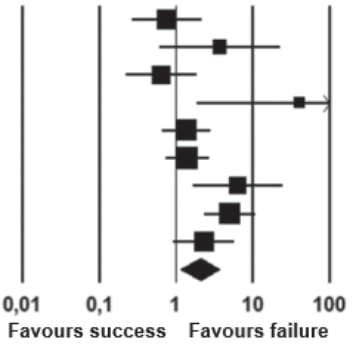

Figure 2.4. Forest plot for the association of **Stress urinary incontinence, SUI** (i.e., pre-existing or de novo SUI) with unsuccessful pessary fitting up to three months follow-up (N= 1065).

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Cheung et al, 2018	1,390	0,631	3,063	0,817	0,414
Clemons et al, 2004	1,846	0,746	4,567	1,326	0,185
Fernando et al, 2006	6,670	2,894	15,370	4,455	0,000
Geoffrion et al, 2013	0,912	0,334	2,489	-0,179	0,858
Jones et al, 2008	1,593	0,667	3,804	1,049	0,294
Manchana et al, 2012	1,568	0,631	3,898	0,968	0,333
Mao et al, 2018	0,774	0,261	2,297	-0,461	0,645
Markle et al, 2011	2,559	1,335	4,907	2,829	0,005
Mutone et al, 2005	2,162	1,430	3,268	3,657	0,000
Nemeth et al, 2017	0,465	0,027	7,856	-0,531	0,595
Nguyen et al, 2005	1,822	0,875	3,797	1,603	0,109
Panman et al, 2017	2,036	0,669	6,190	1,253	0,210
Turel et al, 2020	2,778	0,994	7,766	1,948	0,051
Wu et al, 1997	1,457	0,616	3,448	0,856	0,392
Yamada et al, 2011	0,817	0,085	7,876	-0,175	0,861
Yang et al, 2018	1,411	0,285	6,997	0,422	0,673
	1,882	1,475	2,400	5,094	0,000

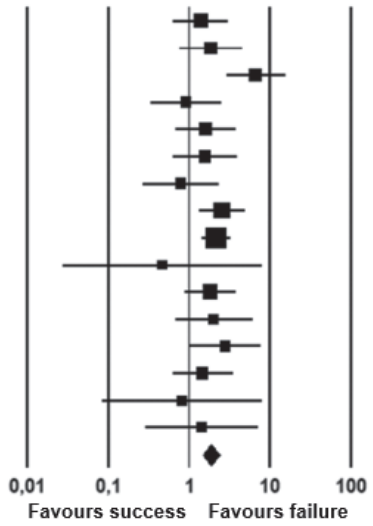

Figure 2.5. Forestplot for the association of **prior hysterectomy** with unsuccessful pessary fitting up to three months follow-up (N=3431).

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Clemons et al, 2004	0,843	0,339	2,094	-0,368	0,713
Fernando et al, 2006	4,330	1,672	11,213	3,019	0,003
Geoffrion et al, 2013	1,126	0,407	3,112	0,228	0,819
Jones et al, 2008	0,857	0,254	2,892	-0,248	0,804
Mao et al, 2018	4,064	1,629	10,141	3,006	0,003
Markle et al, 2011	1,427	0,635	3,207	0,862	0,389
Mutone et al, 2005	1,752	1,139	2,695	2,552	0,011
Nemeth et al, 2017	286,213	17,272	4742,926	3,949	0,000
Nguyen et al, 2005	4,412	1,633	11,917	2,928	0,003
Turel et al, 2020	2,361	0,872	6,391	1,691	0,091
Wu et al, 1997	1,504	0,604	3,746	0,876	0,381
	2,128	1,342	3,375	3,209	0,001

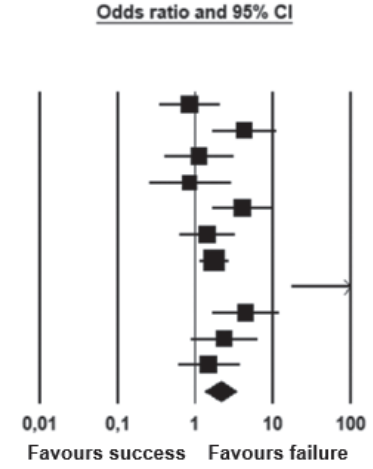

Figure 2.6. Forestplot for the association of **prior prolapse surgery** with unsuccessful pessary fitting up to three months follow-up (N=2330).

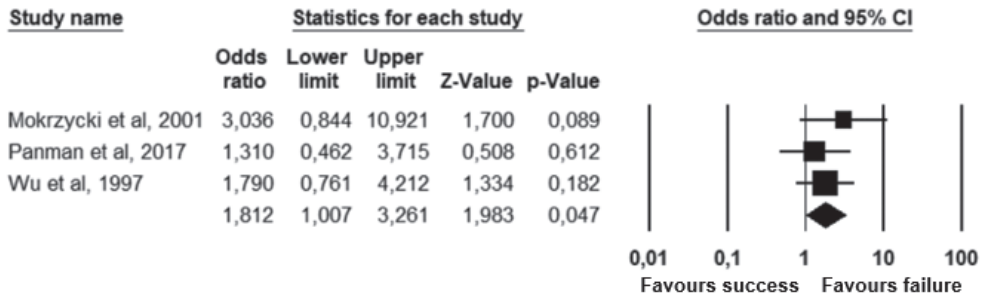

Figure 2.7. Forestplot for the association of **prior pelvic surgery** with unsuccessful pessary fitting up to three months follow-up (N=230).

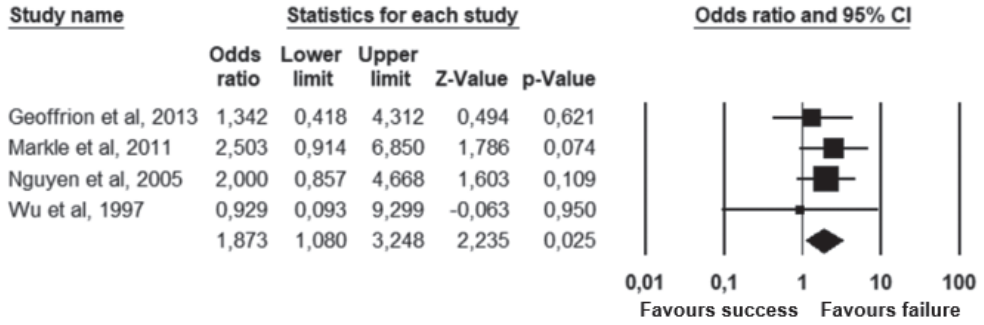

Figure 2.8. Forestfor the association of **prior incontinence surgery** with unsuccessful pessary fitting up to three months follow-up (N=497).

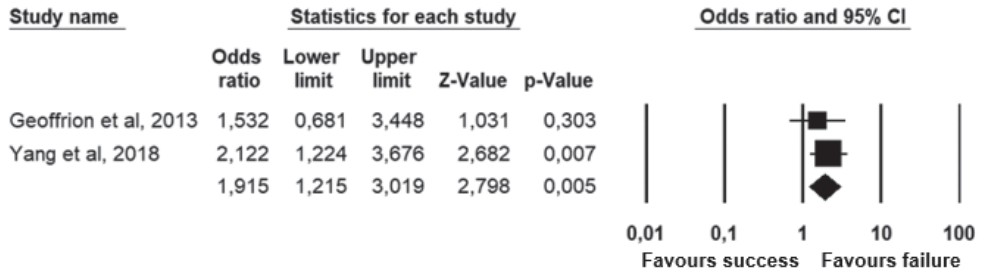

Figure 2.9. Forestplot for the association of **"CRADI-8"** (i.e., Colorectal-Anal Distress Inventory-8) scores with unsuccessful pessary fitting up to three months follow-up (N= 401).

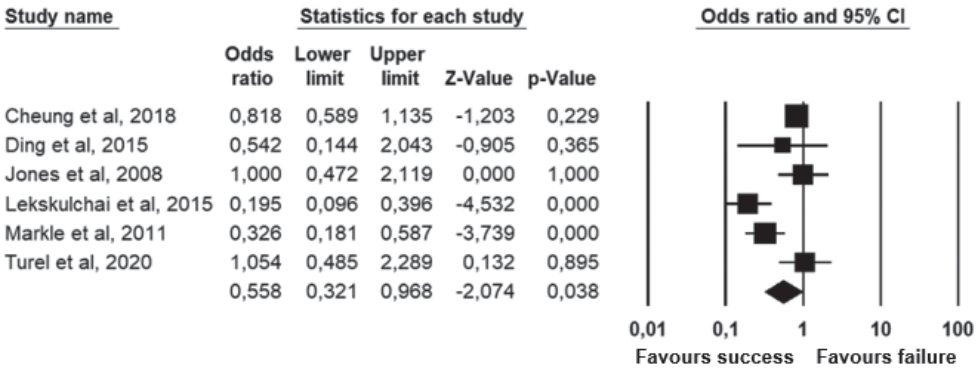

Figure 2.10. Forest plot for the association of **TVL (i.e., total vaginal length)** with successful pessary fitting up to three months follow-up (N=1135).

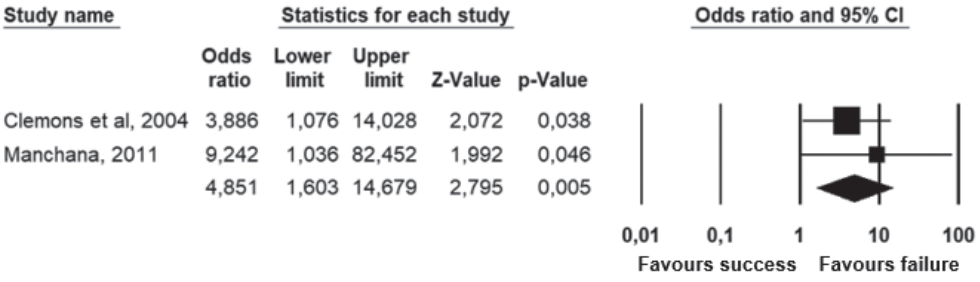

Figure 2.11. Forestplot for the association of **wide introitus** (i.e., ≥ 4 fingerbreadths) with unsuccessful pessary fitting up to three months follow-up (N=200).

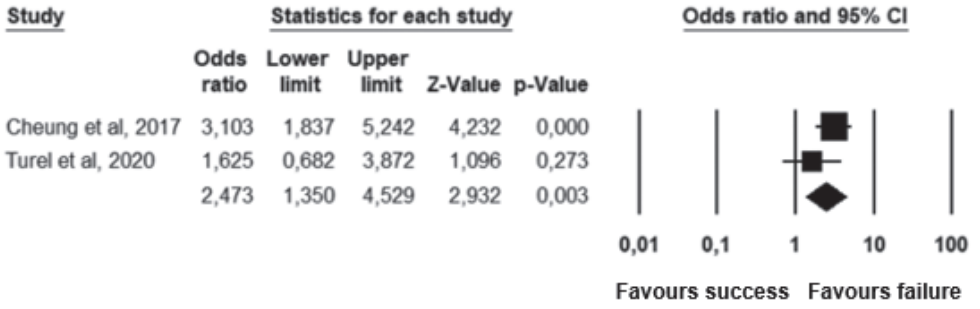

Figure 2.12. Forestplot for the association of **levator ani muscle avulsion** with unsuccessful pessary fitting up to three months follow-up (N=339).

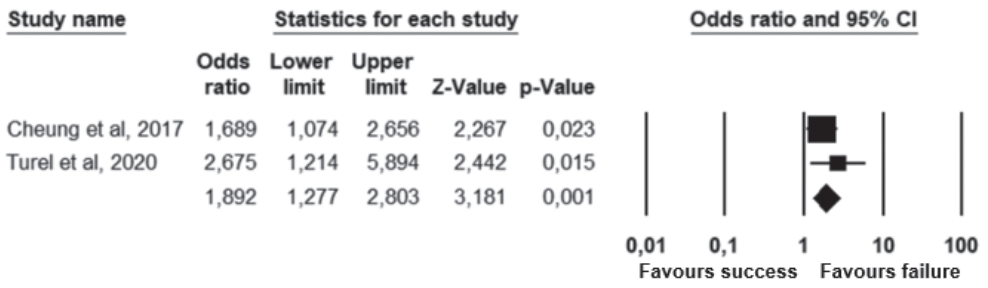

Figure 2.13. Forestplot for the association of **hiatal area on Valsalva** on transperineal ultrasound with unsuccessful pessary fitting up to three months follow-up (N=339).

Parameters associated with unsuccessful pessary fitting are: younger age, higher BMI, pre-menopausal status, stress urinary incontinence (SUI), prior surgery (i.e., hysterectomy, POP surgery, pelvic surgery, and incontinence surgery), higher Colorectal-Anal Distress Inventory-8 (CRADI-8) scores (which assess symptoms of obstructive defecation, anal incontinence, pain during defecation, faecal urgency and rectal bulging), shorter total vaginal length (TVL), wide introitus, levator ani avulsion and larger hiatal area on maximum Valsalva. The heterogeneity between studies and risk of publication bias is low for age, BMI, menopausal status, prior hysterectomy, prior pelvic surgery, and prior incontinence surgery. SUI, prior POP surgery and TVL show a low risk of publication bias, but a relatively high heterogeneity between studies. For CRADI-8 scores, wide introitus, levator ani avulsion and hiatal area on Valsalva the heterogeneity between studies is low, but the impact of publication bias could not be quantified because only two studies could be included in the analysis.

In Appendix E the results of the meta-analysis including imputed data are shown and in Appendix F the corresponding Forest plots. Running the analysis without and with the imputed data, did not qualitatively change the results: significant parameters remained significant and non-significant parameters remained non-significant. Sub-analyses were made for the parameters SUI and predominant posterior compartment. SUI is associated with unsuccessful pessary fitting (OR 2.06, 95% CI 1.15-3.66, z-value 2.45, p-value 0.01). However, grouping the studies in those which assessed pre-existing SUI only, and those which also assessed de novo SUI (alone or in combination with pre-existing SUI), de novo SUI remains significant (OR 5.59, 95% CI 2.24-13.99, z-value 3.68, p value 0.00), while pre-existing SUI does not (OR 1.44, 95% CI 0.88-2.36, z-value 1.45, p value 0.15) with small heterogeneity within groups (Q-value 11.17, p-value 0.13).

Predominant posterior compartment is not associated with unsuccessful pessary fitting (OR 1.78, 95% CI 0.98-3.24, z-value 1.88, p-value 0.06). However, in case of predominant multiple compartments (e.g., maximum POP stadium in the apical and posterior compartment), the patient was included in all relevant groups (e.g., predominant apical compartment POP and predominant posterior compartment POP). Analysing

solitary predominant posterior compartment POP (i.e., excluding women with multiple predominant compartments), a significant association with unsuccessful fitting is observed (OR 1.59, 95% CI 1.08-2.35, z-value 2.37, p-value 0.02, Q-value 4.51, df (Q) 5, Q-test p-value 0.48, I-squared 0.00) with low risk of publication bias (Trim and Fill procedure: OR 1.75, 95% CI 1.21-2.53, Q-value 7.04).

Discussion

The aim of the current review and meta-analysis was to clarify which clinical, demographical, and anatomical parameters are associated with unsuccessful pessary fitting for POP up to 3 months follow-up.

Main findings: Success rate

In the current review the success rate of pessary fitting ranged from 41% to 96%. However, these differences become smaller if sub-analyses are made based on the follow-up time. From initial fitting to three to four weeks follow-up, the mean success rate decreased from 86% (95% CI 78%-92%) to 65% (95% CI 54%-75%). Interestingly, after four weeks the success rate remained substantially stable (success rate of 63% (95% CI 53%-72%) at three months follow-up). This suggests that planning a follow-up at four weeks after initial fitting would ensure the vast majority of the unsuccessful fittings to be identified (as also reported by Lone et al [45]). Studies in which only women with successful initial fitting were included reported higher success rates compared to studies in which also women with unsuccessful initial fitting were included. Therefore, our suggestion for future research is to clearly report whether this selection is made or not.

Main findings: Parameters

Parameters associated with unsuccessful pessary fitting include: younger age, higher BMI, pre-menopausal status, SUI, prior surgery (i.e., hysterectomy, POP surgery, pelvic surgery, and incontinence surgery), higher CRADI-8 scores, shorter TVL, wide introitus, levator ani avulsion and larger hiatal area on maximum Valsalva.

In the case of SUI and prior POP surgery, the risk of publication bias is small, but the heterogeneity is relatively high. With respect to SUI, analysing separately the studies which assessed pre-existing SUI only, and those which also assessed de novo SUI, the heterogeneity within groups becomes smaller. Interestingly, de novo SUI remains significant, while pre-existing SUI does not. This suggests that pre-existing SUI alone is not associated with failure. Therefore, when counselling a patient for pessary treatment for POP, presence of pre-existing SUI should not be considered a reason for advising a different treatment. With respect to prior POP surgery, a possible explanation for the relatively high heterogeneity is that all women of the unsuccessful group in the study of Nemeth et al 2017 had prior POP surgery with consequent extremely high OR in this study compared to the others.

Some parameters that are significant in the meta-analysis have to be taken with caution. First, TVL shows high heterogeneity between studies. Second, the impact of publication bias could not be quantified for CRADI-8, wide introitus, levator ani avulsion and hiatal area on Valsalva because only two studies could be included in the analysis. In addition, levator avulsion shows moderate heterogeneity, which can be explained by the different definitions of unsuccessful pessary fitting: pessary expulsion in the study of Cheung et al, and pessary discontinuation within three months follow-up in the study of Turel et al. The same explanation can be given to the moderate heterogeneity of other non-significant parameters, i.e., predominant apical compartment, advanced POP, and GH. These parameters were associated with pessary dislodgment in the study of Cheung et al, but were not associated with unsuccessful pessary fitting when no distinction was made between different reasons for unsuccessful pessary fitting. The reasons for unsuccessful pessary fitting are numerous, e.g., dislodgment, discomfort/pain, de novo urinary symptoms, and failure to relieve POP symptoms [8]. Some parameters could be associated only with specific reasons for pessary fitting failure, but not others; future research should analyse the association between anatomical parameters and individual causes of pessary fitting failure.

Parameters related to obstetric history, e.g., number of pregnancies, deliveries, and vaginal deliveries, were not found to be associated with unsuccessful pessary fitting. However, no study assessed the influence of prior vaginal delivery vs no prior vaginal delivery on pessary fitting failure. If pessaries are supported by the pelvic floor muscles, prior vaginal delivery (which can cause pelvic floor muscles damage [46]) could be a risk factor for failure, even if POP mostly occurs in parous women. Being sexually active and hormone replacement therapy (HRT) use are not associated with (un)successful pessary fitting. Therefore, a sexually active woman with POP can be encouraged to try this treatment option and prescribing HRT only in case of indication is confirmed to be good practice.

Interestingly, advanced POP stage (3-4) is not associated with unsuccessful fitting. Therefore, pessary treatment can be advised to women with any stage of POP. Predominant anterior, apical, or posterior compartment POP are also not associated with unsuccessful fitting. However, higher CRADI-8 scores (which assess colorectal symptoms) and solitary predominant posterior compartment POP (i.e., maximum POP stage only in the posterior compartment, while women with multiple predominant compartments being excluded) are associated with unsuccessful fitting. These results confirm that pessary treatment is less effective in relieving colorectal symptoms [47].

Recently, a systematic review and meta-analysis has been published on the factors associated with unsuccessful pessary fitting in women with symptomatic POP [48]. Differences between their work and ours are the following. First, the follow-up for pessary fitting was one to three weeks in their work, while we included studies with a follow-up of maximal three months. Second, our search was performed in Embase, PubMed and Cochrane CENTRAL library, while theirs was performed in PubMed and we screened 1084 records, while they screened 350 records. Third, they only included prospective studies,

while we also included retrospective studies. Fourth, we assessed the weighted success rate of pessary fitting at different times to follow-up, which was not assessed in their work, while they assessed the reasons for pessary discontinuation after successful insertion, which we did not assess. Fifth, in our meta-analysis 24 studies were included, while 21 studies were included in theirs. Sixth, we performed a meta-analysis of 29 parameters, while they performed a meta-analysis of seven parameters. Seventh, we performed the analysis without and with data imputation, while they do not specify if imputed data were also included. With respect to the results, BMI and prior POP surgery were associated with pessary fitting failure in both works. In addition, GH was consistently not associated with pessary fitting failure. Different results were obtained for age, TVL, prior hysterectomy and advanced POP, which can be partially due to the differences described above. Furthermore, more studies were included in our meta-analysis which should make our results more solid. Only three studies were included in the meta-analysis of the parameter "advanced POP" in their work. The one with the highest relative weight was the study of Cheung et al in which the definition of failure was pessary dislodgment. It might be that advanced POP is a predictor of pessary dislodgment but not a predictor of other reasons for failure. Lastly, since we analysed more parameters, we also observed that menopausal status, de novo SUI, solitary predominant posterior compartment POP, higher CRADI-8 score, wide introitus, levator ani avulsion and larger hiatal area on maximum Valsalva are associated with unsuccessful pessary fitting.

Strengths and limitations

The current review and meta-analysis has several strengths. It was conducted according to the PRISMA and MOOSE guidelines. Multiple databases were searched. Study selection was made, independently, by two authors. The included papers were, on average, high-quality studies with a low risk of bias, as assessed by the Newcastle-Ottawa Scale. Moreover, authors were contacted in the case of missing information. Some limitations have to be acknowledged. Meta-analyses have the limitation that the interaction between different parameters cannot be assessed. For example, it is highly probable that younger age and pre-menopausal status are correlated. However, we cannot establish if one of the two is a confounder or both are independently associated with unsuccessful pessary fitting. In addition, mean and SD of continuous variables are needed to perform a meta-analysis, but some authors reported only median and range or median and IQR. In order to include these studies in the meta-analysis, mean and SD would have to be imputed. While we decided to exclude these studies from the meta-analysis in order to avoid any possible bias due to data imputation, we note that imputing mean and SD in these studies and including them, does not qualitatively change the results: significant parameters remain significant and non-significant parameters remain non-significant. This suggests that our conclusions are robust.

Conclusions

In women with symptomatic POP, younger age, higher BMI, pre-menopausal status, de novo SUI, prior surgery (i.e., hysterectomy, POP surgery, pelvic surgery, or incontinence surgery), solitary predominant posterior compartment POP, presence of colorectal symptoms, shorter TVL, wide introitus, levator ani avulsion and larger hiatal area on maximum Valsalva are associated with unsuccessful pessary fitting up to three months follow-up.

These results do not imply that an alternative treatment should always be advised to women with these characteristics, but rather that the higher risk of failure should be acknowledged and discussed during counselling for pessary treatment. Women with high risk of unsuccessful fitting because of, among others, a high BMI could work on this modifiable parameter to increase their probability of success, especially if they do not have many other treatment options (e.g., women who wish to have more children, or those unwilling or not suitable to undergo surgery [49]). If pessary treatment is chosen, being aware of the higher risk of failure would relieve some of the frustration related to the unsuccessful pessary fitting process. One might object that such a counselling could lower women's expectation thus increasing the risk of failure. However, any counselling should be evidence based and should allow women to make informed decisions in order to be ethical. In addition, the risk of pessary fitting failure should be weighted against the risks related to other treatments (e.g., surgery), which in many cases would encourage women to try pessary treatment.

Ethnicity, obstetric history, pre-existing SUI, sexual activity, use of HRT, smoking, predominant anterior, apical or multiple compartment POP, and advanced POP are not associated with unsuccessful pessary fitting. Therefore, women with these characteristics can be reassured that they do not have an increased risk of failure, and can be encouraged to try pessary treatment.

With respect to the anatomical parameters (assessed by clinical examination or imaging techniques), more research is needed to investigate their association with specific reasons for unsuccessful pessary fitting, i.e., whether it is dislodgment, discomfort/pain or other reasons. In addition, only two studies included in the meta-analysis assessed the association between TPUS parameters and unsuccessful pessary fitting. Therefore, the added value of TPUS in pessary fitting process should be further investigated.

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Ethics declarations

Conflicts of interest
None.

Appendix A List of the records excluded after full text assessment

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Appendix B List of the authors contacted during the review process

Phase	Authors	Reason contact	Response		Conclusion
Screening process	Triepels et al	Unclear time to follow up	Yes	Less than three months	Abstract included
	Yang et al	Abstract on the same data reported in the paper?	Yes	Abstract on the same data reported in the paper	Abstract considered as a duplicate
	Eberhard et al	Record not retrieved	No		Not included
	Fritzinger et al	Record not retrieved	No		Not included
	Poma	Record not retrieved	No		Not included
Data analysis	Cheung et al	Overlap study populations?[1,2]	Yes	Yes	Paper with the biggest sample for meta-analysis
	Cheung et al	Missing data in the two groups on BMI and n. vaginal deliveries	Yes	BMI: 7 in drop pessary group and 18 in pessary group; vaginal delivery: 7 in drop pessary group and 27 in pessary group.	Data used for meta-analysis
	Clemons et al	Mean and SD of GH and TVL	No		Dichotomous data used in the analysis in which imputed data were included
	Cundiff et al	Mean and SD of age, prevalence of white ethnicity in the two groups	Yes	Data provided	Data used for meta-analysis
	Ding et al	Mean and SD of BMI, gravidity, parity	No		Data imputed for the analysis in which imputed data were included
	Fernando et al	Mean and SD of age, parity	No		OR used as input data (age provided as dichotomous variable: only used in the analysis in which imputed data were included)
	Geoffrion et al	Mean and SD of age	Yes	Data provided	Data used for meta-analysis
	Jones et al	Mean and SD of parity	No		Data imputed for the analysis in which imputed data were included
	Ko et al	Mean and SD of age, BMI, parity	No		Since data could not be imputed, not used for the analysis
	Lekskulchai et al	Mean and SD of age, parity, length of the perineal body, GH	No		Data imputed for the analysis in which imputed data were included
	Maito et al	Mean and SD of age, pelvic floor strength, vaginal parity; prevalence of prior POP procedure, hysterectomy, urinary incontinence procedure, grade 3 or 4 of POP, urinary incontinence in the two groups	No		Since data could not be imputed, study not included in the meta-analysis

Phase	Authors	Reason contact	Response		Conclusion
	Manchana et al	Overlap study populations?[11,12]	No		Paper with the biggest sample for meta-analysis
	Manchana et al	Mean and SD of parity	No		Data imputed for the analysis in which imputed data were included
	Mao et al	Mean and SD of gravidity, n. vaginal deliveries, TVL, vaginal introitus, GH; prevalence of menopausal women in the two groups	No		Data imputed for the analysis in which imputed data were included (when possible)
	Mokrzycki et al	Mean and SD of vaginal parity	No		P-value of a t-test and sample sizes of the two groups used as input data
	Mutone et al	Mean and SD of age, BMI, levator ani strength, GH, perineal body length, TVL	Yes	Data not available	Data imputed and BMI used as dichotomous variable for the analysis in which imputed data were included
	Nemeth et al, 2013	Mean and SD of age, BMI, parity	No		Data imputed for the analysis in which imputed data were included (when possible)
	Nguyen et al	SD of age, mean and SD of parity, number of women with pre-existing SUI and SUI after POP reduction in the two groups	No		P-value of a t-test and sample sizes of the two groups used for age. Largest SD reported by other studies used for parity in the analysis in which imputed data were included. Groups with pre-existing SUI and SUI after POP could not be separated.
	Panman et al	Mean and SD of age, BMI, parity, CRADI-8, pelvic floor strength, GH, TVL	No		Data imputed for the analysis in which imputed data were included
	Paterson et al	Mean and SD of hiatal distance on contraction. Data on levator avulsion.	No		Since data could not be imputed, study not included in the meta-analysis
	Ramsay et al	Prevalence of prior hysterectomy, prior POP surgery, predominant anterior, apical, posterior POP compartment, POP stage 3-4, stress urinary incontinence in the two groups; mean and SD of number of vaginal deliveries	No		Since data could not be imputed, study not included in the meta-analysis
	Wu et al	Mean and SD of age and parity	Yes	Data not available	Not included in the meta-analysis

Phase	Authors	Reason contact	Response		Conclusion
	Cho et al	Clarifications on their results	No		Results described according to our understanding. Conference abstract: not included in the meta-analysis
	Hooper et al	Clarifications on their results	Yes	Grade of POP and prior hysterectomy predictors of unsuccessful fitting at 1 week	Results described according to authors. Conference abstract: not included in the meta-analysis

Appendix C Each table shows the parameters of one specific domain. For each parameter the studies in which it was assessed on univariate and/or multivariate analysis are reported, as well as whether it was significant or not.

Appendix C1 Demographics domain

Parameter	Univariate analysis assessment	Significant univariate analysis	Multivariate analysis Assessment	Significant multivariate analysis
Age	Cheung et al, 2017 Cheung et al, 2018 Clemons et al Cundiff et al Ding et al Fernando et al Geoffrion et al Jones et al Ko et al Lekskulchai et al Manchana, 2011 Manchana et al, 2012 Mao et al Markle et al Mokrzycki et al Mutone et al Nemeth et al, 2013 Nemeth et al, 2017 Nguyen et al Ramsay et al Wu et al Yamada et al Yang et al Turel et al Cho et al	Cundiff et al Fernando et al Geoffrion et al Mao et al Wu et al	Fernando et al Geoffrion et al Maito et al Mao et al Panman et al	Geoffrion et al Panman et al
BMI/weight	Cheung et al, 2017 Cheung et al, 2018 Ding et al Geoffrion et al Ko et al Lekskulchai et al Manchana et al, 2012 Mao et al Markle et al Mutone et al Nemeth et al, 2013 Nemeth et al, 2017 Nguyen et al Yang et al Turel et al Cho et al	Mao et al Mutone et al	Cheung et al, 2018 Maito et al Mao et al Panman et al	Mao et al Panman et al
Menopause	Cheung et al, 2017 Cheung et al, 2018 Geoffrion et al Jones et al Ko et al Manchana et al, 2012 Mao et al Markle et al Mokrzycki et al Nemeth et al, 2013 Nguyen et al Yang et al Turel et al Cho et al	Mao et al Turel et al	Mao et al Turel et al	Turel et al
Ethnicity	Clemons et al Cundiff et al Fernando et al Geoffrion et al Cho et al	Cundiff et al Cho et al	Fernando et al	-

Appendix C2 Obstetric history domain

Parameter	Univariate analysis assessment	Significant univariate analysis	Multivariate analysis Assessment	Significant multivariate analysis
Gravidity	Ding et al Geoffrion et al Mao et al Yang et al	-	-	-
Parity/ n. vaginal deliveries	Cheung et al, 2017 Cheung et al, 2018 Clemons et al Ding et al Fernando et al Geoffrion et al Jones et al Ko et al Lekskulchai et al Manchana, 2011 Manchana et al, 2012 Mao et al Markle et al Mokrzycki et al Nemeth et al, 2013 Nemeth et al, 2017 Nguyen et al Ramsay et al Wu et al Yamada et al Yang et al Turel et al Cho et al	Fernando et al Nemeth et al, 2013 Nemeth et al, 2017 Yang et al	Fernando et al Maito et al Nemeth et al, 2017	Fernando et al
Largest baby	Cheung et al, 2018 Ding et al Geoffrion et al Mao et al	Geoffrion et al	Panman et al Geoffrion et al	-
Assisted vaginal delivery	Geoffrion et al	-	-	-
Tear into rectum	Geoffrion et al	-	-	-

Appendix C3 (Uro)gynecological symptoms and medications domain

Parameter	Univariate analysis assessment	Significant univariate analysis	Multivariate analysis Assessment	Significant multivariate analysis
Urinary symptoms	Clemons et al Ding et al Geoffrion et al Manchana et al, 2012 Mao et al Markle et al Mokrzycki et al Nguyen et al Ramsay et al Wu et al Zhu et al	Mokrzycki et al Nguyen et al Wu et al	Maito et al Nguyen et al	Nguyen et al
De novo urinary incontinence	Ding et al Ko et al Nguyen et al	Ko et al Nguyen et al	-	-
Sexually active	Cheung et al, 2017 Cheung et al, 2018 Clemons et al Geoffrion et al Manchana et al, 2012 Markle et al Ramsay et al Cho et al	Cho et al	-	-
Age of onset/ duration symptoms	Mokrzycki et al Yang et al	-	-	-
Vaginal hormones	Geoffrion et al Jones et al Cho et al	-	-	-
Oral hormones	Clemons et al Geoffrion et al Jones et al Markle et al Nguyen et al Wu et al	-	-	-
Postvoidal residual	Geoffrion et al	-	-	-
Vaginal atrophy	Clemons et al Mokrzycki et al Ramsay et al	-	-	-
Anal incontinence	-	-	Maito et al	-
Pelvic pressure/ lower backache	Nemeth et al, 2013	-	-	-
Discomfort	Ramsay et al	-	-	-
POP necessitating manual reduction	Ramsay et al	-	-	-

Appendix C4 Prior surgeries domain

Parameter	Univariate analysis assessment	Significant univariate analysis	Multivariate analysis Assessment	Significant multivariate analysis
Hysterectomy	Cheung et al, 2017 Cheung et al, 2018 Clemons et al Ding et al Fernando et al Jones et al Geoffrion et al Manchana, 2011 Manchana et al, 2012 Mao et al Markle et al Mutone et al Nemeth et al, 2013 Nemeth et al, 2017 Nguyen et al Ramsay et al Wu et al Yamada et al Yang et al Turel et al Cho et al Hooper et al Umachanger et al	Fernando et al Markle et al Mutone et al Nemeth et al, 2013 Nemeth et al, 2017 Ramsay et al Cho et al Hooper et al Umachanger et al	Fernando et al Maito et al Nemeth et al, 2017 Panman et al Turel et al	Fernando et al Maito et al Turel et al
POP surgery	Clemons et al Ding et al Fernando et al Jones et al Geoffrion et al Mao et al Markle et al Mutone et al Nemeth et al, 2013 Nemeth et al, 2017 Nguyen et al Ramsay et al Wu et al Turel et al Cho et al Zhu et al	Fernando et al Mao et al Mutone et al Nemeth et al, 2013 Nemeth et al, 2017 Nguyen et al Ramsay et al Cho et al	Fernando et al Maito et al Mao et al Nemeth et al, 2017 Nguyen et al Panman et al	Maito et al Nemeth et al, 2017 Nguyen et al
Pelvic surgery	Geoffrion et al Mokrzycki et al Wu et al Zhu et al Umachanger et al	Umachanger et al Wu et al	Panman et al	-
Incontinence surgery	Geoffrion et al Markle et al Nguyen et al Wu et al	-	Maito et al	-

Appendix C5 General history domain

Parameter	Univariate analysis assessment	Significant univariate analysis	Multivariate analysis Assessment	Significant multivariate analysis
Comorbidities	Ding et al Ko et al Manchana et al, 2012 Yang et al	Ko et al	Maito et al	-
Poor surgical candidate	Clemons et al	-	-	-
Smoking	Ding et al Geoffrion et al Nguyen et al Turel et al	Geoffrion et al	Geoffrion et al	Geoffrion et al
Family support	Ding et al Ko et al	Ko et al	-	-
Constipation	Ding et al Ramsay et al	-	Maito et al	-
Desire of surgery at the 1st visit	Clemons et al	-	-	-

Appendix C6 Questionnaires domain

Parameter	Univariate analysis assessment	Significant univariate analysis	Multivariate analysis Assessment	Significant multivariate analysis
PFDI-20	Jones et al Geoffrion et al Yang et al	-	-	-
POPDI-6	Geoffrion et al Yang et al	-	-	-
UDI-6	Geoffrion et al Yang et al	-	-	-
CRADI-8	Geoffrion et al Yang et al	Yang et al	-	-
PFIQ-7	Geoffrion et al Yang et al	-	-	-
POPIQ-7	Geoffrion et al Yang et al	-	-	-
UIQ-7	Geoffrion et al Yang et al	-	-	-
CRAIQ-7	Geoffrion et al Yang et al	-	-	-
PEQ	Geoffrion et al	-	-	-

Appendix C7 POP and pelvic floor assessment domain

Parameter	Univariate analysis assessment	Significant univariate analysis	Multivariate analysis Assessment	Significant multivariate analysis
Compartment	Cheung et al, 2017 Cheung et al, 2018 Clemons et al Ding et al Fernando et al Jones et al Geoffrion et al Lekskulchai et al Mao et al Markle et al Mokrzycki et al Mutone et al Ramsay et al Yamada et al Turel et al Zhu et al	Cheung et al, 2017 Cheung et al, 2018 Lekskulchai et al Mao et al Mutone et al Turel et al Ramsay et al Yamada et al	Cheung et al, 2017 Cheung et al, 2018 Maito et al Mao et al Panman et al	Cheung et al, 2018 Maito et al
Stage	Cheung et al, 2017 Cheung et al, 2018 Clemons et al Ding et al Fernando et al Jones et al Geoffrion et al Ko et al Manchana, 2011 Manchana et al, 2012 Mao et al Markle et al Mokrzycki et al Mutone et al Nemeth et al, 2013 Nguyen et al Ramsay et al Yamada et al Cho et al Hooper et al Zhu et al	Cheung et al, 2017 Cheung et al, 2018 Yamada et al Cho et al Hooper et al	Cheung et al, 2017 Cheung et al, 2018 Geoffrion et al Maito et al Panman et al	Cheung et al, 2017 Cheung et al, 2018 Geoffrion et al
TVL	Cheung et al, 2018 Clemons et al Ding et al Jones et al Lekskulchai et al Manchana, 2011 Mao et al Markle et al Mutone et al Turel et al Zhu et al	Cheung et al, 2018 Clemons et al Lekskulchai et al Manchana, 2011 Mao et al Markle et al	Cheung et al, 2018 Mao et al Markle et al	Mao et al
Introitus width	Clemons et al Manchana, 2011 Mao et al Zhu et al	Clemons et al Manchana, 2011	-	-

Parameter	Univariate analysis assessment	Significant univariate analysis	Multivariate analysis Assessment	Significant multivariate analysis
GH	Cheung et al, 2018 Clemons et al Ding et al Jones et al Lekskulchai et al Manchana, 2011 Mao et al Markle et al Mutone et al Turel et al	Cheung et al, 2018	Cheung et al, 2018	Cheung et al, 2018
Pb	Cheung et al, 2018 Jones et al Lekskulchai et al Markle et al Mutone et al Turel et al Wu et al	Turel et al Jones et al	Turel et al Jones et al	Jones et al
GH + Pb	Turel et al	Turel et al	Turel et al	Turel et al
GH/TVL	Ding et al Geoffrion et al Markle et al	Markle et al	Geoffrion et al Markle et al	Geoffrion et al
Pelvic floor strength	Geoffrion et al Mutone et al Turel et al	-	Maito et al Panman et al	Panman et al

TVL = total vaginal length; GH = genital hiatus; Pb = perineal body

Appendix C8 Pessary domain

Parameter	Univariate analysis assessment	Significant univariate analysis	Multivariate analysis Assessment	Significant multivariate analysis
Type	Fernando et al Jones et al Mutone et al Wu et al Cho et al	Mutone et al Cho et al	Fernando et al	-
Size	Nemeth et al, 2013	-	-	-
Self-insertion	Ding et al Ko et al	-	-	-
Insertion ease	Nemeth et al, 2013	Nemeth et al, 2013	-	-

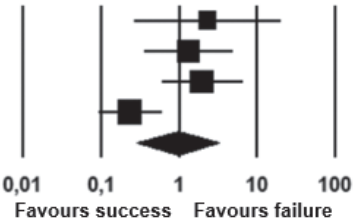
Appendix C9 Imaging domain

Parameter	Univariate analysis assessment	Significant univariate analysis	Multivariate analysis Assessment	Significant multivariate analysis
TPUS	Cheung et al, 2017 Paterson et al Turel et al	Cheung et al, 2017 Paterson et al Turel et al	Cheung et al, 2017 Turel et al	Cheung et al, 2017
MRI	Triepels et al	Triepels et al	-	-

TPUS = transperineal ultrasound; MRI = magnetic resonance imaging

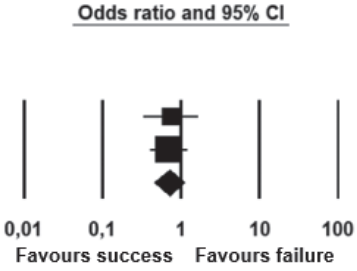
Appendix D Forestplots of the non-significant parameters (imputed data excluded)

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Clemons et al, 2004	2,328	0,267	20,289	0,765	0,444
Fernando et al, 2006	1,320	0,352	4,944	0,412	0,680
Geoffrion et al, 2013	1,969	0,594	6,528	1,108	0,268
Cundiff et al, 2007	0,235	0,093	0,597	-3,047	0,002
	0,960	0,286	3,227	-0,065	0,948



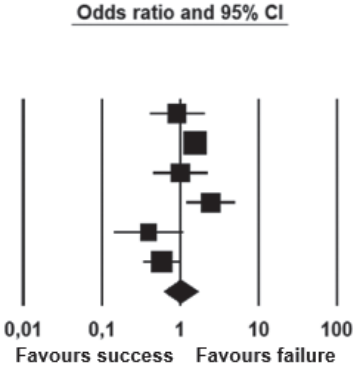
Appendix D.1. Forestplot for the association of **white ethnicity** with the outcome of pessary fitting up to three months follow-up (N=521).

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Geoffrion et al, 2013	0,743	0,330	1,670	-0,720	0,472
Yang et al, 2018	0,696	0,403	1,203	-1,299	0,194
	0,710	0,451	1,118	-1,480	0,139



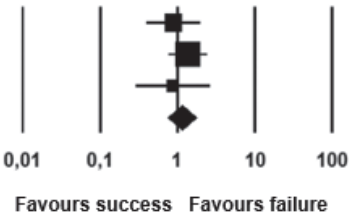
Appendix D.2. Forestplot for the association of **"number of pregnancies"** (N=401) with the outcome of pessary fitting up to three months follow-up.

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Clemons et al, 2004	0,911	0,409	2,029	-0,228	0,820
Fernando et al, 2006	1,550	1,201	2,001	3,363	0,001
Geoffrion et al, 2013	1,000	0,445	2,246	0,000	1,000
Nemeth et al, 2017	2,440	1,179	5,048	2,404	0,016
Yamada et al, 2011	0,396	0,142	1,104	-1,771	0,077
Yang et al, 2018	0,577	0,333	0,997	-1,969	0,049
	1,015	0,617	1,670	0,059	0,953



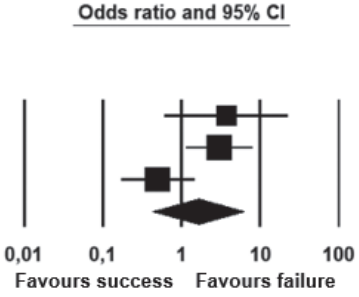
Appendix D.3. Forestplot for the association of **number of deliveries** (N=1402) with the outcome of pessary fitting up to three months follow-up.

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Geoffrion et al, 2013	0,884	0,394	1,986	-0,298	0,766
Markle et al, 2011	1,371	0,771	2,439	1,075	0,282
Mokrzycki et al, 2001	0,866	0,286	2,624	-0,255	0,799
	1,129	0,733	1,738	0,548	0,583



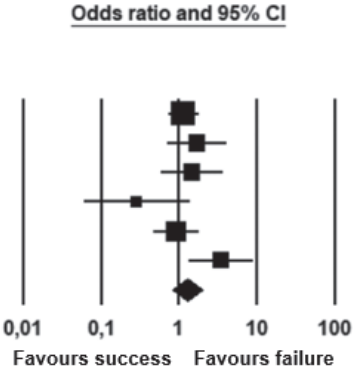
Appendix D.4. Forestplot for the association of **number of vaginal deliveries** with the outcome of pessary fitting up to three months follow-up (N=301).

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Ding et al, 2015	3,722	0,612	22,634	1,427	0,154
Geoffrion et al, 2013	3,016	1,128	8,062	2,200	0,028
Mao et al, 2018	0,496	0,170	1,451	-1,279	0,201
	1,646	0,434	6,248	0,732	0,464

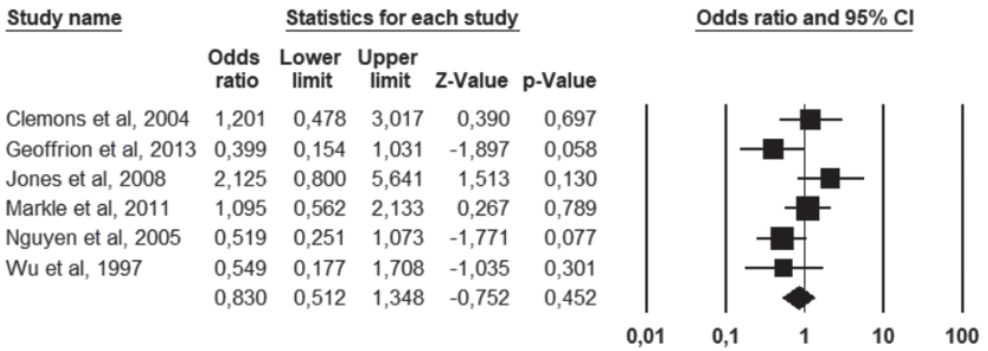


Appendix D.5. Forestplot for the association of **largest baby** (i.e., > 8 lbs in Ding et al and Geoffrion et al; > 4 kg in Mao et al) with the outcome of pessary fitting up to three months follow-up (N=507).

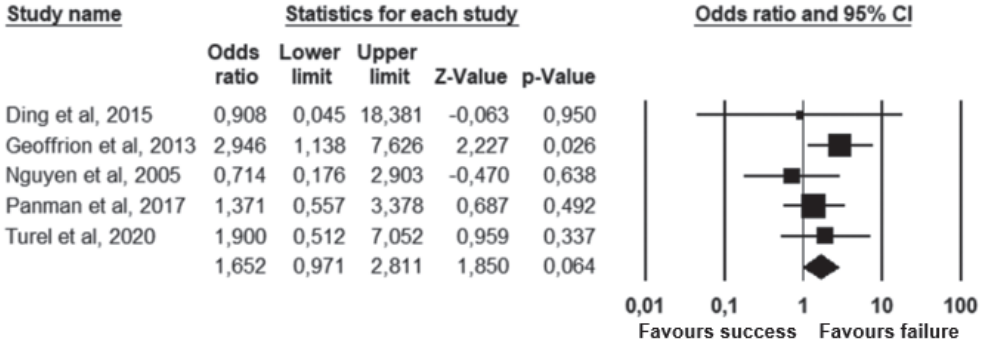
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Cheung et al, 2018	1,130	0,728	1,755	0,544	0,586
Clemons et al, 2004	1,694	0,696	4,123	1,161	0,246
Geoffrion et al, 2013	1,464	0,591	3,625	0,824	0,410
Manchana et al, 2012	0,285	0,060	1,361	-1,573	0,116
Markle et al, 2011	0,907	0,469	1,754	-0,289	0,773
Panman et al, 2017	3,450	1,331	8,941	2,549	0,011
	1,272	0,810	1,998	1,043	0,297



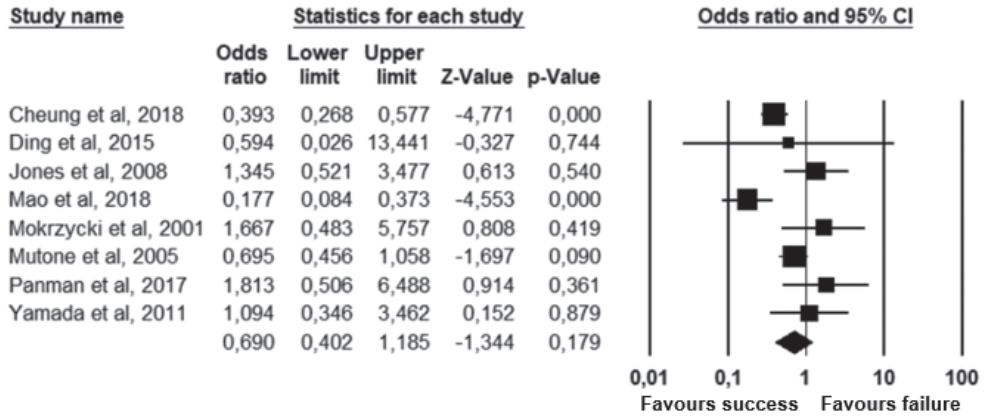
Appendix D.6. Forestplot for the association of **sexually active** with the outcome of pessary fitting up to three months follow-up (N=1085).



Appendix D.7. Forestplot for the association of **hormonal replacement therapy** with the outcome of pessary fitting up to three months follow-up (N=663).

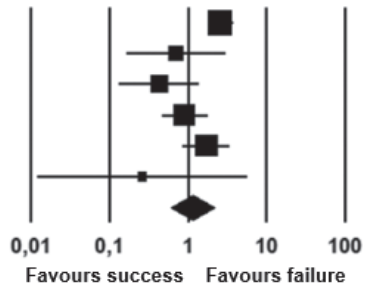


Appendix D.8. Forestplot for the association of **"smoking"** with the outcome of pessary fitting up to three months follow-up (N=470).



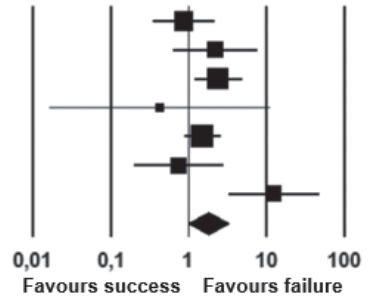
Appendix D.9. Forestplot for the association of **predominant anterior compartment** with the outcome of pessary fitting up to three months follow-up (N=1615). In case of predominant multiple compartments (e.g., maximum POP stadium in the anterior and apical compartment), the patient was included in all relevant groups (e.g., predominant anterior compartment POP and predominant apical compartment POP).

Study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Cheung et al, 2018	2,559	1,763	3,715	4,940	0,000
Ding et al, 2015	0,698	0,162	3,011	-0,483	0,629
Jones et al, 2008	0,426	0,131	1,393	-1,412	0,158
Mao et al, 2018	0,897	0,455	1,768	-0,313	0,754
Mutone et al, 2005	1,703	0,850	3,413	1,502	0,133
Panman et al, 2017	0,260	0,012	5,592	-0,861	0,389
	1,131	0,596	2,147	0,377	0,706



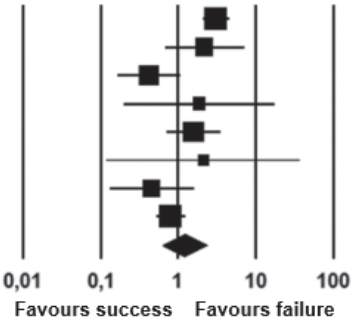
Appendix D.10. Forestplot for the association of **predominant apical compartment** with the outcome of pessary fitting up to three months follow-up (N=1504). In case of predominant multiple compartments (e.g., maximum POP stadium in the anterior and apical compartment), the patient was included in all relevant groups (e.g., predominant anterior compartment POP and predominant apical compartment POP).

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Cheung et al, 2018	0,862	0,348	2,136	-0,321	0,749
Jones et al, 2008	2,192	0,622	7,726	1,221	0,222
Mao et al, 2018	2,397	1,161	4,952	2,362	0,018
Mokrzycki et al, 2001	0,423	0,016	11,009	-0,517	0,605
Mutone et al, 2005	1,491	0,864	2,575	1,434	0,151
Panman et al, 2017	0,749	0,200	2,803	-0,430	0,668
Yamada et al, 2011	12,343	3,198	47,637	3,647	0,000
	1,778	0,975	3,241	1,878	0,060



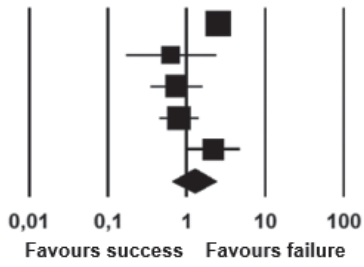
Appendix D.11. Forestplot for the association of **"predominant posterior compartment"** with the outcome of pessary fitting up to three months follow-up (N=1534). In case of predominant multiple compartments (e.g., maximum POP stadium in the anterior and apical compartment), the patient was included in all relevant groups (e.g., predominant anterior compartment POP and predominant apical compartment POP).

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Cheung et al, 2018	3,075	2,067	4,576	5,542	0,000
Clemons et al, 2004	2,170	0,667	7,060	1,287	0,198
Jones et al, 2008	0,416	0,163	1,062	-1,833	0,067
Ko et al, 2011	1,867	0,200	17,459	0,547	0,584
Manchana et al, 2012	1,572	0,703	3,514	1,102	0,270
Mao et al, 2018	2,107	0,118	37,568	0,507	0,612
Mokrzycki et al, 2001	0,455	0,131	1,583	-1,239	0,215
Mutone et al, 2005	0,796	0,520	1,219	-1,048	0,294
	1,200	0,623	2,312	0,544	0,586



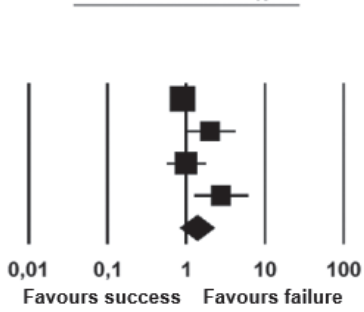
Appendix D.12. Forestplot for the association of **prolapse stage 3 or 4** with the outcome of pessary fitting up to three months follow-up (N=1658).

Study name	Lower limit	Odds ratio	Upper limit	Z-Value	p-Value
Cheung et al, 2018	1,821	2,539	3,540	5,492	0,000
Ding et al, 2015	0,167	0,630	2,372	-0,683	0,495
Jones et al, 2008	0,353	0,749	1,589	-0,753	0,451
Markle et al, 2011	0,451	0,802	1,425	-0,753	0,452
Turel et al, 2020	1,004	2,201	4,826	1,970	0,049
	0,656	1,252	2,390	0,682	0,495



Appendix D.13. Forestplot for the association of **GH (i.e., genital hiatus)** with the outcome of pessary fitting up to three months follow-up (N=941).

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Cheung et al, 2018	0,907	0,654	1,259	-0,584	0,559
Jones et al, 2008	2,018	0,946	4,308	1,816	0,069
Markle et al, 2011	1,000	0,563	1,777	0,000	1,000
Turel et al, 2020	2,774	1,258	6,117	2,528	0,011
	1,373	0,827	2,280	1,225	0,221



Appendix D.14. Forestplot for the association of **perineal body** with the outcome of pessary fitting up to three months follow-up (N=860). A= success, B= failure.

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Ding et al, 2015	0,975	0,259	3,664	-0,038	0,970
Geoffrion et al, 2013	3,928	1,712	9,015	3,228	0,001
Markle et al, 2011	1,420	0,798	2,527	1,194	0,232
	1,865	0,859	4,048	1,575	0,115

Appendix D.15. Forestplot for the association of **GH/TVL** with the outcome of pessary fitting up to three months follow-up (N=340).

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Geoffrion et al, 2013	0,765	0,340	1,719	-0,649	0,516
Turel et al, 2020	1,000	0,460	2,172	0,000	1,000
	0,880	0,502	1,540	-0,449	0,653

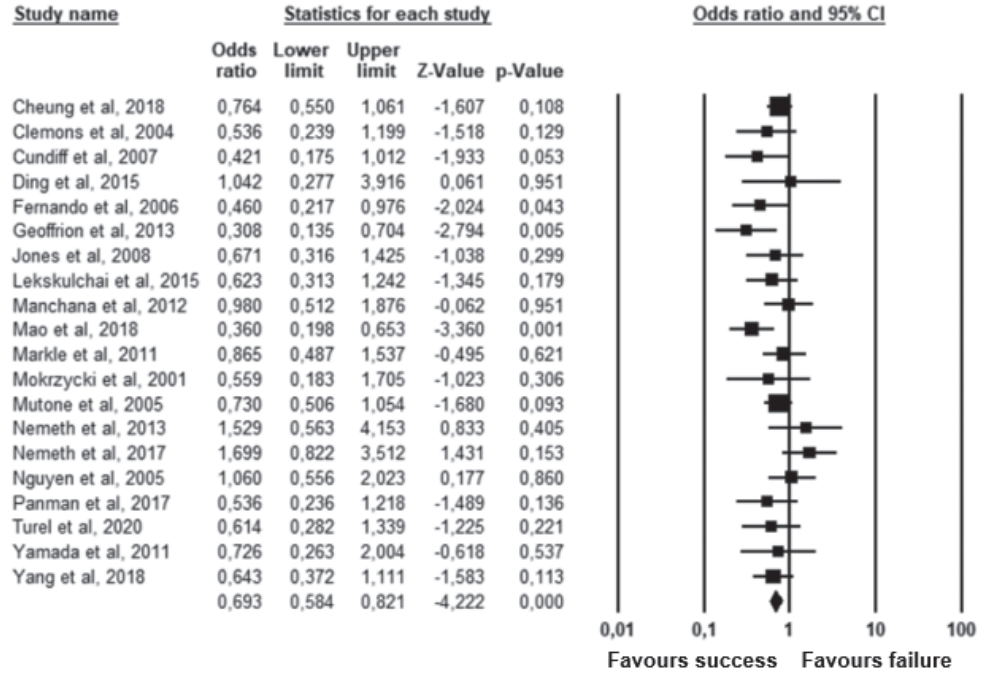
Appendix D.16. Forestplot for the association of **pelvic floor strength** with the outcome of pessary fitting up to three months follow-up (N=185).

Appendix E Results of the meta-analysis including imputed data (only parameters requiring data imputation are shown)

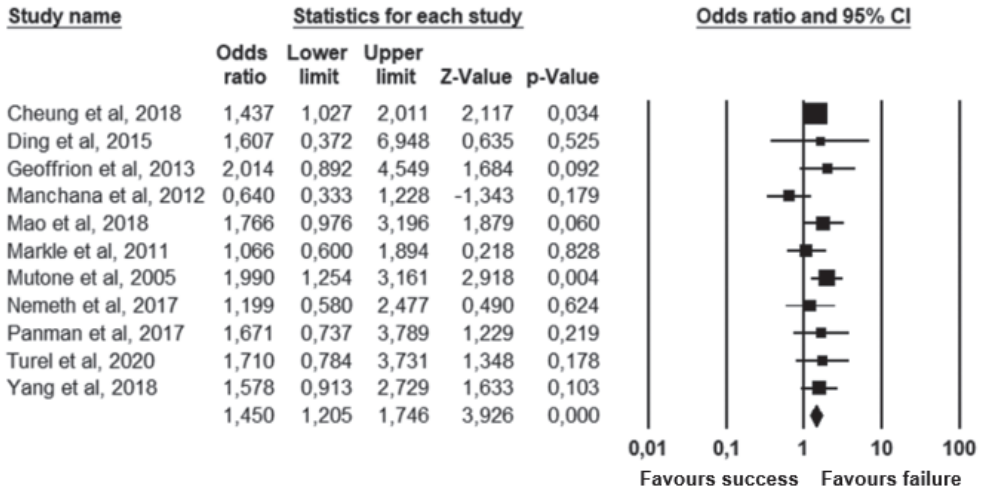
Parameter	OR (95% CI)	z-value	p-value	Heterogeneity				Trim and Fill		Studies included
				Q value	df (Q)	p-value	I-squared	OR (95% CI)	Q value	
Demographics										
Age	0.69 (0.58-0.82)	-4.22	**0.00**	24.26	19	0.19	21.70	0.71 (0.60-0.85)	28.35	2, 3, 4, 5, 6', 7, 8, 10°, 13, 14, 15, 16, 17°, 18°, 19, 20, 21°, 24, 26, 27
BMI	1.45 (1.21-1.75)	3.93	**0.00**	10.67	10	0.38	6.28	1.29 (1.07-1.56)	17.49	2, 5', 7, 13, 14, 15, 17', 19, 21°, 24, 27
Obstetric history										
N. pregnancies	0.80 (0.57-1.14)	-1.24	0.22	0.84	3	0.84	0.00	-	-	5°, 7, 14°, 26
N. deliveries	0.80 (0.59-1.08)	-1.43	0.15	46.62	14	0.00	69.97	-	-	2°, 3, 5°, 6, 7, 8°, 10°, 13°, 18°, 19, 20°, 21°, 24°, 26, 27
N. vaginal deliveries	0.90 (0.65-1.26)	-0.60	0.55	6.05	4	0.20	33.92	-	-	2°, 7, 14°, 15, 16
Largest baby	1.53 (0.81-2.88)	1.30	0.19	10.52	4	0.03	61.97	-	-	2, 5', 7', 14', 21°
Questionnaires										
CRADI-8	2.04 (1.37-3.04)	3.49	**0.00**	0.73	2	0.69	0.00	2.04 (1.37-3.04)	0.73	7, 21°, 27
POP and pelvic floor assessment										
TVL	0.44 (0.25-0.78)	-2.79	**0.01**	75.99	10	0.00	86.84	0.47 (0.27-0.83)	77.81	2, 3', 5, 8, 10, 12', 14°, 15, 17°, 21°, 24
GH	0.51 (0.91-1.62)	-0.33	0.74	90.59	10	0.00	88.96	-	-	2, 3', 5, 8, 10°, 12', 14°, 15, 17°, 21°, 24
Perineal body	1.24 (0.91-1.69)	1.35	0.18	10.07	5	0.07	50.36	-	-	2, 8, 10°, 15, 17°, 24
Introitus width	2.71 (1.61-4.58)	3.73	**0.00**	1.82	2	0.40	0.00	2.29 (1.33-3.94)	4.42	3', 12', 14°
Pelvic floor strength	0.57 (0.29-1.13)	-1.62	0.11	11.04	3	0.01	72.83	-	-	7, 17°, 21', 24

Bold = Statistically significant; *****In case of predominant multiple compartments (e.g. maximum POP stadium in the anterior and apical compartment), the patient was included in all relevant groups (e.g. predominant anterior compartment POP and predominant apical compartment POP); ° Mean and SD imputed; **'** Only available as dichotomous variable; **nm** = not measurable (to run a publication bias procedure at least three studies must be included); **HRT**= hormone replacement therapy; **POP** = pelvic organ prolapse; **CRADI-8** = Colorectal-Anal Distress Inventory-8. The study number refers to Table 2.

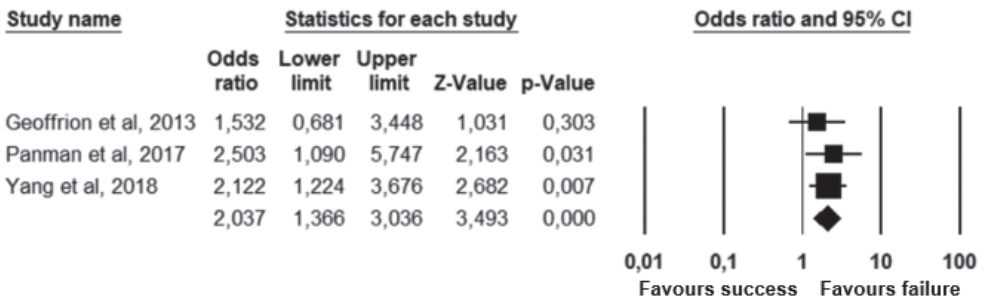
Appendix F1 Forest Plots of the significant parameters including imputed data (only parameters requiring data imputation are shown)



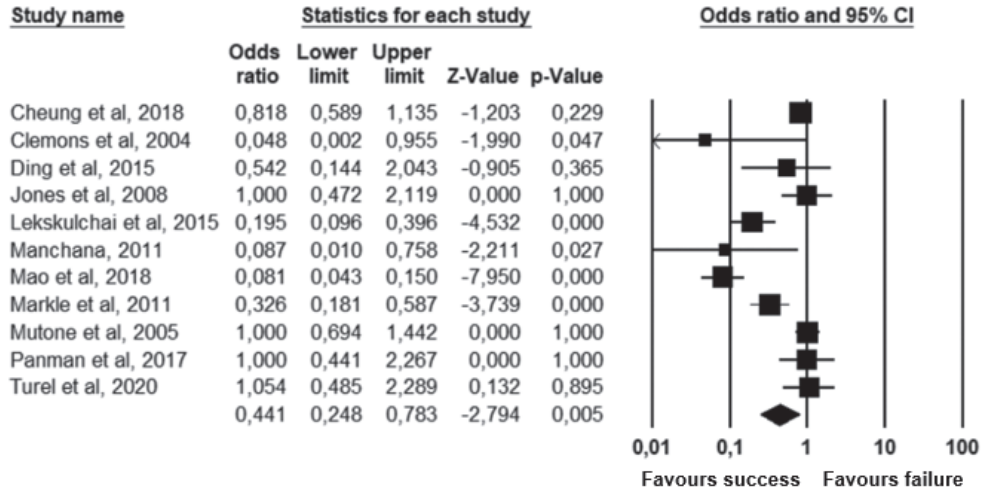
Appendix F1.1 Forestplot for the association of **age** with successful pessary fitting up to three months follow-up (N=3838).



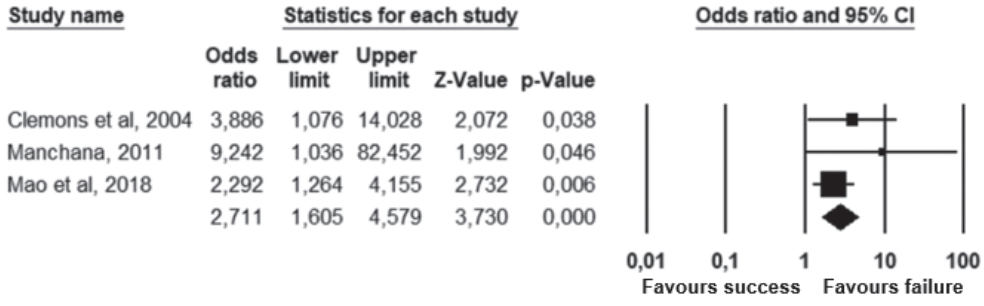
Appendix F1.2. Forestplot for the association of **BMI** (N=2787) with unsuccessful pessary fitting up to three months follow-up.



Appendix F1.3. Forestplot for the association of **CRADI-8** (i.e., Colorectal-Anal Distress Inventory-8) scores with unsuccessful pessary fitting up to three months follow-up (N=478).



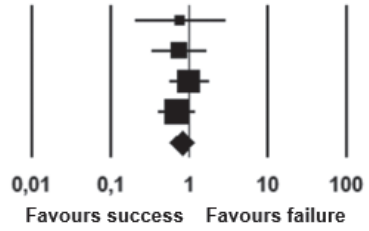
Appendix F1.4. Forestplot for the association of **TVL (i.e., total vaginal length)** with successful pessary fitting up to three months follow-up (N= 2139). A= success, B= failure



Appendix F1.5. Forestplot for the association of **introitus width** with unsuccessful pessary fitting up to three months follow-up (N=543).

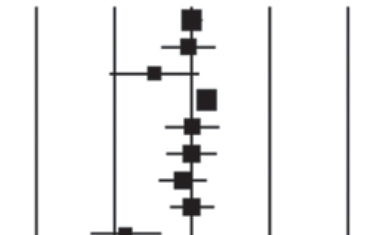
Appendix F2 Forest Plots of the non-significant parameters including imputed data (only parameters requiring data imputation are shown)

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Ding et al, 2015	0,758	0,201	2,849	-0,411	0,681
Geoffrion et al, 2013	0,743	0,330	1,670	-0,720	0,472
Mao et al, 2018	1,000	0,553	1,807	0,000	1,000
Yang et al, 2018	0,696	0,403	1,203	-1,299	0,194
	0,803	0,567	1,136	-1,241	0,215



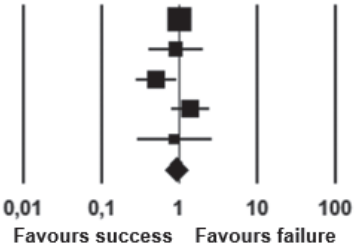
Appendix F2.1. Forestplot for the association of **number of pregnancies** (N=825) with the outcome of pessary fitting up to three months follow-up.

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Cheung et al, 2018	1,000	0,721	1,388	0,000	1,000
Clemons et al, 2004	0,911	0,409	2,029	-0,228	0,820
Ding et al, 2015	0,326	0,086	1,238	-1,646	0,100
Fernando et al, 2006	1,550	1,201	2,001	3,363	0,001
Geoffrion et al, 2013	1,000	0,445	2,246	0,000	1,000
Jones et al, 2008	1,000	0,472	2,119	0,000	1,000
Lekskulchai et al, 2015	0,762	0,380	1,531	-0,762	0,446
Manchana et al, 2012	1,000	0,522	1,915	0,000	1,000
Nemeth et al, 2013	0,140	0,049	0,397	-3,695	0,000
Nemeth et al, 2017	2,440	1,179	5,048	2,404	0,016
Nguyen et al, 2005	0,514	0,268	0,986	-2,001	0,045
Panman et al, 2017	1,000	0,443	2,259	0,000	1,000
Turel et al, 2020	0,612	0,281	1,333	-1,236	0,216
Yamada et al, 2011	0,396	0,142	1,104	-1,771	0,077
Yang et al, 2018	0,577	0,333	0,997	-1,969	0,049
	0,802	0,594	1,084	-1,434	0,152



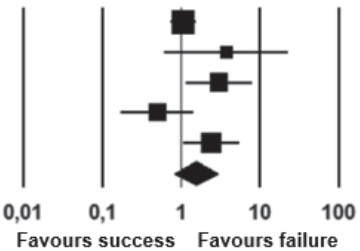
Appendix F2.2. Forestplot for the association of **number of deliveries** with the outcome of pessary fitting up to three months follow-up. (N=2790).

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Cheung et al, 2018	1,000	0,714	1,400	0,000	1,000
Geoffrion et al, 2013	0,884	0,394	1,986	-0,298	0,766
Mao et al, 2018	0,504	0,278	0,912	-2,264	0,024
Markle et al, 2011	1,371	0,771	2,439	1,075	0,282
Mokrzycki et al, 2001	0,866	0,286	2,624	-0,255	0,799
	0,904	0,649	1,260	-0,595	0,552

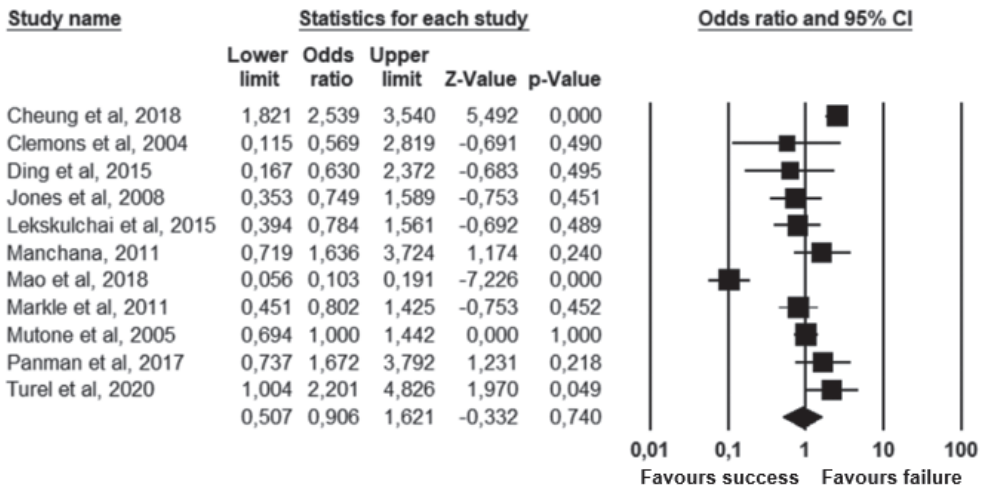


Appendix F2.3. Forestplot for the association of **number of vaginal deliveries** with the outcome of pessary fitting up to three months follow-up (N=1138).

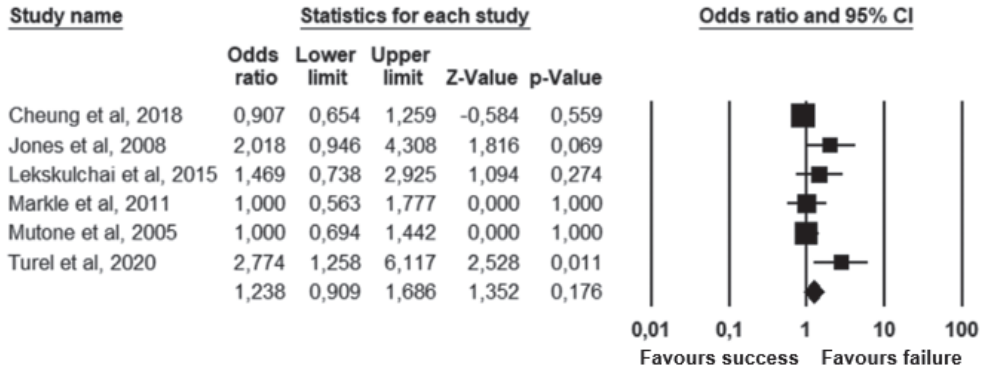
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Cheung et al, 2018	1,058	0,733	1,529	0,302	0,763
Ding et al, 2015	3,722	0,612	22,634	1,427	0,154
Geoffrion et al, 2013	3,016	1,128	8,062	2,200	0,028
Mao et al, 2018	0,496	0,170	1,451	-1,279	0,201
Panman et al, 2017	2,405	1,053	5,496	2,082	0,037
	1,525	0,808	2,876	1,303	0,193



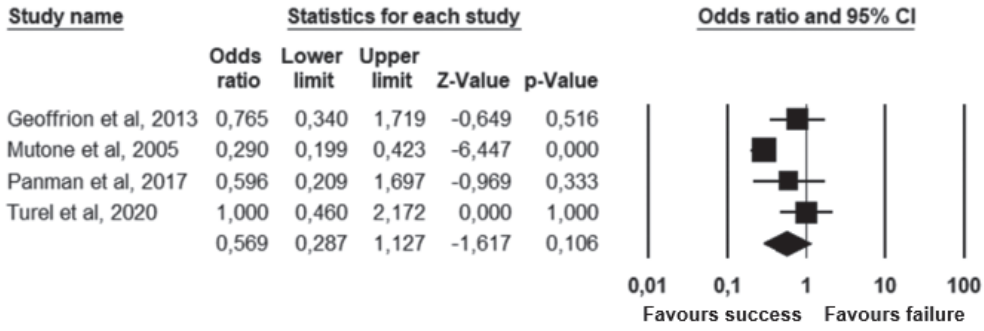
Appendix F2.4. Forestplot for the association of **largest baby** with the outcome of pessary fitting up to three months follow-up (N=997).



Appendix F2.5. Forestplot for the association of **GH (i.e., genital hiatus)** with the outcome of pessary fitting up to three months follow-up (N=2140).



Appendix F2.6. Forestplot for the association of **perineal body** with the outcome of pessary fitting up to three months follow-up (N=1438).



Appendix F2.7. Forestplot for the association of **pelvic floor strength** with the outcome of pessary fitting up to three months follow-up (N=647).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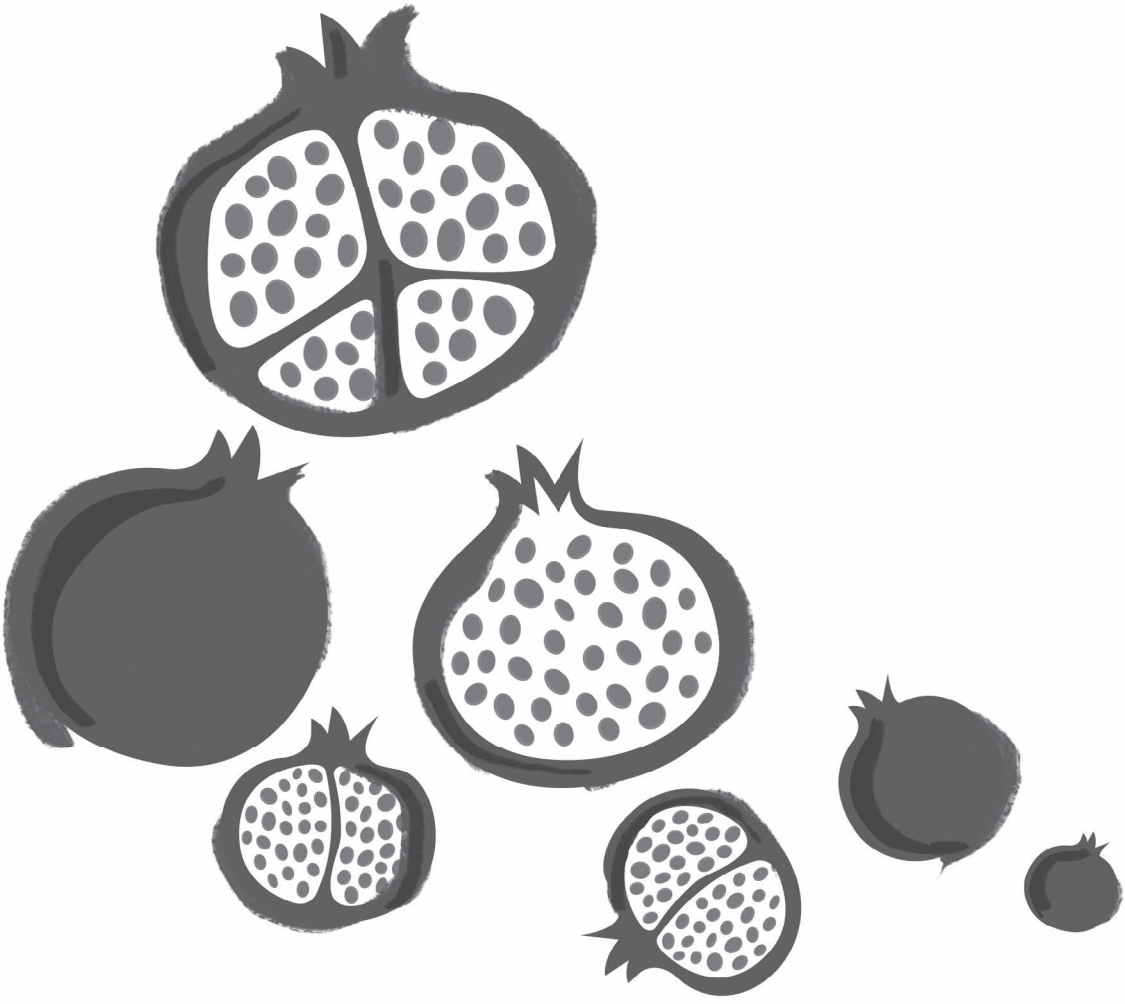

CHAPTER 3

Pessary fitting for pelvic organ prolapse: parameters associated with specific reasons for failure

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Abstract

Introduction and hypothesis: The objective was to assess if specific reasons for unsuccessful pessary fitting have different predictive parameters.

Methods: This is a prospective observational case–control study of women with symptomatic pelvic organ prolapse (POP) choosing pessary treatment. All women underwent an interview, clinical examination, and 3D/4D transperineal ultrasound (TPUS). Groups were defined based on fitting outcome: successful, pessary dislodgment, failure to relieve POP symptoms, pain/discomfort, increased/de novo urinary incontinence, or other reasons. Clinical, demographic, and TPUS parameters were assessed in the prediction of different reasons for unsuccessful fitting and receiver operating characteristic (ROC) curves were constructed.

Results: A total of 162 women were assessed and 130 were included. Levator hiatal area (HA) on maximum Valsalva divided by ring pessary size ("Valsalva HARP ratio") was a predictor of unsuccessful fitting (OR 3.00, 95% CI 1.15–7.81, p = 0.025) with an area under the ROC curve (AUC) of 0.62 (95% CI 0.50–0.74, p = 0.04). Predictors of pessary dislodgment were: complete avulsion (OR 24.20, 95% CI 2.46–237.84, p value 0.01) and Valsalva HARP ratio (OR 2.94, 95% CI 1.32–6.55, p value 0.01) with an area under the ROC curve (AUC) of 0.92 (95% CI 0.84–0.99, p = 0.00). No significant parameter was identified in the prediction of pain/discomfort. Solitary predominant posterior compartment POP was a predictor of failure to relieve POP symptoms (OR 20.00, 95% CI 3.48–115.02, p value 0.00; AUC 0.75, 95% CI 0.53–0.98, p = 0.03).

Conclusion: Complete avulsion and a small ring pessary with respect to the levator HA in Valsalva are predictors of pessary dislodgment, whereas solitary predominant posterior compartment POP is a predictor of failure to relieve POP symptoms.

Introduction

Vaginal pessaries are widely used as a conservative treatment option for pelvic organ prolapse (POP) [1, 2] and have proven effective in relieving POP symptoms [3-7]. However, the success rate of pessary fitting (which is the process of finding a pessary that suits an individual woman) has been reported to be as low as 41% [8]. Numerous studies have been published on the role of demographic and clinical parameters in the prediction of (un)successful pessary fitting for pelvic organ prolapse (POP) [4, 8-18], whereas the role of transperineal ultrasound (TPUS) parameters has been investigated in only a few recent studies [19, 20]. In addition, when comparing successful and unsuccessful groups, past studies did not differentiate between specific reasons for pessary fitting failure. Therefore, the unsuccessful group was heterogeneous, including women with pessary dislodgment, failure to relieve POP symptoms, pain/discomfort, or urinary symptoms [11]. Only Cheung and co-workers analyzed pessary dislodgment separately from other reasons for pessary fitting failure [15, 19]. However, women requiring pessary removal for reasons of failure other than pessary dislodgment were excluded from their analysis.

Our hypothesis is that specific reasons for unsuccessful pessary fitting have different predictive parameters. Knowing which parameters are associated with a specific reason for failure could make the counseling for pessary treatment more effective: a higher risk of dislodgment, failure to relieve POP symptoms, pain/discomfort, or urinary symptoms would be known and discussed, which would in turn allow both clinicians and patients to better manage their expectations and engage in a more evidence-based decision-making process. Furthermore, the association of TPUS parameters with specific reasons for pessary fitting failure could give an indication of the added value of TPUS in pessary fitting. This is the rationale behind the current study in which the association of demographic, clinical, and TPUS parameters with specific reasons for unsuccessful pessary fitting is investigated.

Materials and methods

The data used in the current study were collected as a subset within the GYNecological Imaging using 3D UltraSound (GYNIUS) project on the assessment of pelvic floor contractility with TPUS, which was conducted at our urogynecological center, where secondary and tertiary care are provided. Women were included in the GYNIUS project between May 2018 and December 2019. The Medical Research Ethics Committee (MREC) exempted the project from ethical approval (reference 18/215), because TPUS was part of our routine diagnostic procedures and standard care. All women signed informed consent forms.

Study design and pessary fitting

This was a prospective observational case–control study on parameters associated with specific reasons for unsuccessful pessary fitting. Women with symptomatic POP choosing pessary treatment were included. Women who were already using a pessary at

intake assessment, and those who started pessary fitting more than 4 weeks after intake assessment were excluded. All women underwent an interview, clinical examination, and 3D/4D TPUS. Pelvic organ prolapse was assessed using the Pelvic Organ Prolapse Quantification system (POPQ) [21]. Pessary fitting was performed according to our standard clinical practice, similar to the one described in the literature [8, 9, 10, 11, 22, 23]. In the following, specific terminology will be used to describe different phases of pessary fitting and is presented in Table 1.

Table 1 Terminology used to describe the different phases of pessary fitting and their definitions.

Terminology	Definition
Initial fitting	Pessary fitting at the first visit, which is successful if the patient leaves the clinic with a pessary that stays comfortably in place. It is unsuccessful if the woman cannot be fitted with any pessary type and size and has to undergo a different treatment
Fitting trial	The event of a woman being fitted with a specific pessary size and type, leaving the clinic with the pessary in place, and attending the 2- to 4-week follow-up in which the success of the fitting trial is assessed (i.e., the pessary is still in situ, the woman is satisfied with it and decides to continue using the pessary she was fitted with). It is unsuccessful if, for any reason, the woman does not continue using the specific pessary she was fitted with
Pessary fitting	Study outcome. Process from initial fitting to the last fitting trial. Independently of the number of fitting trials the woman undergoes, it is successful if the last fitting trial is successful (i.e., the pessary is still in situ, the woman is satisfied with it and decides to continue using the last pessary she was fitted with). It is unsuccessful if the woman has to undergo a different treatment because of unsuccessful initial fitting or last fitting trial

A woman could undergo one or more fitting trials until the last trial was successful. In this case, pessary fitting (our study outcome) was considered successful and pessary type and size were recorded. On the contrary, pessary fitting was considered unsuccessful if initial fitting was unsuccessful or, after one or more fitting trials, the woman was not satisfied with any pessary and a different treatment was chosen. In this case, pessary type and size of the last fitting trial were recorded, and the woman was asked which one of the following was the reason for fitting failure: dislodgment (defined as a pessary that did not stay in place because it fell down or was expelled), failure to relieve POP symptoms, pain/discomfort, increased/de novo urinary incontinence, or other reasons. With respect to the pessary type, a ring pessary (without or with support) was always tried first. If, having tried different sizes, a ring pessary was not successful, a different pessary type was tried (i.e., Gellhorn, donut, or cube pessary).

TPUS data acquisition

At intake, the TPUS was performed in supine position after bladder emptying. Women were instructed to perform maximal pelvic floor contraction and maximal Valsalva maneuver according to the method described by Dietz [24]. We used a Philips Epiq 7G machine with a X6-1 transducer covered with a 2-cm thick gel pad and a glove. The gel pad was used to create more distance between the transducer and the woman, so that the levator ani muscle (LAM) could be fully visible within the opening angle on the coronal plane. TPUS volumes analyzed in the current study were acquired without the pessary in situ.

TPUS data assessment

An in-house tool was developed in MeVisLab [25] for TPUS volumes assessment, which was performed by one observer (CM) blinded to all clinical data. As described in the literature, the hiatal area at rest (HArest), maximum pelvic floor contraction (HActx), and maximum Valsalva maneuver (HAval) were manually segmented at the plane of minimal hiatal dimensions [26]. From these parameters, the following were derived: displacement in contraction (DISPL-ctx), which was calculated as (HArest – HActx)/HArest, and displacement in Valsalva (DISPL-Val), which was calculated as (HAval – HArest)/HArest. In addition, we introduced the parameter HARP ratio (i.e., hiatal area to ring pessary ratio), which was calculated as the levator HA divided by the diameter of the ring pessary in centimeters. The HARP ratio enables assessment of the relative dimension of the ring pessary with respect to the levator HA dimension: if the ring pessary is small with respect to the levator HA (which we hypothesized to be associated with pessary dislodgment or failure to relieve POP symptoms), the HARP ratio is high; if the ring pessary is small with respect to the levator HA (which we hypothesized to be associated with pain/discomfort), the HARP ratio is low. Independently of the number of fitting trials a woman underwent, the ring pessary size used to measure the HARP ratio was the successful one or the last one tried in a fitting trial. The HARP ratio was calculated with the levator HA at rest (rest HARP ratio), maximal contraction (contraction HARP ratio), and maximal Valsalva maneuver (Valsalva HARP ratio). The presence of LAM avulsion was assessed on volumes obtained at maximum contraction using tomographic ultrasound imaging (TUI). Complete LAM avulsion was defined as levator–urethra gap ≥25 mm on the three central slices and could be unilateral or bilateral [26].

Predictive parameters and statistical analysis

The successful group was compared with the entire unsuccessful group and with the groups of women reporting a specific reason for unsuccessful pessary fitting. Only groups with more than five women were compared with the successful group. At first, a univariate binomial logistic regression was run. Parameters assessed on univariate analysis were demographic and clinical parameters derived from a review of the literature [4, 8-20]: age, BMI, menopause, prior pelvic surgery (i.e., prior hysterectomy and/or prior POP surgery and/or prior incontinence surgery), and solitary predominant posterior compartment POP (i.e., maximum POP stage in the posterior compartment only). In addition to demographic and clinical parameters, the following TPUS parameters were assessed on univariate analysis: HArest, HActx, HAval, DISPL-ctx, DISPL-Val, rest HARP ratio, contraction HARP ratio, Valsalva HARP ratio, and complete LAM avulsion. Subsequently, a multivariate binomial logistic regression was run. According to Vittinghoff and McCulloch [27], model performance problems are uncommon with 5–9 events per predictor variable (EPV) and still observed with 10–16 EPV. Therefore, a minimum of 5 EPV was accepted; also considering the exploratory nature of our study. Significant parameters on univariate analysis ($p < 0.05$) were selected for multivariate analysis. For both univariate and multivariate analyses, it was tested that the assumptions of the binomial logistic regression were not violated: linearity assumption (i.e., the linear

relationship between the continuous independent variables and the logit transformation of the dependent variable) and absence of significant outliers. No formal sample size could be calculated because no previous study has investigated separately multiple reasons for pessary fitting failure and their predictive parameters. This should thus be considered an exploratory study. If the sample size limited the number of significant parameters that could be tested on multivariate analysis, different combinations of parameters were assessed, and the best model was selected based on Nagelkerke's R-squared [28]. For the parameters significant on multivariate analysis, receiver operating characteristic curves (ROC curves) were constructed, and the area under the ROC curve (AUC) was measured. The statistical analysis was conducted using IBM v 27 SPSS software.

Results

Figure 1 shows the number of women at each stage and the reasons for unsuccessful pessary fitting. The women underwent a maximum of three fitting trials. Therefore, pessary fitting lasted between 2 and 4 weeks, if the woman underwent only one fitting trial, and 6–12 weeks, if the woman underwent up to three fitting trials.

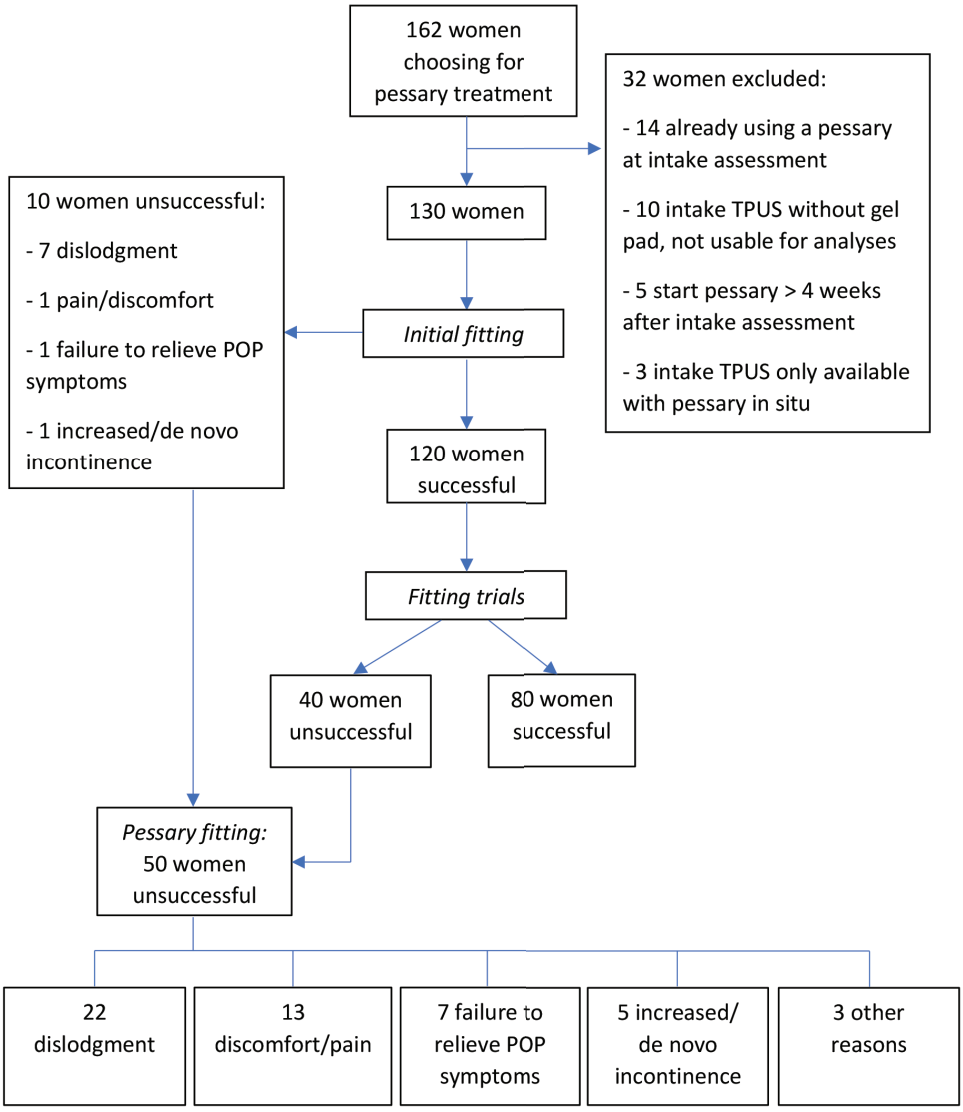

Figure 1 Number of women at each stage and reasons for unsuccessful pessary fitting. In italics the different phases of pessary fitting. *POP* pelvic organ prolapse, *TPUS* transperineal ultrasound

In Table 2 demographic, clinical, and TPUS characteristics of the women included are reported.

Table 2 Demographical, clinical, and transperineal ultrasound (TPUS) characteristics of the women included (N=130).

Parameter	Value
Age (years), median (IQR)	61.5 (14.0)
BMI, median (IQR)	24.0 (5.2)
Post-menopausal, n (%)	97 (74.6)
Vaginal parity, n (%)	128 (98.5)
Assisted vaginal delivery, n (%)	12 (9.2)
Prior pelvic surgery[a], n (%)	25 (19.2)
Predominant compartment POP, n (%)	
• Anterior	73 (56.2)
• Apical	8 (6.2)
• Posterior	12 (9.2)
• Anterior, apical	6 (4.6)
• Anterior, posterior	23 (17.7)
• Apical, posterior	3 (2.3)
• Anterior, apical, posterior	5 (3.8)
POP stage, n (%)	
• I	2 (1.5)
• II	75 (57.7)
• III	53 (40.8)
HArest (cm^2), median (IQR)	20.2 (6.6)
HActx (cm^2), median (IQR)	16.9 (5.1)
HAVal (cm^2), median (IQR)	33.9 (12.8)
DISPL-ctx (%), median (IQR)	15.6 (13.0)
DISPL-Val (%), median (IQR)	51.0 (55.0)
Complete LAM avulsion, n (%)	52 (40.0)
Last pessary type, n (%)	
• Ring	114 (87.7)
• Gellhorn	4 (3.0)
• Cube	1 (0.8)
• Donut	1 (0.8)
• Not available[b]	10 (7.7)
Last ring pessary size (cm), median (IQR)	7.0 (1.2)
Rest HARP-ratio (cm), median (IQR)[c]	2.9 (1.0)
Contraction HARP-ratio (cm), median (IQR)[c]	2.4 (0.7)
Valsalva HARP-ratio (cm), median (IQR)[c]	4.7 (2.0)

HArest levator hiatal area at rest, *HActx* levator hiatal area on maximal contraction, *HAVal* levator hiatal area on maximal Valsalva maneuver, *DISPL-ctx* (HArest-HActx)/HArest, *DISPL-Val* (HAVal-HArest)/HArest, *HARP ratio* levator HA to last ring pessary size ratio

[a]Prior pelvic surgery = hysterectomy and/or POP surgery and/or incontinence surgery

[b]10 women with unsuccessful initial fitting.

[c] Parameter not available for 10 women with unsuccessful initial fitting (no pessary size could be registered), 6 (tried to be) fitted with a pessary type different form a ring pessary, and 3 ring pessary sizes missing.

Table 3 shows median value and interquartile range (IQR) or number of cases and percentage of the parameters assessed per group of women. As the increased/de novo urinary incontinence group and other reasons group did not include more than five women, they were not separately analyzed. Therefore, they are not shown in Table 3.

Table 3 Parameters presented per group of women as median value and interquartile range (IQR) or number of cases and percentage

Parameter	Successful (n=80)	Unsuccessful (n=50)	Dislodgment (n=22)	Pain/discomfort (n=13)	Failure to relieve POP symptoms (n=7)
Age (years), median (IQR)	63.0 (15.0)	58.5 (16.0)	57.5 (13.0)	62.0 (18.0)	61.0 (9.0)
BMI, median (IQR)	24.1 (4.5)	24.0 (6.1)	24.3 (4.8)	22.9 (9.0)	24.4 (5.7)
Menopause, n (%)	62 (77.5)	35 (70.0)	16 (72.7)	9 (69.2)	6 (85.7)
Prior pelvic surgery[a], n (%)	13 (16.3)	12 (24.0)	6 (27.3)	1 (7.7)	3 (42.9)
Solitary predominant posterior compartment POP, n (%)	5 (6.3)	7 (14.0)	1 (4.5)	1 (7.7)	4 (57.1)
HArest (cm^2), median (IQR)	20.1 (6.2)	21.3 (7.3)	23.9 (5.3)	19.5 (10.7)	19.0 (3.1)
HActx (cm^2), median (IQR)	16.9 (5.3)	17.2 (5.3)	20.3 (4.5)	16.1 (6.4)	14.6 (1.9)
HAVal (cm^2), median (IQR)	31.9 (11.4)	37.7 (16.3)	41.3 (9.4)	28.6 (16.8)	33.6 (21.7)
DISPL-ctx (%), median (IQR)	16.2 (14.0)	14.4 (11.0)	12.9 (10.0)	15.6 (6.0)	12.4 (25.0)
DISPL-Val (%), median (IQR)	45.9 (56.0)	60.6 (56.0)	66.4 (44.0)	43.6 (61.0)	66.9 (87.0)
Rest HARP-ratio (cm), median (IQR)[b]	2.9 (0.9)	3.0 (1.1)	3.4 (0.8)	3.0 (1.4)	2.8 (0.5)
Contraction HARP-ratio (cm), median (IQR)[b]	2.4 (0.7)	2.5 (0.9)	3.0 (1.2)	2.4 (0.9)	2.3 (0.7)
Valsalva HARP-ratio (cm), median (IQR)[b]	4.6 (1.6)	5.2 (2.7)	5.8 (2.0)	4.5 (2.8)	5.2 (2.9)
LAM avulsion, n (%)	25 (31.3)	27 (54.0)	18 (81.8)	6 (46.2)	2 (28.6)

HArest levator hiatal area at rest, *HActx* levator hiatal area on maximal contraction, *HAVal* levator hiatal area on maximal Valsalva maneuver, *DISPL-ctx* (HArest-HActx)/HArest, *DISPL-Val* (HAVal-HArest)/HArest, *HARP-ratio* levator HA to last ring pessary size ratio.

[a] Prior pelvic surgery = hysterectomy and/or POP surgery and/or incontinence surgery

[b] Parameter available for 77 women of the successful group, 34 of the unsuccessful group, 11 of the dislodgment group, 12 of the pain/discomfort group, and 6 of the failure to relieve POP symptoms group.

Table 4 shows the parameters that were significant on univariate analysis in the prediction of unsuccessful pessary fitting, pessary dislodgment, and failure to relieve POP symptoms, as well as the results of the multivariate analysis. The analysis of the prediction of pain/discomfort is not shown because no significant parameter was identified. The entire univariate analysis (with significant and nonsignificant parameters) is reported in the Appendix (Tables 5, 6, 7, 8). No parameter violated the assumptions of the binomial logistic regression. On multivariate analysis, Valsalva HARP ratio was a predictor of unsuccessful pessary fitting, when no distinction was made between different reasons for failure. In the case of pessary dislodgment, the sample size limited the number of parameters that could be assessed on multivariate analysis. Combinations of LAM avulsion (i.e., the parameter with the highest OR) with all other parameters that were significant on univariate analysis were tested and the model with the highest Nagelkerke's R squared (46.5%) included LAM avulsion and Valsalva HARP ratio as independent variables. Solitary predominant posterior compartment POP was a predictor of failure to relieve POP symptoms (being the only parameter significant on univariate analysis; a multivariate analysis was not run).

Table 4 Univariate and multivariate analysis in the prediction of unsuccessful pessary fitting (n=50), pessary dislodgment (n=22), and failure to relieve POP symptoms (n=7) vs successful pessary fitting (n=80). Only the significant parameters on univariate analysis are shown.

Prediction of unsuccessful pessary fitting				
Significant parameters on univariate analysis	**Univariate analysis**		**Multivariate analysis**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Age	0.97 (0.94-1.00)	0.04	0.98 (0.94-1.02)	0.24
HAVal	1.05 (1.01-1.09)	0.02	0.90 (0.79-1.02)	0.10
Valsalva HARP-ratio[a]	1.46 (1.06-2.00)	0.02	3.00 (1.15-7.81)	0.03
LAM avulsion	2.58 (1.25-5.36)	0.01	2.41 (0.98-5.94)	0.06
Prediction of pessary dislodgment				
HArest	1.18 (1.05-1.33)	0.01		
HActx	1.23 (1.08-1.41)	0.00		
HAVal	1.12 (1.05-1.20)	0.00		
Rest HARP-ratio[a]	4.09 (1.24-13.49)	0.02		
Contraction HARP-ratio[a]	5.77 (1.59-20.97)	0.01		
Valsalva HARP-ratio[a]	2.53 (1.41-4.54)	0.00	2.94(1.32-6.55)	0.01
LAM avulsion	9.90 (3.04-32.29)	0.00	24.20 (2.46-237.84)	0.01
Prediction of failure to relieve POP symptoms				
Solitary predominant posterior compartment POP	20.00 (3.48-115.02)	0.00		

POP pelvic organ prolapse, *HArest* levator hiatal area at rest, *HActx* levator hiatal area on maximal contraction, *HAVal* levator hiatal area on maximal Valsalva maneuver, *HARP ratio* levator HA to last ring pessary size ratio.

[a] Parameter available for 77 women of the successful group (2 fitted with a Gellhorn pessary, 1 pessary size missing), 34 of the unsuccessful group (10 initial fitting unsuccessful, 4 tried to be fitted with a different pessary type, 2 pessary sizes missing), and 11 women of the dislodgment group (7 initial fitting unsuccessful, 1 tried to be fitted with a Gellhorn, 1 with a cube, 1 with a donut, 1 pessary size missing)

The AUC of Valsalva HARP-ratio in the prediction of unsuccessful pessary fitting was 0.62 (95% CI 0.50-0.74, p=0.04). In the prediction of pessary dislodgment, the combination of LAM avulsion and Valsalva HARP-ratio gave an AUC of 0.92 (0.84-0.99), p= 0.00. Lastly, the AUC of solitary predominant posterior compartment POP in the prediction of failure to relieve POP symptoms was 0.75 (0.53-0.98), p=0.03.

Discussion

Specific reasons for unsuccessful pessary fitting are associated with different predictive parameters, namely pessary dislodgment is associated with LAM avulsion and Valsalva HARP ratio, and failure to relieve POP symptoms is associated with solitary predominant posterior compartment POP. Previous literature on the topic overlooked this aspect [4, 8-18, 20], which might (partially) explain the different results between studies.

Valsalva HARP ratio was a predictor of unsuccessful pessary fitting when no distinction was made between different reasons for failure. Therefore, pessary fitting was more likely to be unsuccessful if a woman was fitted with a relatively small ring pessary with respect to the levator HA on Valsalva. This finding suggests that the support of the LAM plays an important role in holding ring pessaries comfortably in place. However, the AUC showed poor discrimination according to Hosmer et al. [29], which can be explained by the heterogeneity of the unsuccessful group.

Avulsion of LAM and Valsalva HARP ratio were predictors of pessary dislodgment, and the AUC of the combination of the two parameters showed an outstanding level of discrimination [29]. The association between LAM avulsion and pessary dislodgment confirms previous results [19], whereas Valsalva HARP ratio had never been investigated before. If our results were confirmed by more studies from different institutions, they could have the following clinical implications. When a woman chooses pessary treatment for POP, LAM avulsion should be assessed. If present, the higher risk of dislodgment should be discussed. However, pessary treatment should be encouraged, considering the higher risk of recurrence after POP surgery associated with LAM avulsion [30]. To minimize the risk of dislodgment, the maximum ring pessary size the woman can be fitted with should be selected, whilst remembering that the pessary should allow a single examining finger to be passed freely all around its circumference [31]. Research should investigate the added value of TPUS in estimating the ring pessary size that is likely to stay in place. An alternative strategy to minimize the risk of dislodgment might be the use of those pessary types held in place by suction of their surface to the vaginal walls (e.g., Gellhorn, cube pessaries) because the support of the LAM might be less essential for these pessaries compared with ring pessaries. In our study, we tried to fit only one woman with a Gellhorn pessary and one woman with a cube pessary in the dislodgment group. Therefore, we can neither confirm nor exclude this hypothesis. A randomized crossover trial showed no significant difference in effectiveness between ring and Gellhorn pessaries [17]. However, the presence of LAM avulsion was not assessed in

this study. It would be interesting to compare the occurrence of pessary dislodgment in women with complete LAM avulsion fitted with ring pessaries vs Gellhorn or cube pessaries. If Gellhorn or cube pessaries showed a higher success rate, these pessary types should be recommended to women with complete LAM avulsion. In addition, the results on pessary dislodgment indicate that imaging techniques have the potential to provide more insight into what a proper fit is. More research should be done in this direction with the aim of increasing the pessary fitting success rate.

Solitary predominant posterior compartment was a predictor of failure to relieve POP symptoms with an AUC of 0.75. Previous results showed the association of posterior compartment prolapse [13] or higher Colorectal-Anal Distress Inventory-8 (CRADI-8) scores [14] with unsuccessful pessary fitting. Our result confirms the hypothesis that pessary treatment is less effective in relieving symptoms of posterior compartment POP and thus less likely to be successful. We did not attempt to fit any women in the failure to relieve POP symptoms group with a pessary other than a ring pessary. It would be interesting to assess if different pessary types are more effective in this group.

Our study has several strengths. First, a prospective design was used, which reduced the risk of selection bias. Second, all scans and all TPUS assessments were performed by the same clinician, thus reducing a source of variability. Third, TPUS assessment was performed with the observer blinded to all clinical data. Some limitations must also be acknowledged. The size of the outcome groups was relatively small, especially in the case of failure to relieve POP symptoms, and our results should be interpreted with caution. A larger study with a sample size based on our exploratory study is needed to confirm our findings. The parameter HARP ratio could only be assessed for a specific pessary type because measuring HARP ratio for pessaries with different shapes would have provided incomparable measures. Ring pessaries were chosen because they were the most frequently used. In addition, HARP ratio was not available in the case of unsuccessful initial fitting because no pessary could be fitted at the initial visit and the woman did not undergo a fitting trial. This limited the number of parameters that could be assessed on multivariate analysis in the prediction of pessary dislodgment. However, all combinations between LAM avulsion and the other significant parameters on univariate analysis were assessed on multivariate analysis and the best model included LAM avulsion and Valsalva HARP ratio as independent variables. An additional limitation is that parameters that might have been relevant for failure owing to pain/discomfort (i.e., vaginal atrophy and fornix posterior width) were not assessed. Future research on predictors of pain/discomfort should not overlook these parameters. Last, the generalizability of the results might be limited because the study was conducted in a urogynecological center, where primary care is not provided.

In conclusion, specific reasons for unsuccessful pessary fitting have different predictive parameters. LAM avulsion and a high Valsalva HARP ratio are predictors of pessary dislodgment, whereas solitary predominant posterior compartment POP is a predictor of failure to relieve POP symptoms. If confirmed by more studies from different institutions,

our results could make the counseling for pessary fitting more effective. In addition, our study can stimulate future research on the efficacy of different pessary types in women with LAM avulsion or solitary predominant posterior compartment POP and on the added value of imaging techniques in obtaining a proper fit.

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Ethics declarations

Conflicts of interest
None.

Appendix

Table 5 Results of univariate and multivariate binomial logistic regression in the prediction of unsuccessful (n= 50) vs successful pessary fitting (n=80).

Prediction of unsuccessful pessary fitting				
Parameter	**Univariate analysis**		**Multivariate analysis**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Age	0.97 (0.94-1.00)	**0.04**	0.98 (0.94-1.02)	0.24
BMI	0.97 (0.88-1.07)	0.50		
Menopause	0.68 (0.30-1.51)	0.34		
Prior pelvic surgery[a]	1.63 (0.68-3.92)	0.28		
Solitary predominant posterior compartment POP	2.44 (0.73-8.17)	0.15		
HArest	1.06 (0.98-1.15)	0.14		
HActx	1.07 (0.98-1.18)	0.13		
HAVal	1.05 (1.01-1.09)	**0.02**	0.90 (0.79-1.02)	0.10
DISPL-ctx	0.51 (0.01-22.69)	0.73		
DISPL-Val	1.57 (0.71-3.45)	0.26		
Rest HARP-ratio[b]	1.64 (0.86-3.10)	0.13		
Contraction HARP-ratio[b]	1.76 (0.85-3.63)	0.13		
Valsalva HARP-ratio[b]	1.46 (1.06-2.00)	**0.02**	3.00 (1.15-7.81)	**0.03**
LAM avulsion	2.58 (1.25-5.36)	**0.01**	2.41 (0.98-5.94)	0.06

HArest levator hiatal area at rest, *HActx* levator hiatal area on maximal contraction, *HAVal* levator hiatal area on maximal Valsalva maneuver, *DISPL-ctx* (HArest-HActx)/HArest, *DISPL-Val* (HAVal-HArest)/HArest, *HARP-ratio* levator HA to last ring pessary size ratio. Bold indicates statistically significant parameters.

[a] Prior pelvic surgery = hysterectomy and/or POP surgery and/or incontinence surgery.

[b] Parameter available for 77 women of the successful group (2 fitted with a Gellhorn pessary, 1 pessary size missing), and 34 of the unsuccessful group (10 initial fitting unsuccessful, 4 tried to be fitted with a different pessary type, 2 pessary sizes missing).

Table 6 Results of univariate and multivariate binomial logistic regression in the prediction of pessary dislodgment (n= 22) vs successful pessary fitting process (n=80).

Prediction of pessary dislodgment				
Parameter	**Univariate analysis**		**Multivariate analysis**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Age	0.97 (0.93-1.01)	0.16		
BMI	0.93 (0.81-1.08)	0.34		
Menopause	0.77 (0.26-2.27)	0.64		
Prior pelvic surgery[a]	1.93 (0.64-5.87)	0.25		
Solitary predominant posterior compartment POP	0.71 (0.08-6.45)	0.76		
HArest	1.18 (1.05-1.33)	**0.01**		
HActx	1.23 (1.08-1.41)	**0.00**		
HAVal	1.12 (1.05-1.20)	**0.00**		
DISPL-ctx	0.07 (0.00-14.61)	0.33		
DISPL-Val	2.17 (0.77-6.09)	0.14		
Rest HARP-ratio[b]	4.09 (1.24-13.49)	**0.02**		
Contraction HARP-ratio[b]	5.77 (1.59-20.97)	**0.01**		
Valsalva HARP-ratio[b]	2.53 (1.41-4.54)	**0.00**	2.94(1.32-6.55)	**0.01**
LAM avulsion	9.90 (3.04-32.29)	**0.00**	24.20 (2.46-237.84)	**0.01**

HArest levator hiatal area at rest, *HActx* levator hiatal area on maximal contraction, *HAVal* levator hiatal area on maximal Valsalva maneuver, *DISPL-ctx* (HArest-HActx)/HArest, *DISPL-Val* (HAVal-HArest)/HArest, *HARP-ratio* levator HA to last ring pessary size ratio. Bold indicates statistically significant parameters.

[a] Prior pelvic surgery = hysterectomy and/or POP surgery and/or incontinence surgery.

[b] Parameter available for 77 women of the successful group (2 women fitted with a Gellhorn pessary, 1 pessary size missing), and 11 of the dislodgment group (7 initial fitting unsuccessful, 1 tried to be fitted with a Gellhorn, 1 with a cube, 1 with a donut, 1 pessary size missing).

Table 7 Results of univariate binomial logistic regression in the prediction of pain/discomfort (n= 13) vs successful pessary fitting process (n=80).

Prediction of pain/discomfor		
Parameter	**Univariate analysis**	
	OR (95% CI)	**p-value**
Age	0.97 (0.92-1.02)	0.23
BMI	0.10 (0.85-1.17)	0.98
Menopause	0.65 (0.18-2.37)	0.52
Prior pelvic surgery[a]	0.43 (0.05-3.60)	0.44
Solitary predominant posterior compartment POP	1.25 (0.13-11.65)	0.85
HArest	1.01 (0.89-1.15)	0.85
HActx	1.02 (0.88-1.18)	0.80
HAVal	1.01 (0.94-1.07)	0.89
DISPL-ctx	0.35 (0.00-247.01)	0.75
DISPL-Val	1.10 (0.31-3.87)	0.88
Rest HARP-ratio[b]	1.49 (0.60-3.70)	0.39
Contraction HARP-ratio[b]	1.61 (0.58-4.50)	0.36
Valsalva HARP-ratio[b]	1.22 (0.76-1.94)	0.41
LAM avulsion	0.53 (0.16-1.74)	0.30

HArest levator hiatal area at rest, *HActx* levator hiatal area on maximal contraction, *HAVal* levator hiatal area on maximal Valsalva maneuver, *DISPL-ctx* (HArest-HActx)/HArest, *DISPL-Val* (HAVal-HArest)/HArest, *HARP-ratio* levator HA to last ring pessary size ratio. Bold indicates statistically significant parameters.

[a] Prior pelvic surgery = hysterectomy and/or POP surgery and/or incontinence surgery.

[b] Parameter available for 77 women of the successful group (2 fitted with a Gellhorn pessary, 1 pessary size missing), and 12 of the pain/ discomfort group (1 initial fitting unsuccessful).

Table 8 Results of univariate binomial logistic regression in the prediction of failure to relieve POP symptoms (n=7) vs successful pessary fitting process (n=80).

Prediction of failure to relieve POP symptoms		
Parameter	**Univariate analysis**	
	OR (95% CI)	**p-value**
Age	0.98 (0.92-1.05)	0.56
BMI	1.05 (0.85-1.29)	0.66
Menopause	1.74 (0.20-15.43)	0.62
Prior pelvic surgery[a]	3.87(0.77-19.35)	0.10
Solitary predominant posterior compartment POP	20.00 (3.48-115.02)	**0.00**
HArest	0.91 (0.75-1.12)	0.39
HActx	0.84 (0.65-1.08)	0.16
HAVal	1.02 (0.94-1.10)	0.71
DISPL-ctx	17.20 (0.01-22082.73)	0.44
DISPL-Val	1.79 (0.45-7.22)	0.41
Rest HARP-ratio[b]	0.78 (0.18-3.36)	0.74
Contraction HARP-ratio[b]	0.52 (0.09-2.89)	0.45
Valsalva HARP-ratio[b]	1.29 (0.67-2.47)	0.45
LAM avulsion	0.88 (0.16-4.85)	0.88

HArest levator hiatal area at rest, *HActx* levator hiatal area on maximal contraction, *HAVal* levator hiatal area on maximal Valsalva maneuver, *DISPL-ctx* (HArest-HActx)/HArest, *DISPL-Val* (HAVal-HArest)/HArest, *HARP-ratio* levator HA to last ring pessary size ratio. Bold indicates statistically significant parameters.

[a] Prior pelvic surgery = hysterectomy and/or POP surgery and/or incontinence surgery.

[b] Parameter available for 77 women of the successful group (2 fitted with a Gellhorn pessary, 1 pessary size missing), and 6 of the failure to relieve POP symptoms group (1 initial fitting unsuccessful).


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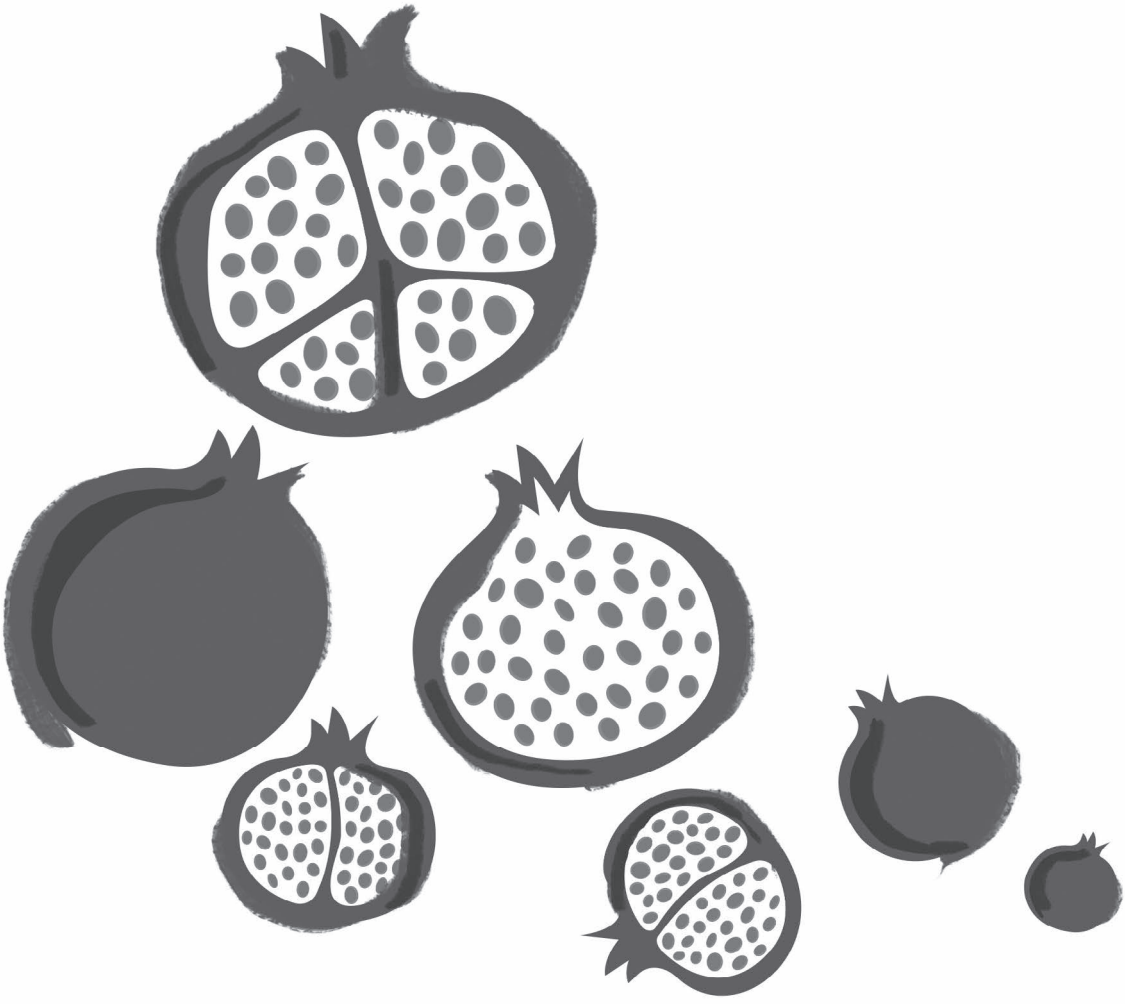

CHAPTER 4

Transperineal ultrasound to estimate the appropriate ring pessary size for women with pelvic organ prolapse

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Abstract

Introduction and hypothesis: The objective was to predict the successful ring pessary size based on the levator hiatal area (HA).

Methods: This is a prospective case–control study. Women with symptomatic pelvic organ prolapse (POP) choosing pessary treatment were included. All women underwent an interview, clinical examination, and 3D/4D transperineal ultrasound (TPUS). The ring pessary size used in each trial and the reason for unsuccessful trials were recorded. In addition, levator hiatal area divided by ring pessary size (HARP ratio) was measured at rest, maximum contraction, and maximum Valsalva. The HARP ratios of successful and unsuccessful trials were compared, receiver operating characteristic curves in the prediction of successful trials were constructed, and the cut-off optimizing sensitivity and specificity was identified.

Results: A total of 162 women were assessed and 106 were included with 77 successful trials, 49 unsuccessful trials owing to dislodgment or failure to relieve POP symptoms, and 20 unsuccessful trials owing to pain/discomfort. Rest HARP ratio and Valsalva HARP ratio were significantly smaller in the successful trials versus dislodgment/failure to relieve POP symptoms trials (mean rest HARP ratio [SD]: 2.93 [0.59] vs 3.24 [0.67], $p = 0.021$; median Valsalva HARP ratio (IQR): 4.65 (1.56) vs 5.32 (2.08), $p = 0.004$). No significant difference was observed between pain/discomfort trials and successful trials. The best cut-off for the prediction of successful trials was Valsalva HARP ratio ≤ 5.00.

Conclusion: Unsuccessful fitting trials due to dislodgment/failure to relieve POP symptoms are associated with a small ring pessary with respect to the levator HA. A ring pessary that produces a Valsalva HARP ratio > 5.00 has a higher risk of dislodgment/failure to relieve POP symptoms.

Introduction

Vaginal pessary is a widely used conservative treatment for pelvic organ prolapse (POP) [1, 2]. In clinical practice, the challenge is finding the right pessary that suits an individual woman ideally within the first trial. This process of pessary fitting is based on clinical examination and proceeds by trial and error [3].

Two recent studies have been published on the association between transperineal ultrasound (TPUS) parameters and (un)successful ring pessary fitting [4, 5]. In the study by Cheung et al. [4], successful fitting was compared with unsuccessful fitting owing to pessary dislodgment. A positive significant association was observed between dislodgment and larger levator hiatal area (HA), as well as levator ani muscle (LAM) avulsion. In the study by Turel Fatakia et al. [5], successful fitting was compared with unsuccessful fitting (without distinction between reasons for failure). A positive significant association was observed between unsuccessful fitting and larger levator HA on Valsalva. However, besides the variation in levator HA dimension, variation in ring pessary size should also be considered. An unsuccessful pessary fitting because of dislodgment or failure to relieve POP symptoms may be due to a pessary size that is too small for a given levator HA. On the contrary, an unsuccessful pessary fitting because of pain/discomfort may be due to a pessary size that is too big for a given levator HA. If these assumptions are correct, measuring levator HA could be of added value in estimating the appropriate ring pessary size.

In this study we set out to compare the relative dimension of the ring pessary with respect to the levator HA between successful and unsuccessful pessary fitting trials and to predict the successful ring pessary size based on the levator HA.

Materials and methods

The data used in the current study were collected as a subset within the GYNecological Imaging using 3D UltraSound (GYNIUS) project on the assessment of pelvic floor contractility with TPUS, which was conducted at our tertiary urogynecological clinic. Women were included in the GYNIUS project between May 2018 and December 2019. The Medical Research Ethics Committee (MREC) exempted the project from ethical approval (reference 18/215), because TPUS was part of our routine diagnostic procedure and standard care. All women signed informed consent forms.

Inclusion and exclusion criteria

This was a prospective case–control study. Women with symptomatic POP choosing pessary treatment were included. Women who were already using a pessary at intake assessment and those who started the pessary fitting process more than 4 weeks after intake ultrasound assessment were excluded. All women underwent an interview, clinical examination, and 3D/4D TPUS. POP was assessed using the Pelvic Organ Prolapse Quantification system (POPQ) [6].

Pessary fitting

Pessary fitting was performed according to our standard clinical practice, similar to that described in the literature [7,8,9,10,11,12], in which the appropriate pessary size is estimated based on clinical examination (i.e., POPQ and digital assessment of fornix posterior width and LAM support). "Fitting trial" was defined as the event of a woman being fitted with a specific ring pessary size, leaving the clinic with the pessary in place, and attending the 2- to 4-week follow-up, in which the success of the fitting trial was assessed. Only fitting trials of ring pessaries (with or without support) were assessed, because the ring pessary is the type most commonly used in our clinic (CooperSurgical®, Milex® pessaries). A fitting trial was considered successful if the specific ring pessary size the woman was fitted with was still in situ at follow-up, if she was satisfied with it, and if she decided to continue using it. On the contrary, if she decided not to continue using the specific ring pessary size she was fitted with, it was considered unsuccessful. In this case, the woman was asked which one of the following was the reason for failure: dislodgment (defined as a pessary that did not stay in place because it fell down or was expelled), failure to relieve POP symptoms, pain/discomfort, increased/de novo urinary incontinence, or other reasons [7]. In the case of unsuccessful fitting, the woman was offered an additional fitting trial with an adjusted ring pessary size. If she agreed, a new pessary was inserted and a 2- to 4-week follow-up was scheduled. One patient could thus have more than one fitting trial, each one with a different ring pessary size. This process continued until an appropriate ring pessary size was found or until pessary treatment was considered not suitable for the woman and a different treatment was chosen. For every fitting trial, the size of the pessary diameter was recorded in centimeters.

TPUS acquisition and assessment

At intake, TPUS was performed in supine position after bladder emptying. Women were instructed to perform maximal pelvic floor contraction and maximal Valsalva maneuver according to the method described by Dietz [13]. We used a Philips Epiq 7G machine with a X6–1 transducer covered with a gel pad 2 cm thick, and a glove. The gel pad was used to create more distance between the transducer and the woman, so that the LAM could be fully visible within the opening angle on the coronal plane. TPUS volumes analyzed in the current study were acquired without pessary in situ.

An in-house tool was developed in MeVisLab 3.0.2. [14] for TPUS volume assessment, which was done by one observer (CM) blinded to all clinical data. As described in the literature [15], hiatal area at rest (HArest), maximal pelvic floor contraction (HActx), and maximal Valsalva maneuver (HAval) were manually segmented at the plane of minimal hiatal dimensions. In addition, the presence of LAM avulsion was assessed on volumes obtained at maximum contraction. Complete avulsion was defined as a levator–urethra gap of ≥25 mm on the three central slices and could be unilateral or bilateral [15].

Levator HA to pessary size ratio and statistical analysis

The levator hiatal area to pessary size (HARP) ratio was calculated as levator HA (cm2) divided by ring pessary size (cm). The HARP ratio at rest (rest HARP ratio), maximum contraction (contraction HARP ratio), and maximum Valsalva (Valsalva HARP ratio) were calculated for each fitting trial. To the best of our knowledge, no studies have been published in which the HARP ratio is used. Therefore, no formal sample size could be calculated, and this work should be considered an exploratory study.

Rest HARP ratio, contraction HARP ratio, and Valsalva HARP ratio of successful trials and unsuccessful trials, which were separately analyzed based on the reason for failure, were compared. A Welch's ANOVA and a Games–Howell post hoc test were used if the data were normally distributed and if there were no outliers, but the assumption of homogeneity of variances for a one-way ANOVA was violated. A Kruskal–Wallis test was run if the data were not normally distributed or if there were outliers in the data. Receiver operating characteristic (ROC) curves of the HARP ratios were constructed in the prediction of successful trials. As the dimension of levator HA can be influenced by the presence of complete avulsion [16], ROC curves were also constructed for trials of women with and without complete avulsion. In addition, the cut-off that optimized sensitivity and specificity was identified. Based on this cut-off two groups were defined (i.e., HARP ratio ≤ cut-off and HARP ratio > cut-off) and their association with fitting trial success was tested with a Chi-squared test. Last, the relative risk (RR) of an unsuccessful/successful trial based on the HARP ratio ≤ cut-off or > cut-off was calculated. The statistical analysis was conducted using IBM v 27 SPSS software.

Results

Figure 1 shows the flow chart with the number of women, number of successful and unsuccessful trials, and reasons for unsuccessful trials. Only 5 trials were unsuccessful owing to de novo/increased urinary incontinence and 2 trials for "other reasons." Because of the small sample size, they could not be separately analyzed and the women who only underwent unsuccessful trials owing to de novo/increased urinary incontinence or for "other reasons" were not included in the analysis. Therefore, 146 trials of 106 women were included in the analysis, with 77 successful trials, 49 unsuccessful trials owing to dislodgment or failure to relieve POP symptoms, and 20 unsuccessful trials owing to pain/discomfort. Of the 106 women included, 49 underwent only one successful trial, 17 only one unsuccessful trial, 28 more than one trial with the last being successful, and 12 more than one trial with the last being unsuccessful.

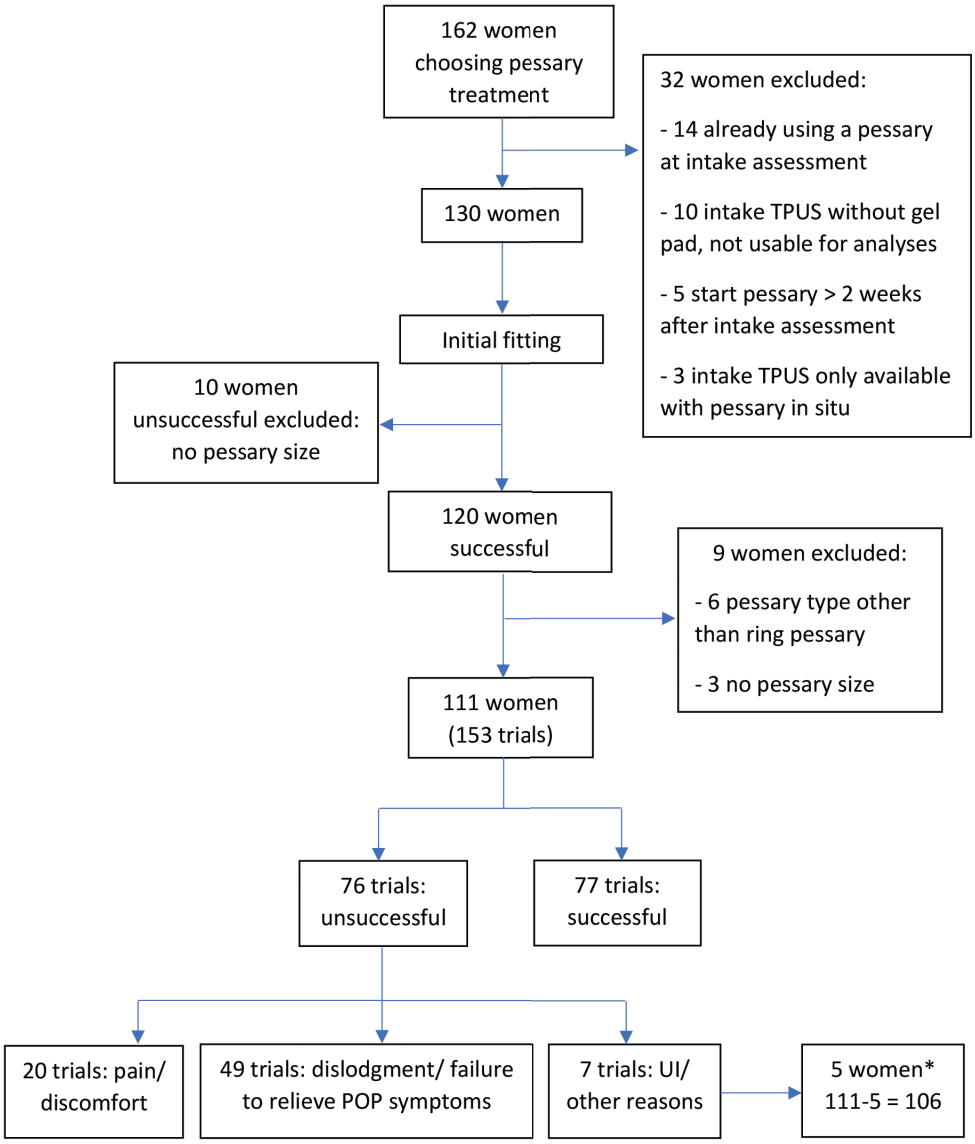

Figure 1 Flow-chart with the number of women, number of successful and unsuccessful fitting trials, and reasons for unsuccessful fitting trial. *5 women only underwent unsuccessful trials owing to de novo/increased urinary incontinence or for "other reasons". As these trials were not analyzed, a total of 106 women (111-5) were included in the analysis. *POP* pelvic organ prolapse, *TPUS* transperineal ultrasound, *UI* urinary incontinence

In Table 1 the demographical, clinical, and TPUS characteristics of the included women are reported.

Table 1 Demographical, clinical, and transperineal ultrasound characteristics (n=106).

Parameter	Value
Age, median (IQR)	62.0 (14)
BMI, median (IQR)	24.2 (5.2)
Post-menopausal, n (%)	81 (76.4)
Vaginal parity, n (%)	104 (98.1)
Assisted vaginal delivery, n (%)	9 (8.5)
Prior hysterectomy*, n (%)	13 (12.3)
Prior POP surgery (hysterectomy excluded), n (%)	9 (8.5)
Predominant compartment POP, n (%)	
• Anterior	63 (59.4)
• Apical	7 (6.6)
• Posterior	8 (7.5)
• Anterior, apical	3 (2.8)
• Anterior, posterior	17 (16.0)
• Apical, posterior	3 (2.8)
• Anterior, apical, posterior	5 (4.7)
POP stage, n (%)	
• I	1 (0.9)
• II	60 (56.6)
• III	45 (42.5)
HA rest (cm^2), median (IQR)	20.13 (6.61)
HA contraction (cm^2), median (IQR)	16.93 (5.31)
HA Valsalva (cm^2), mean (SD)	33.64 (9.85)
Complete avulsion, n (%)	42 (39.6)

BMI body mass index, *HA* hiatal area, *IQR* interquartile range, *POP* pelvic organ prolapse. *4 women (30.8%) underwent a hysterectomy for POP

Ring pessary sizes used ranged from 5.7 cm to 8.9 cm. In Table 2 the comparison of the rest HARP ratio, contraction HARP ratio, and Valsalva HARP ratio between groups is shown. Rest HARP ratio and Valsalva HARP ratio were significantly smaller in the successful trials than in those in which there was dislodgment/failure to relieve POP symptoms (p = 0.021 and 0.004 respectively). Contraction HARP ratio was not significantly different between groups. Therefore, the post hoc test was not performed. No statistically significant difference was observed between pain/discomfort trials and successful trials.

Table 2 Comparison of rest HARP-ratio, contraction HARP ratio, and Valsalva HARP ratio between groups. A Kruskal-Wallis test was run if not otherwise specified.

Parameters	Group 1 Successful (n=77)	Group 2 Dislodgment/Failure to relieve POP symptoms (n=49)	Group 3 Pain/ Discomfort (n=20)	Comparison	Sig.
Rest HARP-ratio. Mean (SD)	2.93 (0.59)	3.24 (0.67)	3.20 (0.99)	All groups	**0.027***
				Group 1 vs 2	**0.021****
				Group 1 vs 3	0.483**
				Group 2 vs 3	0.979**
Contraction HARP-ratio. Median (IQR)	2.42 (0.67)	2.59 (0.72)	2.44 (1.01)	All groups	0.116
Valsalva HARP-ratio. Median (IQR)	4.65 (1.56)	5.32 (2.08)	4.60 (2.46)	All groups	**0.006**
				Group 1 vs 2	**0.004°**
				Group 1 vs 3	1.000°
				Group 2 vs 3	0.605°

Bold indicates the statistically significant parameters * Welch's ANOVA; **Games-Howell post hoc test; ° Bonferroni correction for multiple comparison

Receiver operating characteristic curves of the rest HARP ratio and Valsalva HARP ratio were constructed in the prediction of successful trials versus those in which there was dislodgment/failure to relieve POP symptoms. In addition, sub-analyses were made for the trials of women without and with complete avulsion (Table 3). When no distinction was made based on the presence of complete avulsion, the AUC of Valsalva HARP ratio was 0.67 (0.58–0.77) and the best cut-off in the prediction of successful fitting was 5.00. In the case of complete avulsion, the AUC of Valsalva HARP ratio was 0.79 (0.65–0.92) and the best cut-off was 5.13. Applying the cut-off of 5.00 of the whole group to the group of women with complete avulsion, sensitivity and specificity were 0.67 and 0.84 respectively.

Table 3 Area under the receiver operating characteristic curve (AUC) of the rest HARP ratio and the Valsalva HARP ratio in the prediction of successful trials versus those in which there was dislodgment/failure to relieve POP symptoms. HARP ratio = levator hiatal area to ring pessary size

Trials	Parameter (cm)	AUC (95% CI)	p-value	Best cut-off*
All successful trials or those in which there was dislodgment/failure to relieve POP symptoms (n = 126)	Rest HARP ratio	0.63 (0.53-0.73)	**0.017**	Valsalva HARP ratio ≤ 5.00 (Sens 0.68, Spec 0.67)
	Valsalva HARP ratio	0.67 (0.58-0.77)	**0.001**	
Trials of women without complete avulsion (n=77)	Rest HARP ratio	0.65 (0.51-0.78)	**0.039**	Rest HARP ratio ≤ 2.94 (Sens 0.59, Spec 0.63)
	Valsalva HARP ratio	0.59 (0.45-0.73)	0.222	
Trials of women with complete avulsion (n=49)	Rest HARP ratio	0.56 (0.39-0.72)	0.497	Valsalva HARP ratio ≤ 5.13 (Sens 0.79, Spec 0.72)
	Valsalva HARP ratio	0.79 (0.65-0.92)	**0.001**	

Bold indicates the statistically significant parameters; Sens= sensitivity (i.e., of all successful trials, percentage that the model predicts as successful); Spec= specificity (i.e., of all trials in which there was dislodgment/failure to relieve POP symptoms, percentage that the model predicts as trials in which there was dislodgment/failure to relieve POP symptoms); HAval hiatal area on maximal Valsalva maneuver, HArest hiatal area at rest; *Best cut-off in the prediction of successful trials

A Chi-squared test between Valsalva HARP ratio (≤ 5.00 vs > 5.00) and fitting trial (successful vs unsuccessful owing to dislodgment/failure to relieve POP symptoms) showed a statistically significant association between Valsalva HARP ratio ≤ 5.00 and successful trial and Valsalva HARP ratio > 5.00 and unsuccessful trials (p = 0.00). 76.5% of the trials with a Valsalva HARP ratio ≤ 5.00 were successful, whereas only 43.1% of the trials with a Valsalva HARP ratio > 5.00 were successful. Trials with Valsalva HARP ratio > 5.00 had a RR of 2.42 (1.49–3.92) of being unsuccessful owing to dislodgment/failure to relieve POP symptoms. The RR was 3.62 (95% CI 1.47–8.95) in the case of trials of women with complete avulsion.

Of the 28 women who underwent one or more trials before being successful, 23 had a first unsuccessful trial owing to dislodgment/failure to relieve POP symptoms. In this group a Chi-squared test between Valsalva HARP ratio (≤ 5.00 vs > 5.00) and fitting trial (first unsuccessful versus last successful) showed a statistically significant association between Valsalva HARP ratio > 5.00 and first unsuccessful trials and Valsalva HARP ratio ≤ 5.00 and last successful trial (p = 0.02). In the first unsuccessful trial 56.5% of the women had a Valsalva HARP ratio > 5.00 and 43.5% a Valsalva HARP ratio ≤ 5.00. In the last successful trials 21.7% of the women had a Valsalva HARP ratio > 5.00 and 78.3% a Valsalva HARP ratio ≤ 5.00. Trials with Valsalva HARP ratio ≤ 5.00 had a RR of 2.31 (1.05–5.12) of being successful.

Furthermore, 17 women underwent only unsuccessful trials owing to dislodgment/failure to relieve POP symptoms (10 women one trial, 6 women two trials, and 1 woman three trials). Of these, 14 women (82.4%) received exclusively pessaries that were too small according to our cut-off.

Discussion

In the case of unsuccessful trials owing to dislodgment/failure to relieve POP symptoms, ring pessaries are too small with respect to the levator HA. A ring pessary size that produces a Valsalva HARP ratio > 5.00 has a higher risk of dislodgment and failure to relieve POP symptoms.

As hypothesized, the HARP ratio was significantly bigger in the case of trials in which there was dislodgment/failure to relieve POP symptoms than in successful trials. As levator HA is determined by the status of the LAM, these results suggest that LAM support might play an important role in holding ring pessaries in place. Currently, pessary fitting is based on POPQ and digital assessment of fornix posterior width and LAM support [7,8,9,10,11,12]. In this process, the dimension of the levator hiatus is not formally measured. This could (partially) explain the relatively high rate of unsuccessful pessary fitting, reported to be as high as 59% [12].

When no distinction was made between complete avulsion and no avulsion, the AUC of the Valsalva HARP ratio was 0.67. In the case of complete avulsion, the Valsalva HARP ratio showed an almost excellent level of discrimination (according to Hosmer et al. [17]). 76.5% of the trials with a Valsalva HARP ratio ≤ 5.00 were successful, whereas only 43.1% of the trials with a Valsalva HARP ratio > 5.00 were successful, with an RR of 2.4 of being unsuccessful (RR of 3.62 in the case of complete avulsion). By analyzing women who underwent a first unsuccessful trial owing to dislodgment/failure to relieve POP symptoms and a last successful trial, we observed an RR of 2.31 of being successful in the case of a Valsalva HARP ratio ≤ 5.00, compared with a ratio > 5.00. These results suggest that measuring the Valsalva HARP ratio could allow for a faster selection of the successful size, thus reducing the need for extra visits for pessary refitting and the discomfort due to multiple fitting trials. After the disappointment of one or more unsuccessful trials, some women refuse to undergo an additional one, thus missing the chance of a successful fitting. In these cases, a faster selection of the successful size could increase the pessary fitting success rate by reducing the number of unsuccessful trials.

In our study 82.4% of the women who only underwent unsuccessful trials owing to dislodgment/failure to relieve POP symptoms received exclusively pessaries that were too small: if our cut-off were applied, the pessary fitting success rate could have been higher or the women could have been spared unnecessary trials. A comparative study, with a sample size based on our data, is needed to confirm that using the Valsalva HARP ratio for selecting the pessary size does indeed reduce the need for pessary refitting and increases the chance of a successful initial fitting.

No significant difference was observed between successful trials and unsuccessful trials owing to pain/discomfort. This suggests that pain and discomfort might not be related to the size of the pessary with respect to the levator HA. However, complications such as pain/discomfort and vaginal bleeding due to ulceration might be related to the size of the

pessary with respect to the vaginal space. Future studies should test this hypothesis and focus on a quantitative method to assess the maximal pessary size that can be placed without causing the complications mentioned above. Knowing the minimal ring pessary size that is likely to stay in place (through the HARP ratio) and the maximal ring pessary size that is unlikely to cause complications, would help the clinician to estimate whether a ring pessary is a good option for a specific woman or not.

Literature on the association between anatomical parameters and pessary size is very limited: Nager et al. showed that POPQ measures do not predict the incontinence pessary size in women with POP stage ≤2 [18].

Strengths of our study include the prospective design, which reduced the risk of selection bias. All scans and TPUS assessments were performed by the same clinician, thus reducing a source of variability. In addition, TPUS assessment was performed blinded to all clinical data and to the pessary size. Some limitations have to be acknowledged. HARP ratio analyses are only applicable to fitting trials performed with one pessary type because different pessary types cannot be compared. We selected the ring pessary because it is the pessary type most commonly used in our clinic. An additional limitation is that the generalizability of the results might be limited because the study was conducted in a urogynecological center where primary care is not provided.

In conclusion, unsuccessful fitting trials owing to dislodgment or failure to relieve POP symptoms are associated with a small ring pessary with respect to the levator HA: a ring pessary size that produces a Valsalva HARP ratio > 5.00 has a higher risk of dislodgment and failure to relieve POP symptoms. These results suggest that TPUS might be of added value in the ring pessary-fitting process.

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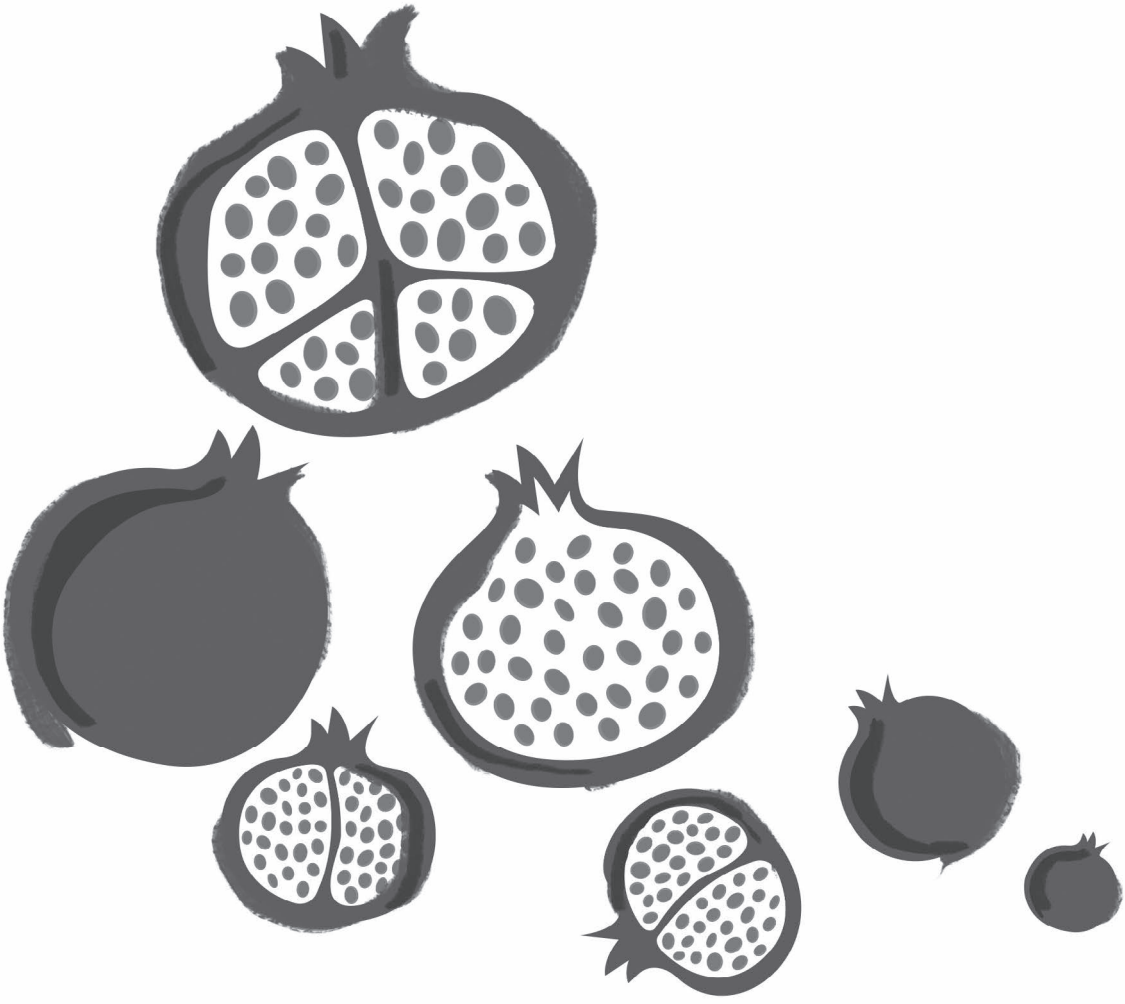
Ethics declarations

Conflicts of interest
None.



CHAPTER 5

The effect of pessary treatment on puborectalis muscle function

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Abstract

Introduction and hypothesis: The objective was to assess if puborectalis muscle (PRM) function changes in women with pelvic organ prolapse (POP) undergoing pessary treatment.

Methods: This was a prospective cohort study of women with symptomatic POP choosing pessary treatment. An interview, clinical examination and 3D/4D transperineal ultrasound were performed at baseline and at 3-month follow-up. POP was assessed using the Pelvic Organ Prolapse Quantification system (POPQ). Parameters compared between baseline and follow-up were: hiatal area at rest (HArest), maximal contraction (HActx), and maximal Valsalva maneuver (HAVal), displacement in contraction (DISPL-ctx, i.e., relative difference between HArest and HActx), and displacement in Valsalva (DISPL-Val, i.e., relative difference between and HAVal and HArest). Parameters were compared in women with and those without complete avulsion.

Results: A total of 162 women were assessed and 34 were included. Mean age was 64 years (SD 11.4), and mean BMI 24 kg/m2 (SD 3.1). Thirty-one women had a cystocele, 8 a uterine prolapse, and 12 had a posterior compartment prolapse. Twenty-one women (61.8%) had a POP stage II, and 13 (38.2%) a POP stage III. Ring pessaries were most frequently used (97%). In the entire group a statistically significant increase in DISPL-ctx was observed (mean difference 2.1%, $p = 0.017$). In the no avulsion group HArest and DISPL-ctx increased significantly (mean difference 4.1%, $p = 0.016$ and 2.7%, $p = 0.016$ respectively) and the increase in DISPL-ctx was higher than in the avulsion group (mean difference 2.7% vs 0.2%, $p = 0.056$).

Conclusion: Our results show that PRM function changes in women with POP undergoing pessary treatment and suggest that such change occurs mainly in the absence of complete avulsion.

Introduction

The levator ani muscle (LAM) plays a crucial role in the pathophysiology of pelvic organ prolapse (POP) [1, 2]. Under normal conditions, the LAM tightens the levator hiatus (i.e., the area encircled by the pubic bone and LAM) and provides a lifting force, making the pelvis an isobaric chamber [3]. One of the current theories of POP development [3] proposes that, if the LAM is damaged, the levator hiatus is widened and the vagina becomes exposed to the pressure differential between abdominal and atmospheric pressures. As a consequence, a pressure gradient arises in the pelvis, and the pelvic organs descend. On transperineal ultrasound (TPUS) the levator hiatus can be visualized as the area encircled by the puborectalis muscle (PRM, one of the LAM subdivisions) and the pubic bone. TPUS studies confirmed the association between enlarged levator hiatus and POP [4]. Furthermore, computer simulation studies showed the role of an increased hiatus size (defined as the distance between pubic symphysis to the ventral tip of the perineal body) in the development of POP [5]. Given the crucial role of the LAM in POP pathophysiology, treatments aimed at improving LAM function, such as pelvic floor muscle treatment (PFMT), are beneficial [6].

Pessary treatment is the other conservative option for POP [7, 8] and has proven effective in relieving POP symptoms by physically supporting the vaginal walls and the pelvic organs behind them [9,10,11,12]. Our hypothesis is that pessary treatment, by supporting the vaginal walls and the pelvic organs, counteracts the abnormal pressure gradient that has arisen during POP development. In this way, the pressure the LAM is exposed to could be reduced and the LAM, or some of its subdivisions (such as the PRM), could partially regain their function as the result of tissue remodeling or a physical effect [13].

Evidence in this respect is limited. Jones and coworkers observed a decrease in genital hiatus size (i.e., GH of the Pelvic Organ Prolapse Quantification system, POPQ) after 3 months of pessary use. They concluded that pessary use may result in some degree of LAM recovery [13]. However, genital hiatus size only provides an indirect assessment of the LAM. In order to determine the status of the LAM, it has to be visualized using imaging techniques. The aim of our study is to investigate with TPUS if an average of 3 months of pessary treatment is associated with changes in PRM function. We refer to PRM function instead of LAM function, because, as mentioned before, the PRM is the LAM subdivision surrounding the levator hiatus as assessed on TPUS. In addition, we analyzed the influence of avulsion on the change in PRM function observed during pessary treatment.

Materials and methods

The data used in the current study were collected as a subset within the GYNecological Imaging using 3D UltraSound (GYNIUS) project on the assessment of pelvic floor contractility with TPUS, which was conducted at our urogynecological center, where secondary and tertiary care are provided. Women were included in the GYNIUS project

between May 2018 and December 2019. The Medical Research Ethics Committee (MREC) exempted the project from ethical approval (reference 18/215), because TPUS was part of our routine diagnostic procedures and standard care. All women signed informed consent forms.

This was a prospective cohort study. Inclusion criteria were: women with symptomatic POP choosing pessary treatment, and successful pessary use during the study period. Exclusion criteria were: women already using a pessary at baseline; pessary fitting started more than 4 weeks after baseline assessment; women not attending the 3-month follow-up at our clinic; women undergoing pelvic floor muscle training (PFMT) in combination with pessary treatment during the study period. POP stage was not an inclusion/exclusion criterium. The rationale of the second exclusion criterium (i.e., pessary fitting started more than 4 weeks after baseline assessment) was the following. In the case of a long period between baseline TPUS and the start of pessary fitting, the baseline PRM function could have been unreliable because the hiatal dimensions might have changed in the meantime for reasons other than pessary treatment. To avoid this possible confounder, a maximum of 4 weeks between baseline assessment and start of pessary fitting was accepted.

At baseline and regular follow-up, all women underwent an interview, clinical examination, and 3D/4D TPUS. POP was assessed using the Pelvic Organ Prolapse Quantification system (POPQ) [14]. At baseline, pessary fitting was performed according to our standard clinical practice, similar to that described in the literature [15,16,17,18,19,20]. Based on clinical examination, a ring pessary of appropriate size (without or with support) was inserted at the initial fitting. If a ring pessary was not suitable, Gellhorn, donut or cube pessaries were tried. The following appointment was scheduled after 2–4 weeks to assess if the first pessary fitting trial was successful. A fitting trial was considered successful if the woman decided to continue using the pessary she was fitted with. If not, a different pessary size or type could be tried, and another pessary fitting trial was performed. This process was repeated until a successful fitting was achieved or pessary treatment was considered not suitable for the woman. The follow-up for pessary management and repeated TPUS was scheduled 3 months after successful pessary fitting. The choice of having the second assessment 3 months after successful pessary fitting was based on the study of Jones and coworkers [13] (in which the change in genital hiatus size was assessed 3 months after pessary use) and on convenience because our standard clinical practice consists of a follow-up 3 months after successful pessary fitting.

The TPUS was performed in supine position with an empty bladder. Women were instructed to perform maximal pelvic floor contraction and maximal Valsalva maneuver according to the method described by Dietz [21]. We used a Philips Epiq 7G machine with a X6–1 transducer covered with a 2 cm thick gel pad, and a glove. The gel pad was used to create more distance between the transducer and the women, so that the LAM could be fully visible within the opening angle on the coronal plane. TPUS volumes analyzed in the current study were acquired without pessary in situ. At follow-up the pessary was removed around 20 min before performing the TPUS.

Transperineal ultrasound volumes were assessed by the first author, using a tool developed by the second author in the image processing software MeVisLab [22]. This tool enables the selection of the correct frame and plane and the assessment of levator hiatal areas and avulsion. The first author was blinded against all clinical data and did not know which TPUS was acquired at baseline and which one at follow-up. As described in the literature [23], hiatal area at rest (HArest), on maximal pelvic floor contraction (HActx), and on maximal Valsalva maneuver (HAVal) were manually segmented at the plane of minimal hiatal dimensions (Appendix 1). If a woman could not perform pelvic floor contraction, HArest was also used for HActx. In Table 1 the parameters derived per woman from the manual segmentations are listed.

Table 1 Parameters derived per woman (i) from the manually segmented hiatal dimensions.

Parameter	Formula
DISPL-ctx$_i$	(HArest$_i$ - HActx$_i$)/ HArest$_i$
DISPL-Val$_i$	(HAVal$_i$ - HArest$_i$)/ HArest$_i$
Δ HArest$_i$	(HArest at follow-up$_i$ –HArest at baseline$_i$)/ HArest at baseline$_i$
Δ HActx$_i$	(HActx at follow-up$_i$ –HActx at baseline$_i$)/ HActx at baseline$_i$
Δ HAVal$_i$	(HAVal at follow-up$_i$ –HAVal at baseline $_i$)/ HAVal at baseline$_i$
Δ DISPL-ctx$_i$	DISPL-ctx at follow-up$_i$ – DISPL-ctx at baseline$_i$
Δ DISPL-Val$_i$	DISPL-Val at follow-up$_i$ – DISPL-Val at baseline$_i$

DISPL-ctx displacement in contraction, *DISPL-Val* displacement in Valsalva, *HArest* hiatal area at rest, *HActx* hiatal area on maximal pelvic floor contraction, *HAVal* hiatal area on maximal Valsalva maneuver

After having segmented HArest, HActx, and HAVal, the presence of avulsion was assessed at a later stage by the first author on baseline volumes obtained at maximum contraction. The assessor was blinded against all levator HA measurements while performing avulsion assessment. On tomographic imaging (TUI) a 2.5-mm interslice interval was set. The central slice was placed at the plane of minimal hiatal dimensions, showing the symphysis pubis closing medially. Complete avulsion was defined as a levator–urethra gap of ≥25 mm on the three central slices on the right side, on the left side (unilateral) or both sides (bilateral), as shown in Appendix 2 [23]. Avulsion was defined based on the presence of complete unilateral or bilateral avulsion.

To the best of our knowledge, TPUS parameters have never been used to assess the effect of pessary treatment on PRM function. Therefore, no formal sample size could be calculated, and this work can be considered an exploratory study.

Our primary outcome was to assess if the deltas (i.e., relative differences between follow-up and baseline calculated per woman) were significantly different from zero in the entire group, and if parameters were significantly different between the avulsion group and no-avulsion group. A t test was performed in the case of normally distributed data, as assessed by the Shapiro–Wilk test ($p > 0.05$), and if there were no outliers in the data.

Otherwise, a one-sample Wilcoxon signed rank test or an independent samples Mann–Whitney U test was run. The effect size was calculated using Cohen's d, when appropriate [24]. The statistical analysis was conducted using IBM v 27 SPSS software.

Results

Figure 1 shows the number of women at each stage. Initially, 162 women choosing pessary treatment were included in the GYNIUS project. Inclusion and exclusion criteria left 34 women to be included in the current study.

Mean age was 64 years (SD 11.4), and mean BMI 24 kg/m2 (SD 3.1). Thirty (88%) women were postmenopausal, and 32 (94%) vaginally parous with only one vacuum-extraction and one forceps delivery. Ten (29%) women had undergone prior gynecological surgeries, i.e., 3 vaginal hysterectomies, 3 abdominal hysterectomies, 2 anterior repairs, 2 posterior repairs, 1 sacrospinous fixation, and 1 POP surgery not specified. On clinical examination 31 (91%) had a significant (POPQ ≥2) cystocele, 8 (24%) a uterine prolapse, and 12 (35%) a posterior compartment prolapse. Twenty-one women (61.8%) had a POP stage II, and 13 (38.2%) had a POP stage III. For 19 women (56%) pessary fitting was successful at the first trial, whereas 15 women (44%) needed adjustment of the pessary size or type before being successful. Thirty-three (97%) were successfully fitted with a ring pessary (without or with support), and 1 (3%) with a Gellhorn pessary. The second TPUS was performed an average of 3.5 months (SD 1.1) after the insertion of the successful pessary.

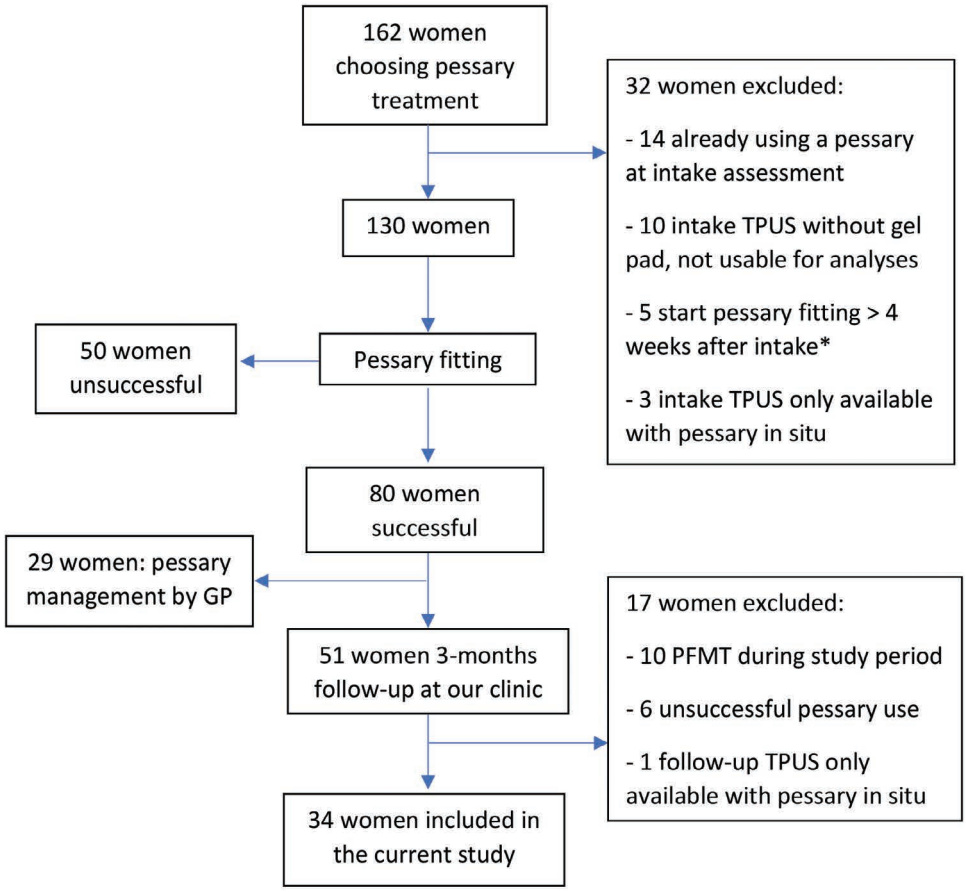

Figure 1 Number of women at each stage. *Of these 5 women 3 had an additional exclusion criterium: 2 did not attend the follow-up at our clinic (1 attended it at the GP clinic and the other had a telephone appointment because of the COVID-19 pandemic) and 1 underwent PFMT. The 2 women who were excluded only based on this criterium had an intake assessment to pessary fitting interval ≥12 weeks. TPUS transperineal ultrasound, GP general practitioner, PFMT pelvic floor muscle treatment

Table 2 shows median and interquartile range (IQR) of HArest, HActx, HAVal, DISPL-ctx, and DISPL-Val at baseline and follow-up. One woman was unable to perform pelvic floor contractions. Therefore, HArest was also used for HActx.

Table 2 Median an interquartile range of hiatal area at rest (HArest), maximal pelvic floor contraction (HActx) and maximal Valsalva maneuver (HAVal), displacement in contraction (DISPL-ctx), and displacement in Valsalva (DISPL-Val) at baseline and follow-up.

Parameter	Baseline (n=34) Median (IQR)	Follow-up (n=34) Median (IQR)
HArest (cm^2)	19.8 (4.7)	20.2 (5.9)
HActx (cm^2)	16.7 (4.2)	16.3 (4.6)
HAVal (cm^2)	30.6 (13.5)	31.8 (9.5)
DISPL-ctx (%)	17.2 (14.0)	19.0 (19.0)
DISPL-Val (%)	50.7 (45.0)	52.9 (40.0)

DISPL-ctx (HArest – Hactx)/HArest, *DISPL-Val* (HAVal – HArest)/HArest

Table 3 shows the results of a one-sample t test assessing the relative difference between follow-up and baseline of ∆ HArest, ∆ HActx, ∆ DISPL-ctx, and ∆ DISPL-Val. DISPL-ctx increased significantly from baseline to follow-up. On a one-sample Wilcoxon signed rank test the median of ∆ HAVal was not significantly different from zero (median (IQR) 3.8 (16), p = 0.14).

Table 3 Results of a one-sample T-test (test value: 0) assessing the relative difference between follow-up and baseline (n=34).

Parameter	Mean difference (SD) %	p-value	95% CI (%)	
Δ HArest	3.0 (9.3)	0.073	-0.3	6.2
Δ HActx	-0.1 (7.6)	0.910	-2.8	2.5
Δ DISPL-ctx	2.1 (4.9)	**0.017**	0.4	3.8
Δ DISPL-Val	0.6 (18.0)	0.836	-5.6	6.9

Δ *HArest* (HArest at follow-up – HArest at baseline)/HArest at baseline, Δ *HActx* (HActx at follow-up – HActx at baseline)/HActx at baseline, Δ *DISPL-ctx* DISPL-ctx at follow-up – DISPL-ctx at baseline, Δ *DISPL-Val* DISPL-Val at follow-up – DISPL-Val at baseline. Bold indicates the significant parameters

Parameters of the avulsion and no-avulsion groups were compared. The results of this analysis are reported in Table 4.

Table 4 Comparison between avulsion group and no-avulsion group (independent samples T-test if not otherwise specified).

Parameter	No-avulsion group (n=26)	Avulsion group (n=8)	p-value
HArest at baseline, median (IQR)	19.8 (4.5)	19.7 (10.0)	0.436*
HArest at follow-up, mean (SD)	20.6 (3.5)	22.1 (6.4)	0.387
Δ HArest, mean (SD) %	4.1 (8.0)	-0.6 (12.6)	0.351
HActx at baseline, median (IQR)	16.1 (3.9)	17.4 (7.8)	0.077*
HActx at follow-up, mean (SD)	15.8 (2.9)	19.2 (4.8)	**0.020**
Δ HActx, mean (SD) %	0.1 (6.5)	-1.0 (11.1)	0.806
HAVal at baseline, median (IQR)	30.3 (13.2)	35.6 (13.5)	0.253*
HAVal at follow-up, median (IQR)	29.3 (9.3)	34.8 (14.5)	0.327*
Δ HAVal, median (IQR) %	5.5 (16.0)	-0.9 (11.0)	0.327*
DISPL-ctx at intake, mean (SD) %	19.9 (10.0)	11.7 (10.1)	**0.049**
DISPL-ctx at follow-up, mean (SD) %	22.6 (11.7)	11.8 (10.3)	**0.025**
Δ DISPL-ctx, mean (SD) %	2.7 (5.4)	0.2 (2.0)	0.056
DISPL-Val at intake, median (IQR) %	50.7 (46.0)	51.6 (36.0)	0.618*
DISPL-Val at follow-up, mean (SD) %	54.2 (29.0)	55.2 (17.7)	0.923
Δ DISPL-Val, mean (SD) %	0.7 (18.9)	0.5 (15.5)	0.979

DISPL-ctx (HArest – Hactx)/HArest, DISPL-Val (HAVal – HArest)/HArest, Δ DISPL-ctx DISPL-ctx at follow-up – DISPL-ctx at baseline, Δ DISPL-Val DISPL-Val at follow-up – DISPL-Val at baseline
Bold indicates the significant parameters
*Independent Samples Mann-Withney U Test

In addition, the deltas were assessed in the two groups, separately (Table 5). In the no-avulsion group HArest and DISPL-ctx increased significantly from baseline to follow-up with an effect size of 0.51 and 0.50 respectively, whereas the median of Δ HAVal was not significantly different from zero on a one-sample Wilcoxon signed rank test (median (IQR) −5.5 (16.0), p = 0.086).

Table 5 Results of a one-sample T-test (test value: 0) assessing the relative difference between follow-up and baseline in the no-avulsion group and avulsion group, separately

Group	Parameter	Mean difference (SD) %	p-value	95% CI (%)	
No-avulsion (n=26)	Δ HArest	4.1 (8.0)	**0.016**	0.8	7.3
	Δ HActx	0.1 (6.5)	0.940	-2.5	2.7
	Δ DISPL-ctx	2.7 (5.4)	**0.016**	0.5	4.9
	Δ DISPL-Val	0.7 (18.9)	0.855	-7.0	8.3
Avulsion (n=8)	Δ HArest	-0.6 (12.6)	0.894	-11.2	10.0
	Δ HActx	-0.9 (11.1)	0.816	-10.2	8.3
	Δ HAVal	-0.4 (7.6)	0.891	-6.7	5.9
	Δ DISPL-ctx	0.2 (2.0)	0.792	-1.5	1.9
	Δ DISPL-Val	0.5 (15.5)	0.931	-12.5	13.5

Bold indicates the significant parameters

There was no difference in the deltas between women with POP stage II and women with POP stage III.

Discussion

A statistically significant increase in DISPL-ctx was observed 3 months after successful pessary fitting. This result is consistent with the hypothesis that pessary treatment is associated with changes in PRM function. Moreover, in the no-avulsion group HArest and DISPL-ctx increased significantly and the increase in DISPL-ctx was higher than in the avulsion group (p = 0.056).

DISPL-ctx can increase from baseline to follow-up as a result of a decrease in HActx, an increase in HArest, or both. We found a very small, nonsignificant decrease in HActx, whereas HArest increased (p = 0.07). This implies that the increase in DISPL-ctx was more driven by an increase in HArest than by a decrease in HActx, which is also confirmed by the statistically significant increase in HArest in the no-avulsion group. Whether the changes observed can be interpreted as a regain of PRM function or not is questionable. A possible explanation for these findings is that women with POP try to relieve their POP symptoms by contracting the PRM, which counteracts the abnormal pressure gradient originating during POP development. Vaginal pessaries, by supporting POP, could reduce

the need for this continuous contraction, allowing the PRM to relax (which was measured as an increase in HArest). From this perspective, the increase in DISPL-ctx is the result of a more physiological resting position. In the following, we refer to this explanation of our results as the "contraction hypothesis." An alternative explanation is that a progressive relaxation of the resting tone occurs in women with POP undergoing pessary treatment, which can be clinically experienced by the need for a bigger pessary size after some time of pessary use. In the following, we refer to this alternative explanation as the "relaxation hypothesis". The difference between the two hypotheses lies in the baseline resting tone of the PRM, which is not fully relaxed in the "contraction hypothesis", whereas it is fully relaxed in the "relaxation hypothesis".

At baseline and follow-up, women with complete avulsion had significantly lower DISPL-ctx than those in the no-avulsion group, which confirms previous results [25]. Moreover, no significant change in DISPL-ctx was observed during pessary treatment in the avulsion group, whereas a significant increase was observed in the no-avulsion group (with a medium effect size). The difference in DISPL-ctx between the two groups was almost significant ($p = 0.056$). These findings are more consistent with the "contraction hypothesis" and can be explained by the impaired ability to contract of women with complete LAM avulsion. These results are more difficult to explain with the "relaxation hypothesis" because a higher relaxation of the resting tone over time can be expected in the case of a damaged muscle.

A few studies investigated whether pessary treatment has an effect on pelvic floor anatomical parameters. Jones and coworkers compared the genital hiatus size of 42 women at baseline and after 3 months of pessary use [13]. They observed a decrease in genital hiatus size at rest and in Valsalva, with the greatest change registered in women using a Gellhorn pessary. There are several possible explanations for the discrepancy between their results and ours. First, we included only women who did not undergo PFMT, whereas they did not specify if this selection was made (and PFMT has proven to be associated with a reduction in HArest in women with POP [26]). Second, a larger proportion of women used a Gellhorn pessary in their study, and the greatest change in genital hiatus was registered in this subgroup. Third, genital hiatus and levator HA on TPUS are different measurements: genital hiatus is the distance between the middle of the external urethral meatus and the posterior margin of the hymen, whereas the levator HA on TPUS is the area encircled by the pubic bone and PRM. Therefore, they could reflect the function of different pelvic floor muscles (i.e., the puboperineal muscle and the PRM respectively [3]). Fourth, TPUS allows for the visualization and thus for a better assessment of the pelvic floor muscles compared with clinical examination. Last, we observed a significant increase in DISPL-ctx, which they did not assess.

Lone and coworkers evaluated levator hiatus dimensions using 3D endovaginal ultrasound before and 1 year after surgery, no treatment, or pessary treatment for POP [27]. No change was observed after pessary treatment. However, DISPL-ctx was not assessed in their study because only dimensions at rest can be measured with endovaginal

ultrasound. They did not assess women with and without avulsion separately. Moreover, only 6 scans of the 10 women undergoing pessary treatment were analyzable at follow-up. Therefore, a significant change was unlikely to be measured in this group.

Our study has several strengths. First, all scans were performed by the same clinician, thus reducing a source of variability. Second, the assessor was blinded to all clinical data and did not know which TPUS was acquired at baseline and follow-up. Intra-observer variability is not expected to introduce a bias in levator HA measurements, as their repeatability has been proven to be very high [28, 29]. Third, the assessor was blinded against all levator HA measurements while performing avulsion assessment. Fourth, to eliminate a possible confounder, only women who did not undergo PFMT were included. Although we cannot exclude that women performed pelvic floor exercises by themselves, none had supervised PFMT and at follow-up all denied having exercised themselves.

Some limitations must also be acknowledged. We did not have a control group. Therefore, it cannot be excluded that the changes we observed reflect the natural course of POP. However, we measured a statistically significant increase in DISPL-ctx and HArest (in the no-avulsion group) in a relatively small sample and in a short period of time, which is unlikely to be observed in women who do not undergo any treatment. The changes we observed were statistically significant but relatively small. Therefore, their clinical significance has to be further investigated in larger studies. In addition, the size of the avulsion group might have limited the detection of significant changes in this group. However, the differences between avulsion group and no-avulsion group are clear. A 3-month follow-up might have been short to fully appreciate the effect of pessary treatment on PRM function and future studies with a long-term follow-up should be performed. An additional limitation is the relatively large proportion of dropouts, which might have introduced a selection bias. Last, our results may not be extended to all women with POP successfully fitted with any type of vaginal pessary: the study was conducted in a urogynecological center (where primary care is not provided) and the majority of women were fitted with a ring pessary.

Being aware of these limitations, the results of our exploratory study can stimulate future research. Women without avulsion can have a normally functioning, underactive or overactive pelvic floor. It would be interesting to compare the effect of pessary treatment on PRM function between these groups. One randomized control trial showed the benefit of adding pessary treatment to PFMT for POP symptoms improvement [30]. If the “contraction hypothesis” is correct (i.e., if pessary treatment enables the PRM to fully relax at rest), pessary treatment might also allow for a better PRM function improvement in women undergoing PFMT. Our study provides an outcome measure (i.e., DISPL-ctx) that can be used to test this hypothesis.

In conclusion, our results show that PRM function changes in women with POP undergoing pessary treatment and suggest that such change occurs mainly in the absence of complete avulsion.

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Ethics declarations

Conflicts of interest
None.

Appendix 1

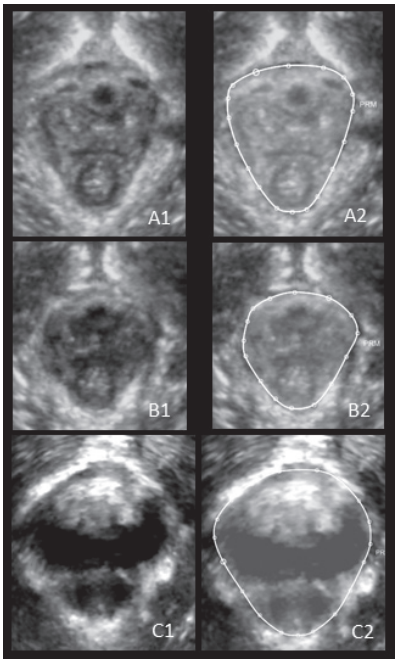

Figure 2. Hiatal areas without (1) and with (2) segmentation. A: Hiatal area at rest (14.81 cm2). B: Hiatal area at maximal contraction (12.05 cm2). C: Hiatal area on maximal Valsalva (29.32 cm2)

Appendix 2

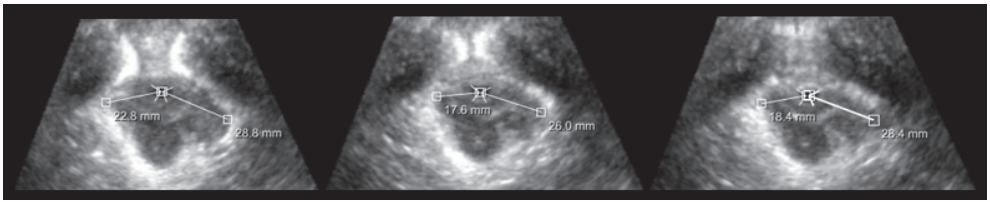

Figure 3. Transperineal ultrasound of a woman with complete unilateral avulsion showing the three central slices. On one side the levator–urethra gap is <25 mm (i.e., intact), whereas on the other side it is ≥25 mm (i.e., complete avulsion)


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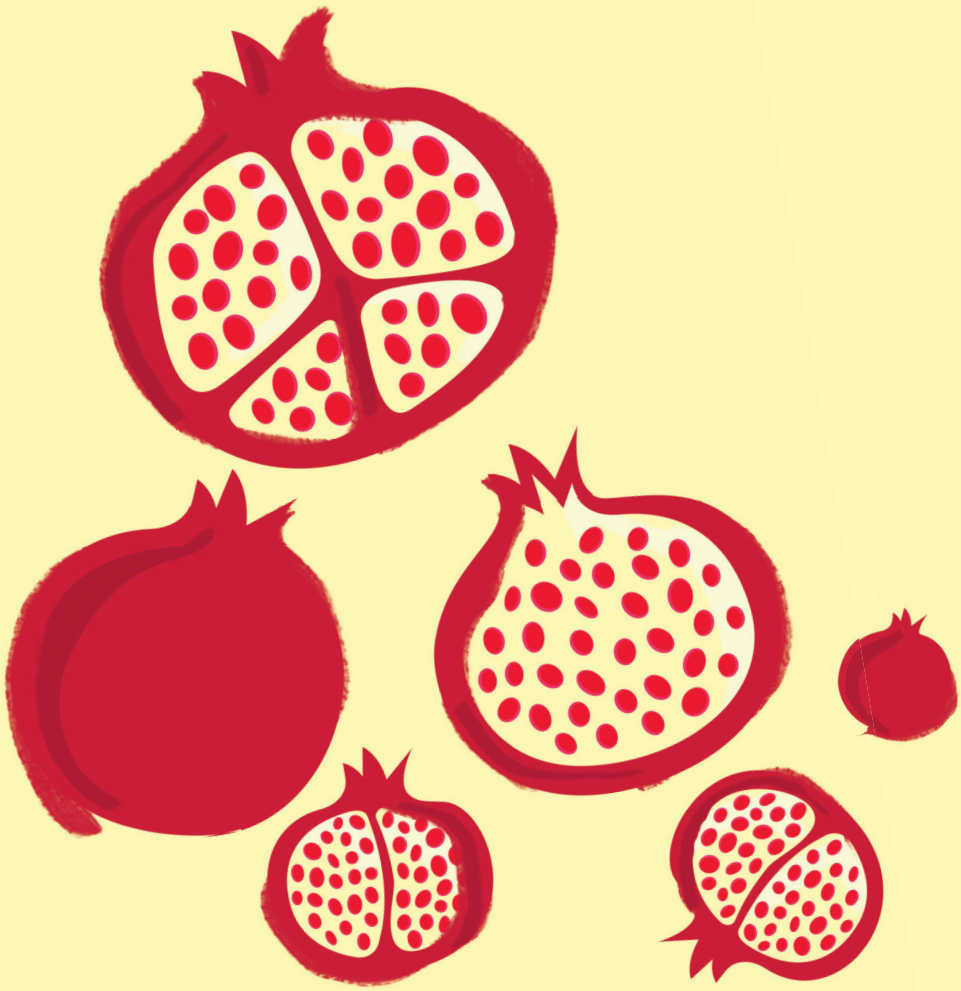
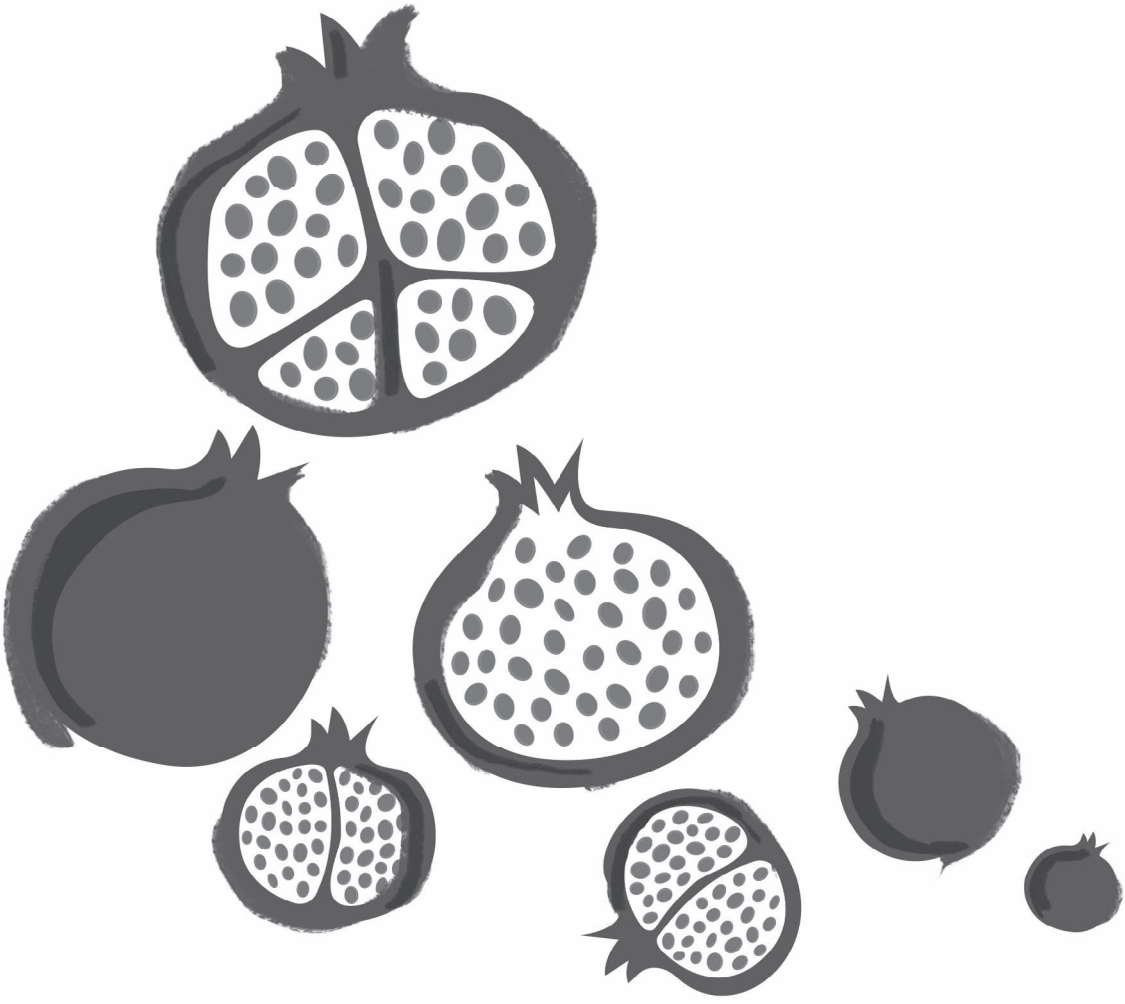


IMAGE ANALYSIS ADVANCEMENTS



CHAPTER 6

Automatic identification and segmentation of the slice of minimal hiatal dimensions in transperineal ultrasound volumes

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Abstract

Objectives: Automatic selection and segmentation of the slice of minimal hiatal dimensions (SMHD) in transperineal ultrasound (TPUS) volumes.

Methods: The SMHD was manually selected and the urogenital hiatus (UH) segmented in TPUS volumes of 116 women with symptomatic pelvic organ prolapse (POP). These data were used to train two deep learning algorithms: the first one provides an estimation of the position of the SMHD. Based on this estimation a slice is selected and fed into the second algorithm, which automatically segments the UH. From this segmentation measurements of hiatal area (HA), anteroposterior (APD) and coronal (CD) diameter are computed. The mean absolute distance between manually and automatically selected SMHD, the overlap (dice similarity index (DSI)) between manual and automatic UH segmentation and the intraclass correlation coefficient (ICC) between manual and automatic UH measurements were assessed on a test set of 30 TPUS volumes.

Results: The mean absolute distance between manually and automatically selected SMHD was 0.20 cm. DSI values between manual and automatic segmentation were all above 0.85. The ICC values and 95% confidence interval between manual and automatic levator hiatus measurements were 0.94 (0.87-0.97) for levator HA, 0.92 (0.78-0.97) for APD and 0.82 (0.66-0.91) for CD.

Conclusions: Our deep learning algorithms allow for reliable automatic selection and segmentation of the SMHD in TPUS volumes of women with symptomatic POP. These algorithms can be implemented in the software of TPUS machines, thus reducing clinical analysis time and easing the examination of TPUS data for research or clinical purposes.

Introduction

Transperineal ultrasound (TPUS) is an imaging technique used to investigate pelvic floor dysfunction [1] and enables assessment of the urogenital hiatus (UH) and levator ani muscle (LAM) [2-4]. The UH, whose surface is measured as the levator hiatal area (HA) on TPUS, is the opening encircled by the pubic bone and the puborectalis muscle (PRM) and is the largest potential hernial portal in the female human body. Pelvic organ prolapse (POP), which is one of the most common pelvic floor dysfunctions, is the herniation of the pelvic organs through the hiatus [5]. An enlarged levator HA on TPUS is a sign of impaired pelvic organ support and is associated with POP [2].

The LAM is the biggest muscle complex of the pelvic floor. The disconnection of its most medial part from the insertion on the inferior pubic ramus can occur during vaginal delivery and is called LAM avulsion [3]. LAM avulsion is associated with POP and reduced pelvic floor muscle function [3,7,8].

A crucial step for the assessment of both levator HA and LAM avulsion on TPUS is the identification of the slice of minimal hiatal dimensions (SMHD), which is performed as follows [6]: on the midsagittal slice one locates the shortest line between the pubic symphysis and the anorectal angle. The SMHD is the slice passing through this line, perpendicular to the midsagittal plane. On this slice, levator HA and diameters can be segmented and LAM avulsion can be assessed.

The limitation is that the selection of the SMHD and UH measurements are currently performed manually; meaning that the analysis is time-consuming and that each observer needs to complete a learning curve to properly perform the measurements [9]. In addition, even though previous studies showed good inter- and intraobserver variability [10,11], automating this procedure might reduce this variability even more.

Several papers have recently been published on the automatic segmentation of the levator HA [12-14]. However, this automatic segmentation was based on a manually selected SMHD, which means that the selection of the SMHD itself has not been automated, yet. Our aim is to use deep learning (DL) to develop a tool which includes both automated SMHD selection and levator HA segmentation, with the purpose of reducing analysis time and observer variability.

Methods

Data

The data used for the current study were collected as a subset within the GYNecological Imaging using 3D UltraSound (GYNIUS) project on the assessment of pelvic floor contractility with TPUS, which was conducted at a tertiary urogynecological clinic. Women were included in the GYNIUS project between May 2018 and December 2019. The

Medical Research Ethics Committee (MREC) exempted the project from ethical approval (reference 18/215), and all women signed informed consent forms.

The TPUS was performed in supine position after bladder emptying. Women were instructed to perform maximal pelvic floor contraction and maximal Valsalva maneuver according to the method described by Dietz [5]. A Philips Epiq 7G machine was used with a X6-1 transducer covered with a 2 cm thick gel pad, and a glove. The gel pad was used to create more distance between the transducer and the pelvic floor, such that the LAM is fully visible within the opening angle on the coronal plane.

The ultrasound scans used in this study were selected and segmented for analysis in two previous clinical studies [17, 18]. The HA was segmented manually by one observer (CM) at rest, maximal contraction and maximal Valsalva maneuver in the plane of SMHD. These segmentations were performed using an in-house developed software, which was implemented in MeVisLab 3.0.2 [19]. All steps for the selection of the SMHD were saved with this software, which enabled the automation of the process: the position of the SMHD in the 3D volume was saved, as well as the segmentation of the levator HA on the SMHD.

Deep learning

Deep learning (DL) is a set of (image processing) algorithms that try to mimic the learning of the human brain. Therefore, they are called neural networks. After an important image analysis competition was won convincingly by a convolution neural network (CNN) in 2012 [15], CNNs quickly became state-of-the-art for (medical) image analysis which often resulted in human level performance [16] in tasks like image segmentation or classification.

Segmentation CNNs are trained by providing them with manually labeled data. During training, the CNN learns the patterns that are needed to perform the segmentation task by minimizing a loss function that is designed to quantify the performance of the network. The more data (preferably a representative sample of the entire population) are used, the better a CNN is able to generalize the learned task to the entire population. An independent validation set is used to check during training how well the CNN performs on data that are not part of the training, which is a measure of the generalization capabilities of the CNN. The CNN that performs best on the validation set is used for further analysis, i.e., when the loss function has the lowest value on the validation set. Subsequently, a test set is used to analyze the resulting performance of the CNN on new (unseen) data (i.e., differently from the training set), as well as on data the CNN is not optimized for (i.e., differently from both training set and validation set). We have randomly assigned our data to either the training (104 patients, 381 frames, 337 2D slices), validation (2 patients, 12 frames, 6 2D slices) or test set (10 patients, 30 frames, 30 2D slices).

Selection and segmentation pipeline

To automatically select the SMHD and segment the levator HA, we have trained two different CNNs that can operate in a pipeline to make the process fully automated, see Figure 1. The first CN is a SMHD-selection-CNN (SS-CNN), which has the same network architecture as the one we have previously presented to automatically segment the PRM in 3D on TPUS volumes [20]. This network processes the data slice-by-slice, but 'remembers' inter-slice information, enabling full usage of the 3D context. We used the same segmentation network for the estimation of the position of SMHD. We trained this network on the sagittal slices, because the manual selection of the SMHD is done using mainly the mid-sagittal slice.

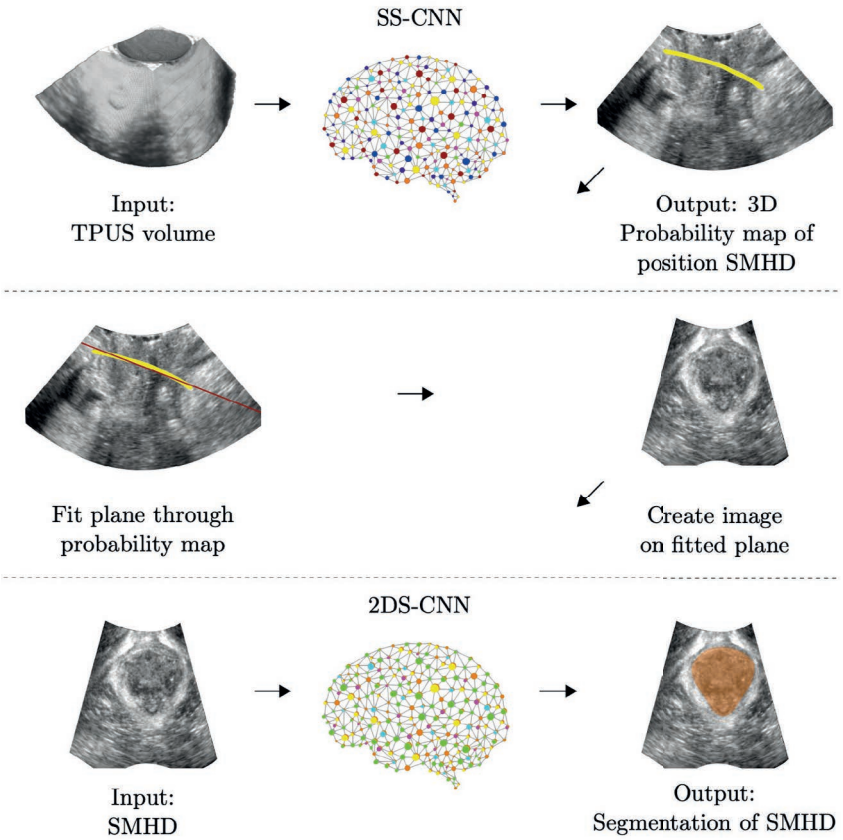

Figure 1. The pipeline used to select and segment the slice of minimal hiatal dimensions (SMHD) in a transperineal ultrasound (TPUS) volume is shown in three rows: A TPUS volume is fed in to the trained SMHD-selection-convolutional-neural-network (SS-CNN). This SS-CCN provides a 3D probability map (depicted in yellow) of the position of the hiatus on the SMHD in this TPUS volume. A plane (red) is fitted through this probability map, which is used to create a 2D image of the SMHD, provided that the SS-CCN correctly finds the hiatus. This SMHD is fed into the trained 2D-segmentation-CNN, yielding the segmentation of the urogenital hiatus (orange) on the SMHD. From this segmentation the area and the anterior-posterior and coronal diameter of the urogenital hiatus are calculated.

The labels of the manual hiatal segmentation are only one slice thick. However, a shift of a few slices also results in a correct visualization of the UH. Such shift occurs between observers or if the same observer repeats the selection of the SMHD. Therefore, we enlarged the segmentation mask to cover 5 slices by performing dilatation operation in order not to restrict the SMHD segmentation to the slice of the label.

The choice of 5 slices was arbitrary. We trained the network to maximize the overlap with this enlarged mask by using the Dice Similarity Index (DSI) loss function (DSI-LF) [21]. However, since overlap (DSI) is not always the perfect indicator of a successful estimation of the position of the SMHD, we also added a loss function that integrated the position of the SMHD estimation with respect to the manual mask (see Appendix S1).

After training, the network provides estimates of the position of the hiatal segmentation in 3D, which is often not a perfectly straight plane. Therefore, we fit a plane (least-square-error) through the data points of the estimation and we interpolate the 3D-data on this plane to obtain a 2D slice, which is the SMHD.

The second network is our 2D-segmentation-CNN (2DS-CNN), which we already presented in our previous work on 2D SMHD segmentation of the PRM and levator HA [14]. For the current study the network is trained (with DSI-LF) on the manual selected 2D SMHD to perform the levator HA segmentation. Based on the output of this CNN we automatically measure relevant parameters like levator HA, anteroposterior diameter (APD) and coronal diameter (CD).

Validation

The different steps of the pipeline are validated separately to ensure their proper functioning. The functioning of SS-CNN and plane fitting is validated by measuring the mean absolute distance (MAD) and the Hausdorff distance (HDD), i.e., the maximal absolute distance, between the manual hiatal segmentation and the automatically segmented SMHD of the test set. In addition, a non-quantitative measure consists of visual inspection of the manual and automatic SMHD. The 2DS-CNN is validated by applying the trained CNN to the SMHD of the test set. The overlap between automatic and manual levator HA segmentation can be quantified using the DSI: $DSI=2(X \cap Y)/(X+Y)$. Here $(X \cap Y)$ is the number of overlapping pixels of the two segmentations and X and Y are the number of pixels of respectively both segmentations. A DSI of 1 represents maximum segmentation overlap and a DSI of 0 no segmentation overlap. Lastly, the results of the complete pipeline are investigated by comparing the manual and automatic measurements of levator HA, APD and CD. We calculate their intraclass correlation coefficients (ICCs) with 95% CI and these ICCs are evaluated according to the subgroup definitions of Landis and Koch [22]. Furthermore, we create box plots to compare the distribution of both manual and automatic measurements and we investigate the mean difference and limits of agreement (LOA) with a Bland-Altman analysis. [23].

Results

Table 1 shows the demographical and clinical characteristics of the included patients (n=116). Mean age was 59.5 years (SD 11.8) and mean BMI was 24.7 (SD 3.6). 114 women (98.3%) were vaginally parous and 45 (38.8%) had a complete levator avulsion. Two women (1.7%) had a stage I POP, 67 (57.8%) a stage II POP, and 47 (40.5%) a stage III POP.

Table 1 Demographical and clinical characteristics of the included patients (N=116)

Parameter	Mean or N.	SD or %
Age, years (mean, SD)	59.5	11.8
BMI (mean, SD)	24.7	3.6
Menopause (N, %)	88	75.9
Vaginal delivery (N, %)	114	98.3
Hysterectomy (N, %)	16	13.8
POP surgery (hysterectomy excluded) (N, %)	12	10.3
Incontinence surgery (N, %)	3	2.6
Type of POP		
• Anterior (N, %)	66	56.9
• Apical (N, %)	6	5.2
• Posterior (N, %)	11	9.5
• Anterior and apical (N, %)	4	3.4
• Anterior and posterior (N, %)	21	18.1
• Apical and posterior (N, %)	3	2.6
• Anterior, apical and posterior (N, %)	5	4.3
Stadium POP		
• I (N, %)	2	1.7
• II (N, %)	67	57.8
• III (N, %)	47	40.5
Complete avulsion (N, %)	45	38.8

In some cases, data of the same patient were acquired and analyzed more than once, resulting in 423 frames on which the 3D position of the SMHD was successfully saved (150 rest, 137 contraction, 136 Valsalva). The 2D segmentations were not always successfully saved, resulting in a dataset of 112 women and 373 training images.

Figure 2 and 3 show all manually and automatically selected SMHD of the test set, which allows for visual comparison.

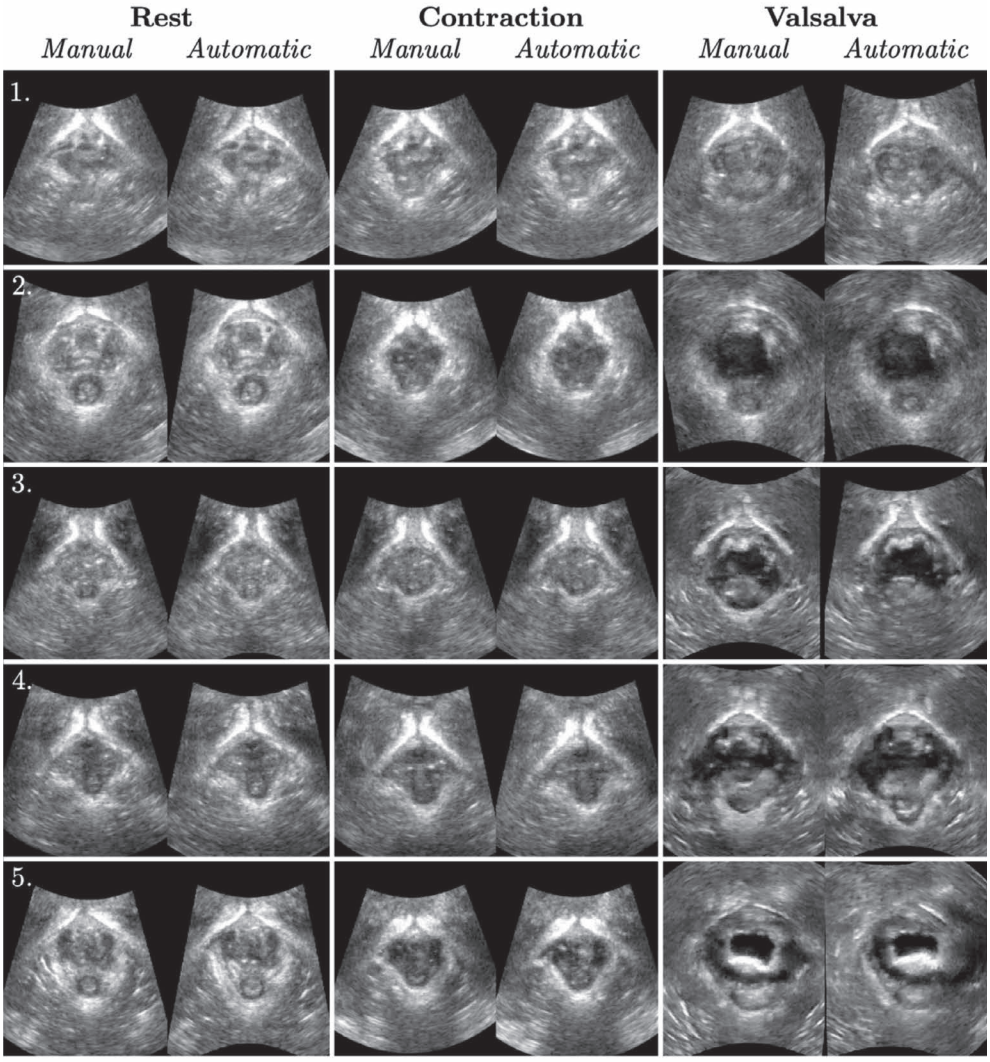

Figure 2. The visual comparison of the manual and automatic SMHD selection of the data from patient 1-5 of the test set.

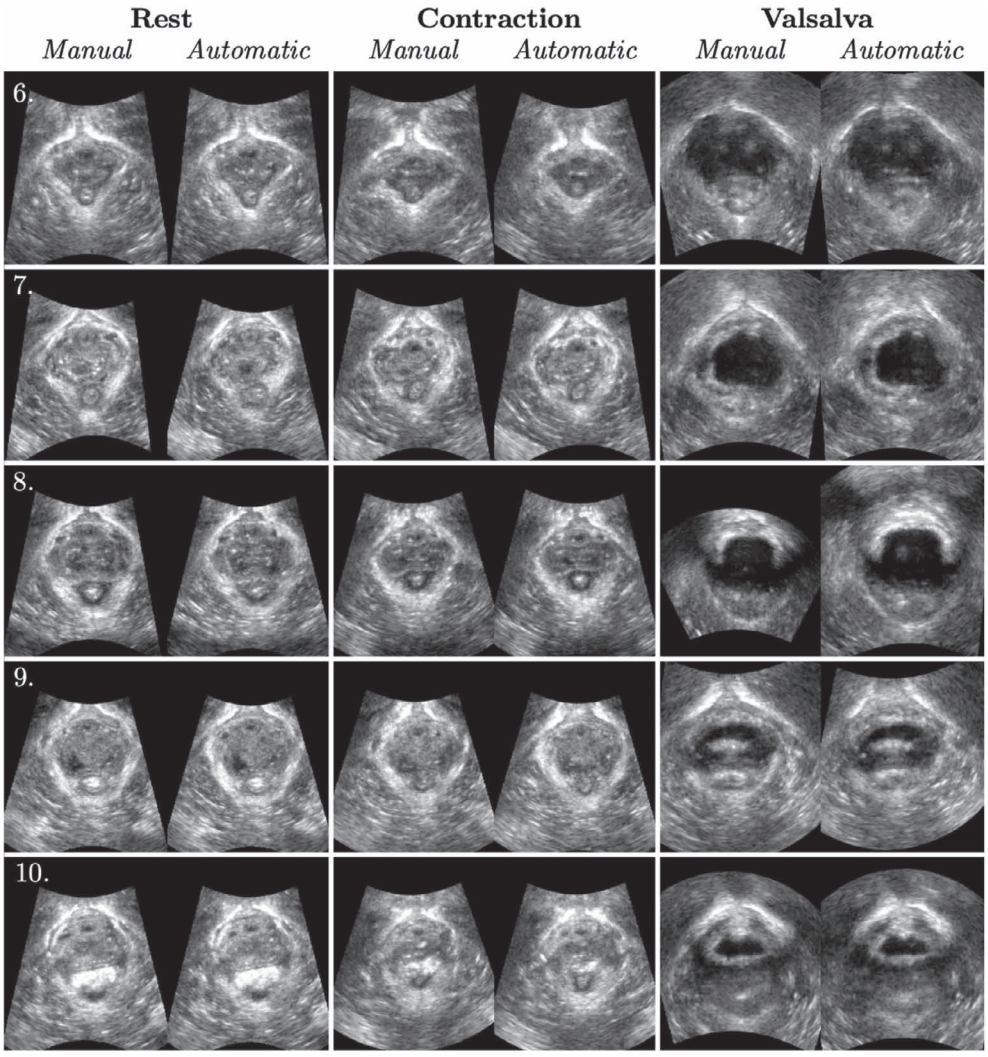

Figure 3. The visual comparison of the manual and automatic SMHD selection of the data from patient 6-10 of the test set.

The left side of Figure 4 reports the box-plot of the DSI between manual and automatic 2D segmentation, whereas the right side reports the box-plots of the MAD and HDD between the manually segmented levator HA and the automatically selected SMHD. The average MAD between manually and automatically selected SMHD is 0.20 cm.

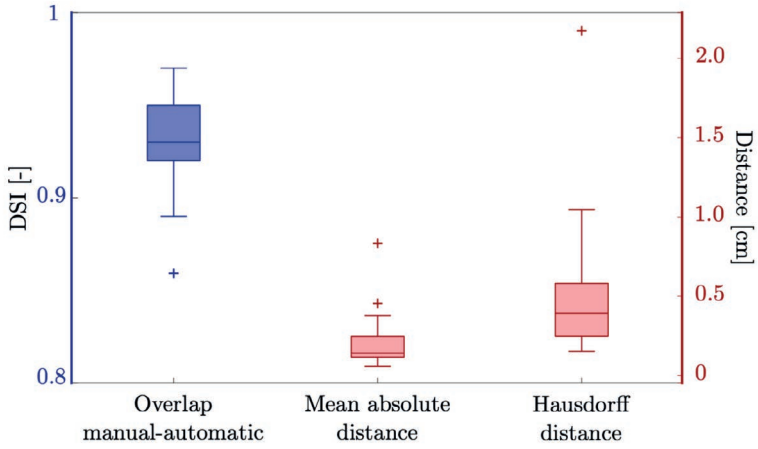

Figure 4. Boxplot of the dice similarity index (DSI) between manual and automatic segmentation and the mean absolute and Hausdorff distance between the manual hiatal segmentation and the automatic detected SMHD. Boxes with internal lines represent median and interquartile range (IQR), whiskers are range excluding outliers (+) larger than 1.5 IQR from upper and lower quartile.

To show the performance of the complete pipeline, the box-plots of the manual and automatic measurements of levator HA, APD and CD are presented in Figure 5.

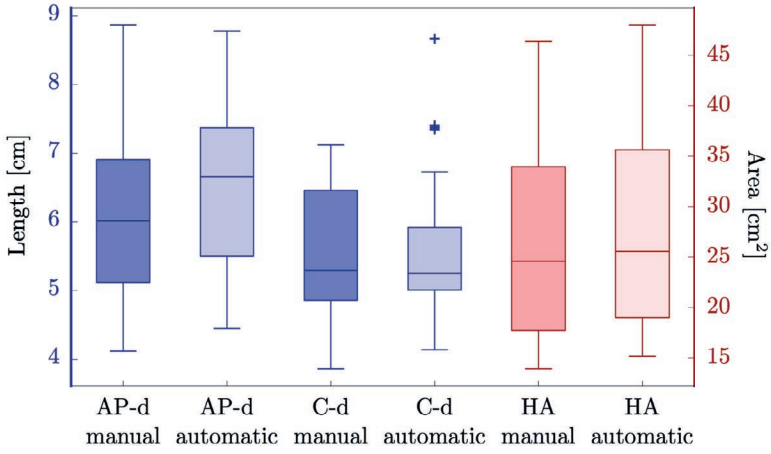

Figure 5. Boxplots of the manual and automatic measurement of the anterior-posterior diameter (AP-d), coronal diameter(C-d) and hiatal area (HA) on the test set data. Boxes with internal lines represent median and interquartile range (IQR), whiskers are range excluding outliers (+) larger than 1.5IQR from upper and lower quartile.

In Figure 6 we show the Bland-Altman plot of the HA measurements. Table 2 provides the ICC values, the mean, standard deviation, mean difference and LOA of the manual and automatic pipeline HA, APD and CD measurements.

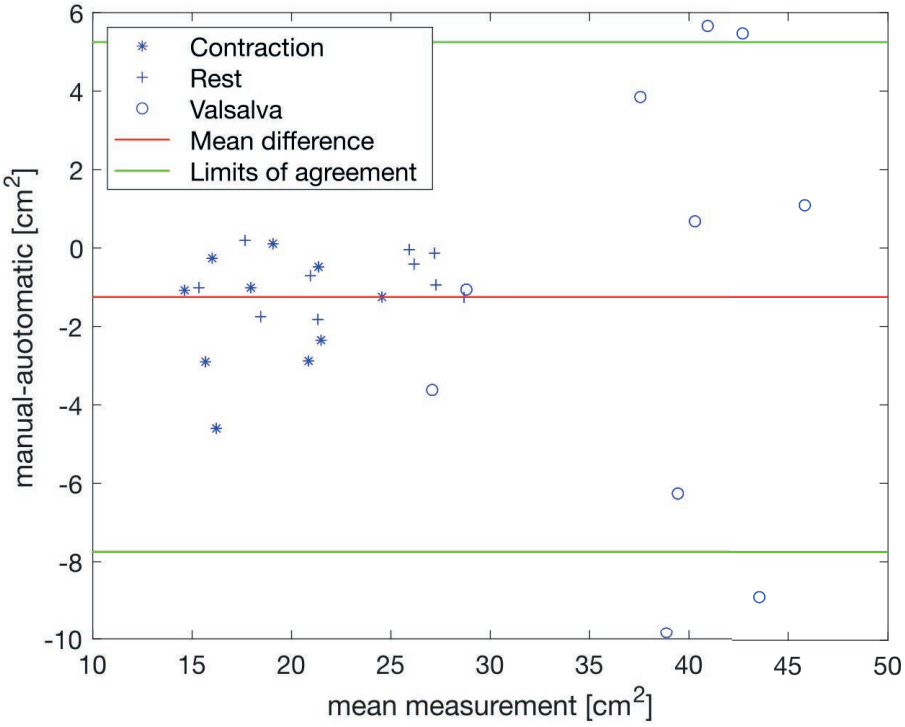

Figure 6. A Bland-Altman plot of the hiatal area measurements. The individual measurements are plotted with the labels rest, contraction and Valsalva. The mean difference and limits of agreement are visualized as well.

Table 2 Comparison of manual and automatic pipeline measurements of the hiatal dimensions; Hiatal areal, anterior-posterior diameter and coronal diameter.

	Hiatal area (cm²)	Anterior-posterior diameter (cm)	Coronal diameter (cm)
ICC (95% CI)	0.94 (0.87-0.97)	0.92 (0.78-0.97)	0.82 (0.66-0.91)
Automatic pipeline	27.4 (±9.8)	6.5 (±1.2)	5.6 (±0.9)
Manual	26.1 (±10.1)	6.2 (±1.3)	5.5 (±1.0)
Mean difference	-1.3 (±3.3)	-0.3(±0.4)	-0.1 (±0.6)
LOA	-7.7 to 5.2	-1.1 to 0.8	-1.3 to 1.1

Data are given as mean ± standard deviation. ICC (95% CI), intraclass correlation coefficient with 95% confidence interval; Mean difference is Manual-Automatic pipeline LOA, limits of agreement.

Discussion

In this work we present a pipeline for a fully automated selection of the SMHD and levator HA segmentation through which levator HA, APD and CD are automatically measured. The automated selection of the SMHD has not been previously reported in literature. We presented the results of the performance of both CNNs independently and the accuracy of the measurements of the complete pipeline. These validation statistics comparing automatic and manual measurements showed excellent agreement, which demonstrates high reliability of the automatic pipeline.

The selection of the SMHD is difficult because the SMHD is not aligned with any of the principal anatomical slice orientations (i.e., coronal, sagittal or axial orientation). In the literature, there are several examples of slice detection methods for other imaging tasks, like L3 slice detection in CT data [24,25] or slice detection in fetal ultrasound data [26-29]. Among these examples, the only method detecting a slice that is not aligned with the principal anatomical slice orientations is the one described by Li et al. [28]. Although their approach is different than the one presented in this work, their results in terms of distance between manually and automatically selected slices are comparable to ours, with our results being slightly better (average MAD of 0.20 cm for our data vs 0.34 cm and 0.35 cm for theirs). However, we restrict the distance calculation to the area of the manual hiatus segmentation, which is our region of interest, instead of calculating the average between manual and automatic SMHD. This restriction may have a slight positive influence on our results.

Only one automatically selected slice is more than 0.5 cm apart from the manually selected slice (see MAD boxplot in Figure 4), which corresponds to the Valsalva image of patient 8 in Figure 3. However, such distance had little influence on the hiatal measurements. The clear outlier in the CD measurements (see Figure 5) is the CD in Valsalva of patient 10 and can be explained by the unclear borders of the automatically selected SMHD, which hindered a proper automated segmentation.

Figure 6 shows that the Valsalva measurements have the largest difference between manual and automatic measurements. However, the average HA measurements for Valsalva of most women in the test set are almost twice as large as the those of contraction and rest. The error seems therefore proportional to the size of the measured area. There seems to be a small overestimation (average of 1.3 cm^2) of all measured parameters by the automatic pipeline. The error seems similar to interobserver measurement in humans [30].

The overlap results of the 2DS-CNN are comparable to other (semi-)automated methods presented in literature [12-14], which report average DSI values of 0.92-0.94 (0.93 for this study). The ICC of levator HA, CD and APD measurements between manual analysis and the fully automated pipeline are excellent, comparable to our previous results on automatic segmentation of levator HA, APD and CD [14]. This indicates that automating

the slice selection (SS-CNN) does not negatively influence the segmentation results. The interobserver variability for the manually performed measurements, reported in literature [9,10,30,31], differ substantially. Our ICC-values are higher than those reported in literature, proving the success of the presented automated SMHD selection and segmentation pipeline.

The presented, fully automated pipeline requires a few seconds to process a single volume. Therefore, it can be implemented in the software of TPUS machines, which will make the analysis of TPUS data less time consuming and less observer dependent, thus reducing clinical training and analysis time and easing the examination of TPUS data for research or clinical purposes. This will lower the barriers that clinicians might experience in using TPUS in their clinical practice.

The data of this study were acquired from women with symptomatic POP, which are more complex to analyse compared to data of women with intact LAM and/or without pelvic floor dysfunction [9]. Due to its reproducibility, our pipeline is an excellent tool to standardize the UH measurements in complex patient populations, making them less observer dependent. However, it should be noted that the training data of the pipeline were obtained from manual analysis of a single experienced observer. Therefore, it can be assumed that they are biased towards the way this specific observer analyzes the data. Before implementation in clinical practice, we recommend to add training data from multiple observers, which would eliminate the personal bias in the network.

For a more reliable analysis of the minimal hiatal dimensions in Valsalva, a rendered volume [32] and OmniView-VCI [33] were previously suggested in literature. Those methods, however, require the (approximate) position of the SMHD to compute their interpolated 2D images. Since these images look very similar to a single slice SMHD we expect the 2D segmentation results on these images to be similar the presented results. Even when the pipeline generates some errors, these can easily be identified in clinical practice by a quick visual examination of the selected and segmented SMHD. In these cases, manual analysis is recommended, which can also be used to update the pipeline, making it more robust over time. The only step that still needs automation is the selection of the correct frames (i.e., rest, contraction or Valsalva). However, this is the least time-consuming step in the manual examination and, based on previous results in literature [26,27,29], it can be expected that its automation is feasible.

To conclude, we present a pipeline that reliably selects and segments the SMHD and thus automates the analysis of the SMHD on TPUS data of women with symptomatic POP. Implementing this pipeline in the software of TPUS machines will make the analysis of TPUS data less time consuming and less observer dependent. This will reduce clinical training and analysis time and ease the examination of TPUS data for research or clinical purposes.

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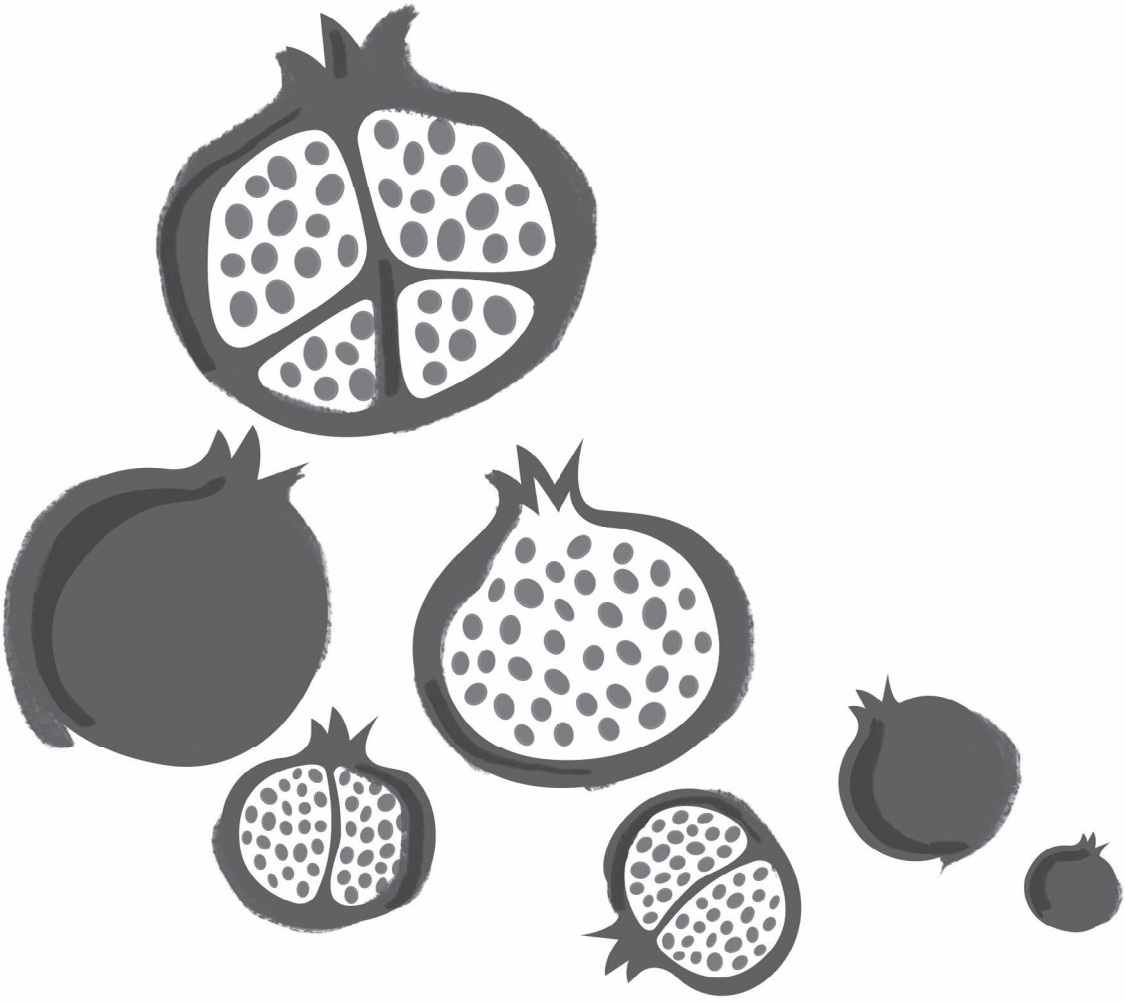

CHAPTER 7

Appearance of the levator ani muscle subdivisions on 3D transperineal ultrasound

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Abstract

Background: The levator ani muscle (LAM) consists of different subdivisions, which play a specific role in the pelvic floor mechanics. The aim of this study is to identify and describe the appearance of these subdivisions on 3-Dimensional (3D) transperineal ultrasound (TPUS). To do so, a study designed in three phases was performed in which twenty 3D TPUS scans of vaginally nulliparous women were assessed. The first phase was aimed at getting acquainted with the anatomy of the LAM subdivisions and its appearance on TPUS: relevant literature was consulted, and the TPUS scan of one patient was analyzed to identify puborectal, iliococcygeal, puboperineal, pubovaginal, and puboanal muscle. In the second phase, the five LAM subdivisions and pubic bone and external sphincter, used as reference structures, were manually segmented in volume data obtained from five nulliparous women at rest. In the third phase, intra- and inter-observer reproducibility were assessed on twenty TPUS scans by measuring the Dice Similarity Index (DSI).

Results: The mean inter-observer and median intra-observer DSI values (with interquartile range) were: puborectal 0.83 (0.13) / 0.83 (0.10), puboanal 0.70 (0.16) /0.79 (0.09), iliococcygeal 0.73 (0.14) / 0.79 (0.10), puboperineal 0.63 (0.25) / 0.75 (0.22), pubovaginal muscle 0.62 (0.22) / 0.71 (0.16), and the external sphincter 0.81 (0.12) / 0.89 (0.03).

Conclusion: Our results show that the LAM subdivisions of nulliparous women can be reproducibly identified on 3D TPUS data.

List of abbreviations

3D/2D: 2/3 dimensional
ATLA: arcus tendinous levator ani
DSI: Dice similarity index
ES: external sphincter
ICM: iliococcygeal muscle
LAM: levator ani muscle
MRI: magnetic resonance imaging
PAM: puboanal muscle
PB: pubic bone
PF: pelvic floor
PPM: puboperineal muscle
PRM: puborectal muscle
PVM: pubovaginal muscle
TPUS: transperineal ultrasound

Background

The prevalence of pelvic floor disorders is high (1,2), and the long-term effectiveness of treatments relatively limited (3,4). This prompted DeLancey to publish a paper in 2005 in which a goal was set to achieve 25% reduction in occurrence and 25% improvement in treatment success by 2025 (5). In 2017 it was acknowledged that measurable improvements were not yet achieved. However, the scientific community was (and is) gaining the quantitative framework necessary to spur the progress (6). This quantitative framework includes pelvic floor (PF) biomechanical analyses (7-10), which allow us to get insight into PF functionality and understand the functional impact of PF damage. To perform biomechanical analyses, computer simulations and measurements are produced from image data. This implies that interpreting image data accurately is fundamental, if we want to draw meaningful conclusions. Moreover, the functional consequence of LAM injury may depend on the region of muscle affected (11). To test this hypothesis in imaging studies, the different LAM regions (or subdivisions) have to be correctly identified, which prompted the current study.

The 3D appearance of the levator ani muscle (LAM) subdivisions of nulliparous women has been described on magnetic resonance imaging (MRI) and endovaginal ultrasound, respectively (12,13). To the best of our knowledge, this has not yet been achieved with transperineal ultrasound (TPUS). Compared to MRI, TPUS is less expensive and data acquisition is faster. The advantage is that a large dataset can be easier collected, providing statistically robust results. Differently from endovaginal ultrasound, TPUS can capture PF motion, thus providing the functional information that is necessary to validate biomechanical analyses (14).

TPUS is currently used in scientific research on and clinical assessment of PF disorders: it allows for the assessment of the anterior, apical and posterior compartment, LAM avulsion, anal sphincter, and implants materials (15-19). In addition, TPUS has been applied for investigating the consequences of pregnancy and delivery on PF biometry and integrity (20-26). Analyses and measurements are mostly performed in 2D.

In 2018 we have published a protocol for reproducible 3D segmentation (27) for the part of the LAM surrounding the hiatal area, without discriminating between the different LAM subdivisions. During the last years, advancements in TPUS hardware and software led to significant improvements in image quality. Therefore, the aim of this study is to identify and describe the separate appearance of LAM subdivisions on 3D TPUS of vaginally nulliparous women.

Methods

The ultrasound data used for the present study were collected as a subset within the GYNecological Imaging using 3D UltraSound (GYNIUS) project on the assessment of pelvic floor contractility with TPUS, which is conducted at our tertiary urogynecological clinic.

The data were acquired with a Philips Epiq 7G ultrasound machine connected to a X6-1 matrix transducer. The volume angle was 90° in both azimuthal and elevational direction and probe consists out of 9212 elements. Post-processing filters were set off, the scan depth was 9 cm. The resolution of the image was 0.6 mm between the 229 sagittal slices, 0.4 mm between the 352 coronal slices and 0.3 mm between the 277 axial slices. In order to make the LAM fully visible within the coronal opening angle, the transducer was covered with a 2 cm thick gel pad, which created more distance between the patient and the probe. All scans were performed in supine position with empty bladder. Since the aim of our study was to describe the appearance of the LAM subdivisions of an intact pelvic floor, only vaginally nulliparous women were included. The Medical Research Ethics Committee (MREC) UMC Utrecht exempted the project from approval (reference 18/215), because the Medical Research Involving Human Subject Act (WMO) does not apply, and all women signed a research consent form.

We conducted the study in three phases. The first phase was aimed at gaining familiarity with the anatomy of the LAM subdivisions. Initially, we consulted relevant literature about the topic (12,13,28) to evaluate if the definition of the different subdivisions was consistent between authors in terms of nomenclature, shape, and orientation. Having done this, we aimed at identifying on TPUS the following LAM subdivisions: puborectal muscle (PRM), iliococcygeal muscle (ICM) and pubovisceral muscle, the latter consisting of puboperineal muscle (PPM), pubovaginal muscle (PVM), and puboanal muscle (PAM). For this purpose, one TPUS was analyzed and the five LAM subdivisions were identified using the following criteria (12): a distinct and consistently visible separation between a structure and adjacent structures and/or differing origin or insertion of the muscle.

In the second phase of the study, pubic bone (PB) and external sphincter (ES), used as reference structures, and the LAM subdivisions were manually segmented on five TPUS scans. To perform the segmentations an in-house software was developed in MeVisLab (29) (Figure 1 and 2). The following manual segmentation protocol was used:

- Reference structures, i.e., pubic bone (PB) and external sphincter (ES)

In order to have a ventral and dorsal reference the PB and ES were segmented first. Analyzing the TPUS volumes on the axial plane in the caudal-cranial direction, the PB is the first structure visualized, appearing hyperechoic at its boundaries and hypoechoic internally, which makes it easy to recognize and segment it. For a correct segmentation of the ES it is useful to identify its boundaries on the midsagittal plane, where its separation with the LAM appears as a hypoechoic line between two hyperechoic structures. Having done this, the coronal plane has to be rotated perpendicular to the anal canal. On this plane the ES appears as a hyperechoic circle which surrounds a hypoechoic circle, the internal anal sphincter (30) (Figure 1).

- LAM subdivisions, i.e., puboperineal muscle (PPM), puboanal muscle (PAM), puborectal muscle (PRM), iliococcygeal muscle (ICM), and pubovaginal muscle (PVM)

In the axial direction the most superficial LAM subdivision is the PPM, which is a symmetrical hyperechoic structure attaching ventrolaterally to the PB and dorsomedially to the area between anal canal and vagina, where the perineal body is located. To visualize PAM, PRM and ICM, the axial plane must be rotated to the plane of minimal hiatal dimensions (31) (Figure 2D). In this plane, from medial to lateral, PAM, PRM, and ICM can be recognized as three symmetrical structures, separated by a hypoechoic line. The PAM is located lateral to the vagina, and attaches ventrally to the PB, and dorsally to the fibers of the ES. The PRM, located laterally to the PAM, attaches ventrally to the PB and passes dorsally behind the rectum. Cranially from the plane of minimal hiatal dimensions, the most lateral part of the LAM appears highly hyperechoic. Here the ICM attaches to the arcus tendinous levator ani (ATLA), a condensation of connective tissue coursing along the surface of the obturator internus muscle (32). The ATLA cannot be separated from the ICM on TPUS. Therefore, they were segmented as a single structure. From the attachments to the ATLA the ICM courses in the direction of the coccyx, curving around the PRM. The PVM is a small hypoechoic symmetrical structure between the PB and the anterior lateral edges of the vagina, medial to the PAM (Figure 2). The appearance of PRM and ICM on the mid-sagittal plane, and of PRM, ICM, and PAM on the coronal plane was used as a reference for the segmentation on the axial plane (Figure 1).

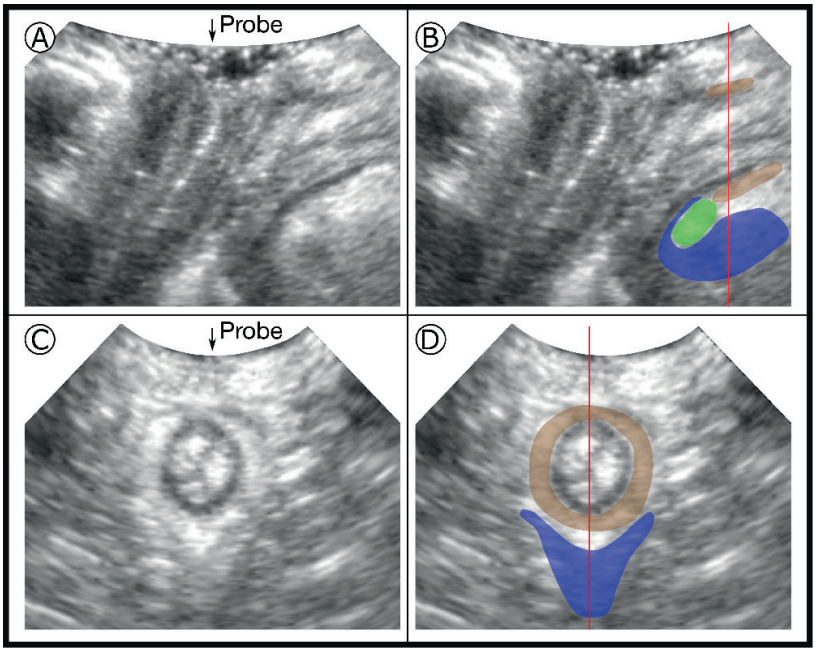

Figure 1. Midsagittal ("A" and "B") and coronal ("C" and "D") plane, without and with segmentation. In "B" the C shape of the iliococcygeal muscle (ICM) (blue) surrounding the puborectal muscle (PRM) (green); in "D" the round shape of the external sphincter (brown). The red line in "B" shows the position of the coronal plane and in "D" the position of the midsagittal plane (A and B). The ultrasound probe position with respect to the images is indicated by the arrows.

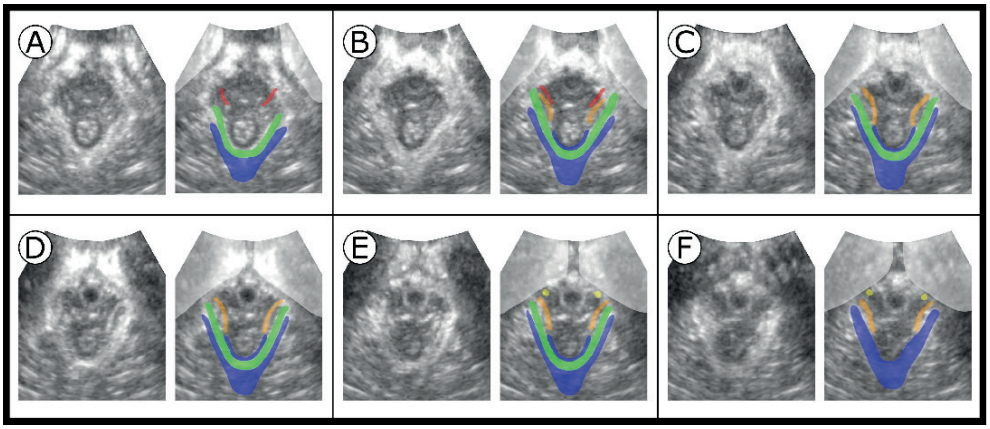

Figure 2. Slices parallel to the plane of minimal hiatal dimensions (2.4 mm between subsequent slices). The image without (left) and with segmentation (right) is displayed for each slice. From "A" to "F" the slices are ordered in the caudal-cranial direction. Slice "D" shows the plane of minimal hiatal dimensions. Segmented structures: pubic bone (PB, grey), puboperineal muscle (PPM, red), puboanal muscle (PAM, orange), pubovaginal muscle (PVM, yellow), puborectal muscle (PRM, green) and iliococcygeal muscle (ICM, blue).

The slice-by-slice 2D segmentations were used to produce 3D models in MeVisLab in order to visualize the structures in their entirety.

The third phase of the study aimed at assessing the reproducibility of the segmentation procedure. For this purpose, we use the five TPUS of the second phase plus 15 new TPUS. The following four slices were selected in the ultrasound volumes:

1. Minimal hiatal dimensions slice where the PAM, PRM and ICM are visible (Figure 2D);
2. An axial slice showing the PPM (similar to Figure 2A);
3. An axial slice with the PVM (similar to figure 2F);
4. A slice perpendicular to the anal canal where the circular structure of the ES is visualized (Figure 1D).

CM and FN performed, independently, the segmentation of the four slices for all the 20 images, in order to assess inter-observer reproducibility. After more than one week, FN repeated all measurements on the 20 TPUS, segmented in a random order, to assess intra-observer reproducibility. To measure the intra- and interobserver overlap between segmentations, we use the Dice Similarity Index (DSI): $DSI=2(X\cap Y)/(X+Y)$. This formula states that two times the overlapping area is divided by the sum of the area of segmentation X and segmentation Y; DSI=0 corresponds to no overlap and DSI=1 to maximum possible overlap. In Figure 3 a flow-chart summarizes the three study phases.

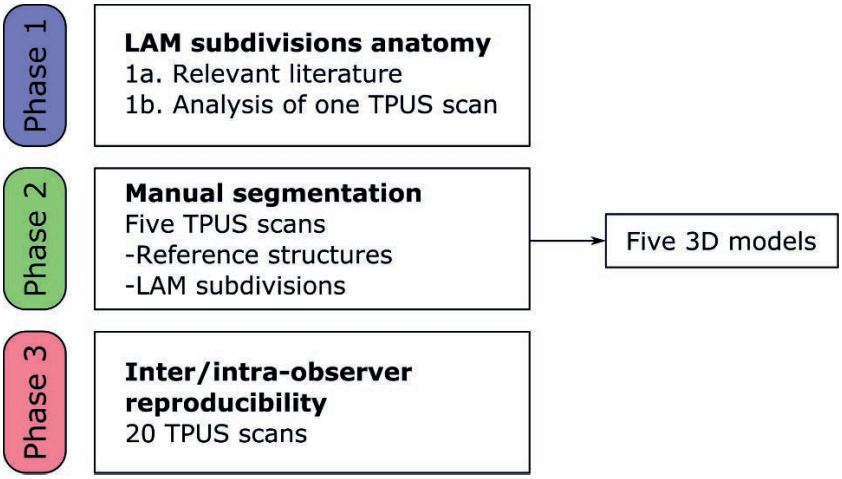

Figure 3. Flow chart showing the different study phases.

Results

The 20 patients included in the study presented with symptoms of overactive pelvic floor confirmed by physical examination. The mean age was 39 years (range 19-68), and mean body mass index 22.7 (range 17.0-29.0). None of them had vaginally delivered before nor had any prior pelvic floor surgeries.

From literature research and visual examination of TPUS data we were able to develop a manual segmentation protocol for the five LAM subdivisions. Applying our protocol, we were able to segment all LAM subdivisions in the five TPUS scans used for this purpose. The five 3D models (generated in MeVisLab) let appreciate the segmented structures in their entirety, their spatial direction, and the spatial relation between different structures (Figure 4 and Appendix 1).

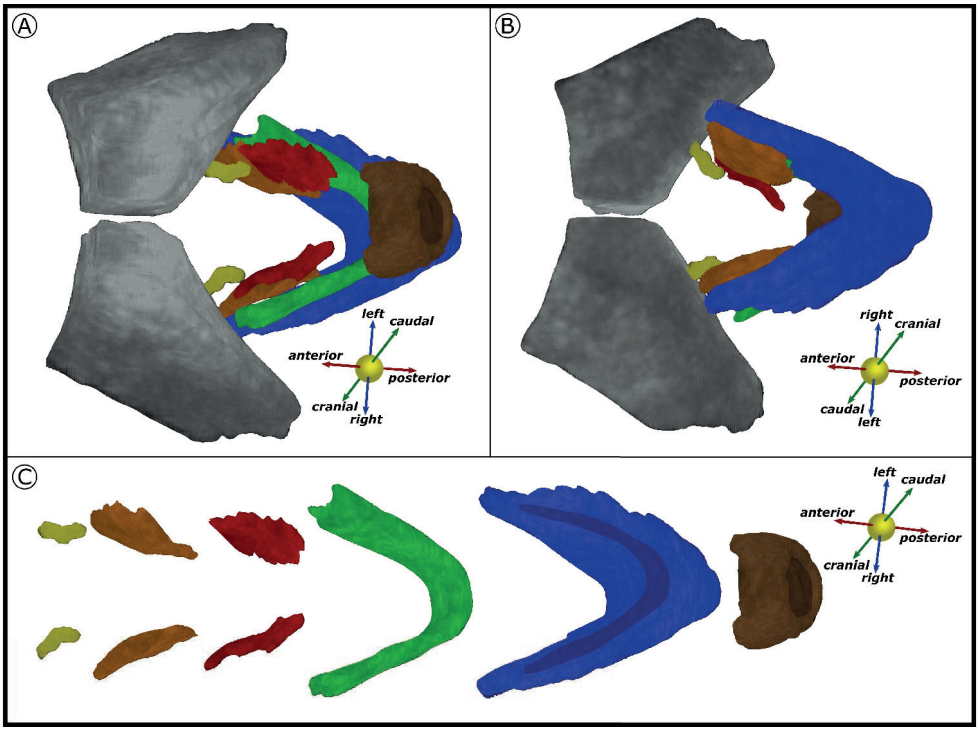

Figure 4. 3D model showing the segmented structures: Pubic bone (PB, grey), external sphincter (ES, brown), puboperineal muscle (PPM, red), puboanal muscle (PAM, orange), pubovaginal muscle (PVM, yellow), puborectal muscle (PRM, green) and iliococcygeal muscle (ICM, blue). "A" shows the view from caudal to cranial; "B" shows the view from cranial to caudal. In "C" the model is disassembled to appreciate the single structures separately.

Figure 5 shows a Box and Whisker plot of the inter- and intraobserver DSI values of the 2D segmentations of 20 patients. All median DSI values of ES, PRM, PAM and ICM were ≥ 0.7. In the case of intra-observer overlap, this was also true for PPM and PVM. In the case of inter-observer overlap, the median DSI values of PPM and PVM were below 0.7.

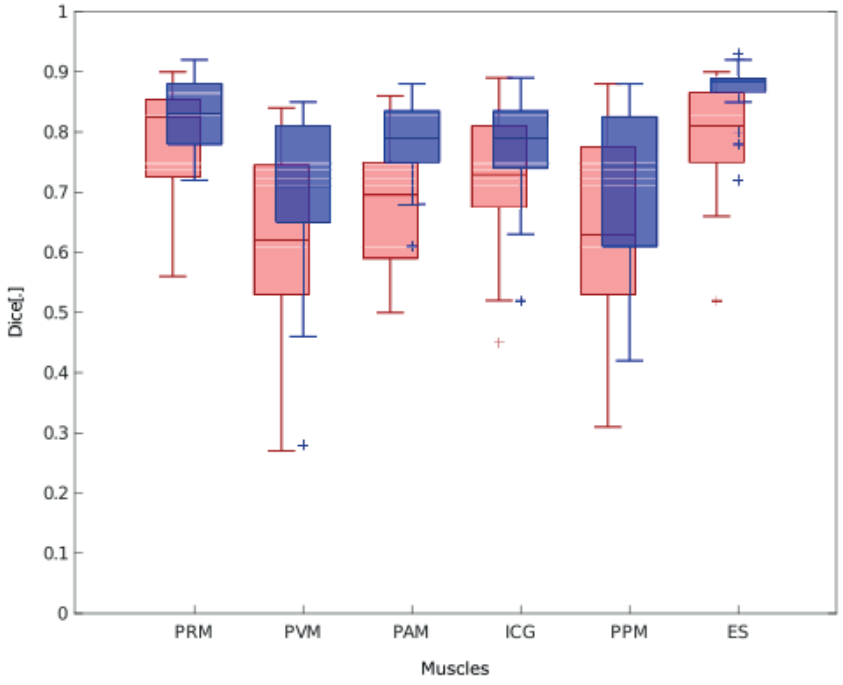

Figure 5. Box-and-whisker plots of Dice Similarity Index for inter-(red) and intraobserver (blue) overlap between segmentations of puborectal (PRM), pubovaginal (PVM), puboanal (PAM), iliococcygeal (ICM) and puboperineal muscle (PPM) and extrernal anal sphincter (ES). Boxes with internal lines represent median and interquartile range (IQR), whiskers are range excluding outliers more than 1.5 IQR from upper and lower quartile, and + are outliers.

Discussion

Our results demonstrate that the separate LAM muscle subdivisions can be identified in 3D TPUS images of vaginally nulliparous women, which has not been reported in literature.

In the literature, a DSI > 0.7 is described as excellent agreement (33,34). However, the DSI is influenced by the shape and size of the segmented structure: small and/or elongated structures are more likely to have a lower DSI because a mismatch of a few pixels has relatively more influence. The DSI values of the PRM, PAM, ICM and ES show good segmentation reproducibility (comparable to previous results on the PRM (35)). The smallest structures (i.e., PVM and PPM) are most of the time less than 5 mm thick. With voxel sizes of around 0.5 mm, a 1-2 voxels mismatch produces already a relatively

large overlap mismatch, which can explain the lower DSI values. The DSI values of PVM and PPM thus indicate that their identification is successful. However, in order to obtain reliable segmentation of these small structures a higher resolution would be needed.

Our study has several strengths. First, the 20 TPUS scans used were all acquired by the same clinician; thus, reducing a potential source of variability. Second, the segmentation protocol we have developed proved effective for all five TPUS scans used for this purpose. Third, to assess the reproducibility of our results, we measure the actual spatial overlap between different segmentations, i.e., a quantitative method, while in previous studies interrater reliability was assessed by evaluating whether a muscle was visible or not (12,13). Using this method, different observers can theoretically agree on the visibility of a muscle, while recognizing two different structures. This would result in 100% agreement when there is no actual agreement. This potential bias is avoided by calculating the actual spatial overlap between different segmentations.

Due to technical limitations, mainly related to resolution, we were unable to segment the most cranial structures of the PF, thus missing the upper border of ICM and PAM. Additionally, we could not segment the most dorsal part of PAM and PPM because of the presence of the perineal body in this area. Therefore, our 3D models may suggest that these muscles stop more ventrally than expected. However, the spatial relations between different LAM subdivisions can be fully appreciated.

Lastly, the same observers performed first and third phase of the study (i.e., LAM subdivisions identification and assessment of segmentations reproducibility). One might thus object that the assessment of the reproducibility could have been biased towards higher scores. However, without prior identification of the structures of interest no reproducibility assessment is possible. In addition, the LAM subdivisions were reproducibly identified also on the TPUS never analyzed before the third phase of the study.

Currently TPUS data are analyzed in 2D, with the most important analysis method being the one developed by Dietz et al. (31). Since TPUS can capture muscle movement in 3D, 2D analysis is a very low dimensional representation of the data. Our study opens the possibility to analyze static TPUS images in 3D. Additionally, having identified and segmented the different LAM subdivisions, TPUS-based biomechanical analyses can be applied on intact LAM. Das et al. (36) used the PRM segmentations from this study and successfully estimated 3D displacement and strain of the PRM, which has not been reported in literature before. These strain and displacement measurements provide a unique measurement of in vivo movement and function of the LAM and its subdivisions. This is the biggest advantage of TPUS over endovaginal ultrasound because it is not possible to capture movement with endovaginal ultrasound. With respect to MRI, dynamic MRI does exist but it is much less available than TPUS. The work of Das et al. (36) demonstrates that our study is an important step in the direction of in vivo 3D biomechanical analysis of the pelvic floor function. This analysis could allow for a reliable quantitative assessment of the pelvic floor function to be used for diagnostic purposes

and for the assessment of functional changes over time (e.g., during treatment).

Considering that the LAM subdivisions of women with normal pelvic organ support have different fiber directions, it was proposed that the functional consequence of LAM injury depends on the region of muscle affected (11). Therefore, the appearance of LAM subdivisions on TPUS collected from vaginally nulliparous women can be used as a reference for studies in vaginally parous patients to identify selective damage to single pelvic floor structures. Shortly after the successful identification of the intact LAM subdivisions on MRI (12), Margulies et al. (37) analyzed 14 MRI scans of women with unilateral LAM defect and were able to identify the damaged portion as pubovisceral muscle. This shows that the ability to discriminate the intact LAM subdivisions allows for the recognition of the damaged LAM subdivisions. The same study, focusing on LAM damage, is to be replicated on TPUS and extended with in vivo muscle strain and displacement measurements. If successful, TPUS-based biomechanical analyses could be then performed to understand the functional consequences of this and other types of damage and, eventually, implement appropriate treatment strategies.

Conclusion

In conclusion, the LAM subdivisions were successfully and reproducibly identified on 3D TPUS data of vaginally nulliparous women. This paves the way for in vivo biomechanical analyses of the LAM which enables a better understanding of its (dys)function.

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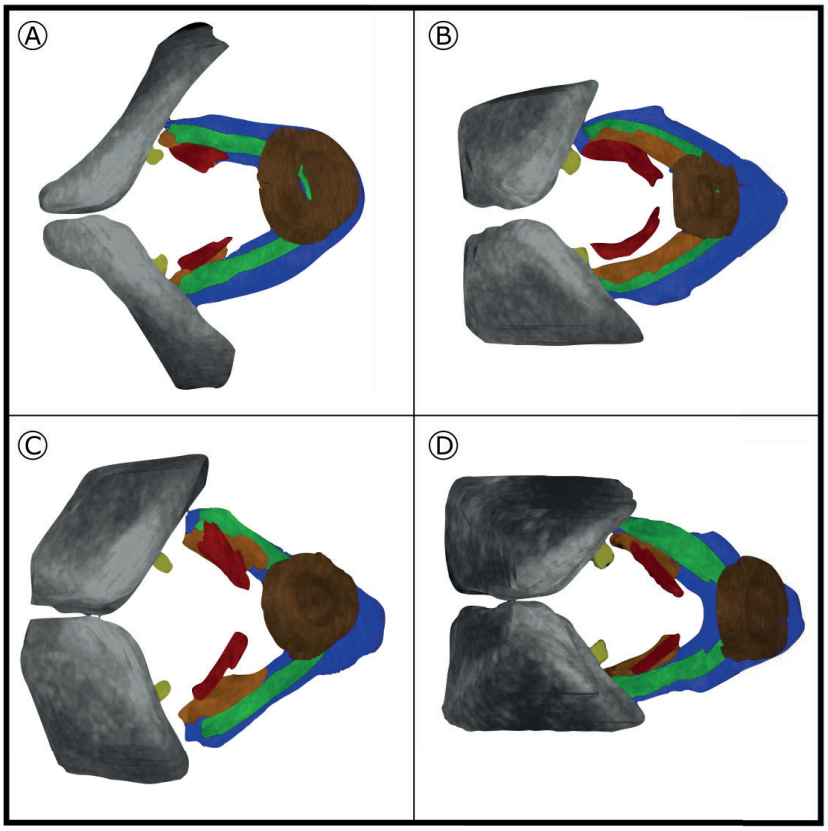
Appendix



Appendix 1. 3D models of the four patients (A-D) not shown in the paper. Pubic bone (PB, grey), external sphincter (ES, brown), puboperineal muscle (PPM, red), puboanal muscle (PAM, orange), pubovaginal muscle (PVM, yellow), puborectal muscle (PRM, green) and iliococcygeal muscle (ICM, blue). As in figure 4A, the view from below

Declarations

Ethics approval and consent to participate
The Medical Research Ethics Committee (MREC) UMC Utrecht exempted the project from approval (reference 18/215), because the Medical Research Involving Human Subject Act (WMO) does not apply, and all women signed a research consent form

Consent for publication
Authors consent to publication

Availability of data and material
Due to privacy regulations the data used in this study is not publicly available. In order to see and discuss the data the authors can be contacted. If needed we can arrange approval to share the data with individual researchers.

Competing interests
Authors declare no conflict of interest

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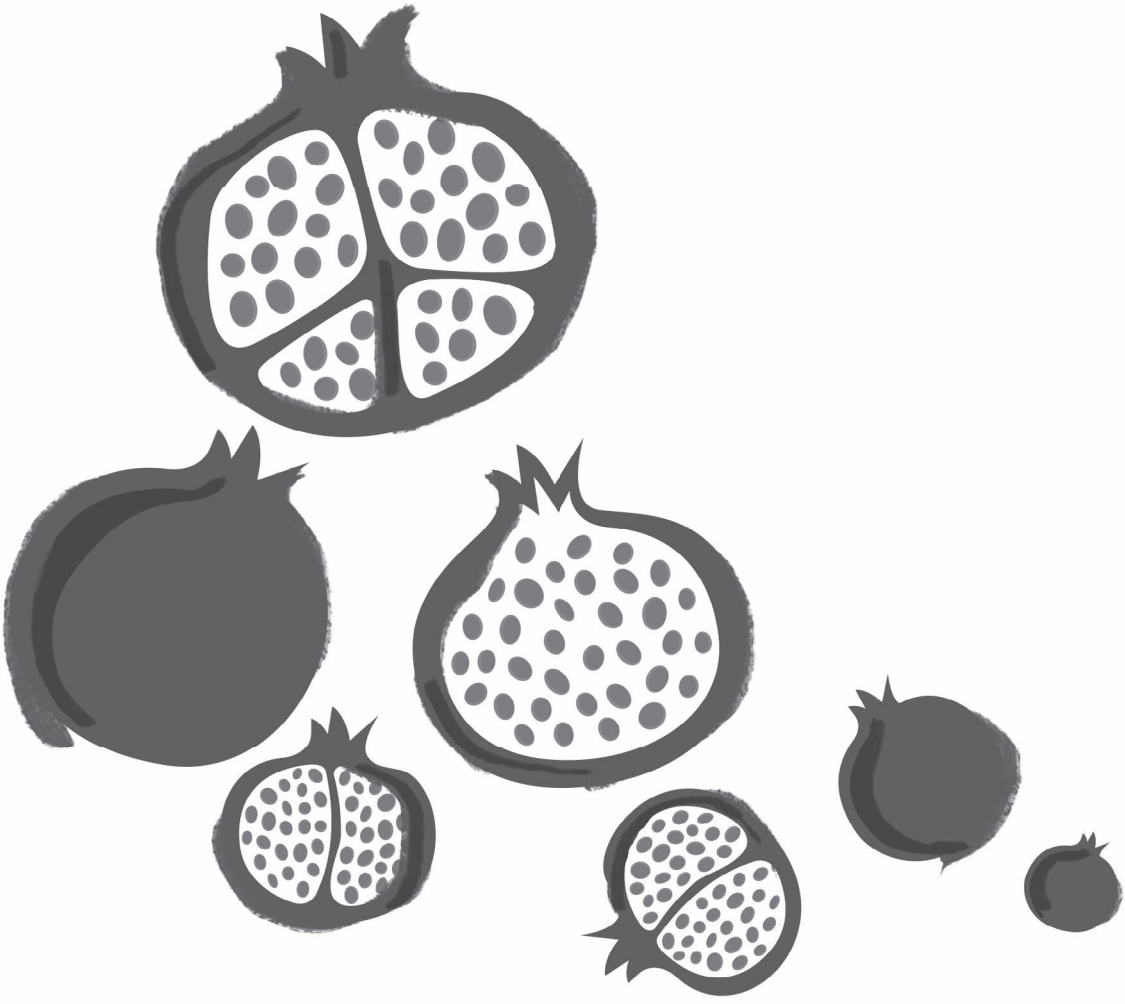
Authors' contributions
C. Manzini - Project development, Data collection, Data analysis and interpretation, Manuscript writing and editing.
F. van den Noort - Project development, Data analysis and interpretation, Manuscript writing and editing, Analysis tool development.
A.T.M. Grob - Data interpretation, Manuscript editing.
M.I.J. Withagen - Data interpretation, Manuscript editing.
C.H. Slump - Data interpretation, Manuscript editing.
C.H. van der Vaart - Project development, Data interpretation, Manuscript editing.



CHAPTER 8

General discussion

The aims of the current thesis were:

1. To clarify which parameters are associated with unsuccessful pessary fitting up to three months follow-up.
2. To test the hypothesis that different reasons for pessary fitting failure are associated with different predictive parameters and to identify which parameters are associated with a specific reason for pessary fitting failure.
3. To assess the added value of transperineal ultrasound (TPUS) in identifying the ring pessary size that properly fit a woman without causing pain/discomfort and without being dislodged or failing to relieve POP symptoms.
4. To assess the functional changes of the puborectalis muscle (PRM) three months after successful pessary fitting.
5. To automatically identify the plane of minimal hiatal dimensions and to automatically segment levator hiatal area (HA) and levator diameters.
6. To identify and describe the separate appearance of levator ani muscle (LAM) subdivisions on 3D TPUS.

Parameters associated with unsuccessful pessary fitting

At first, a systematic review and meta-analysis on the parameters associated with unsuccessful pessary fitting for symptomatic pelvic organ prolapse (POP) up to three months follow-up was conducted (Chapter 2). Since multiple studies had been published with different results [1-23], our aim was to give an overview of the literature and a clarification of the topic. Our meta-analysis shows that younger age, higher body mass index (BMI), pre-menopausal status, de novo stress urinary incontinence (SUI), prior surgery (i.e., hysterectomy, POP surgery, pelvic surgery, or incontinence surgery), solitary predominant posterior compartment POP, presence of colorectal symptoms, shorter total vaginal length (TVL), wide introitus, LAM avulsion and larger levator HA on maximum Valsalva are associated with unsuccessful pessary fitting. BMI is a potentially modifiable factor and should be addressed during counselling for pessary treatment. The association of anatomical parameters with unsuccessful pessary fitting suggests that imaging techniques (e.g., TPUS) could provide more insight into what a proper fit is and, ultimately, be used for developing strategies to increase pessary fitting success rate.

The role of TPUS in pessary fitting

Interestingly, no study included in the systematic review assessed the association of specific reasons for pessary fitting failure (i.e., pessary dislodgment, discomfort/pain, urinary symptoms, and failure to relieve POP symptoms [2]) with different predictive parameters. Only one research group investigated pessary dislodgment and its predictors [3,4], while excluding other reasons for pessary fitting failure from the analysis. Therefore, in Chapter 3 we set out to test the hypothesis that specific reasons for pessary fitting failure are associated with different predictive parameters. Our results confirm this hypothesis: pessary dislodgment is associated with LAM avulsion and a small ring pessary with respect to the levator HA on maximal Valsalva (big Valsalva HARP-ratio),

while failure to relieve POP symptoms is associated with solitary predominant posterior compartment POP.

Pessary dislodgment

Both LAM avulsion and hiatal area to ring pessary ratio (HARP-ratio) can be assessed with TPUS. Therefore, TPUS can help the clinician in estimating the risk of pessary dislodgment of an individual woman and discuss it during counselling for POP treatment. In the case of LAM avulsion, the higher risk of dislodgment should be addressed. However, pessary treatment should be encouraged, considering the higher risk of recurrence after POP surgery associated with LAM avulsion [24]. Since LAM avulsion is not a modifiable factor, Valsalva HARP-ratio is the only parameter that can be manipulated to increase pessary fitting success in the case of LAM avulsion. In Chapter 4, we investigated the added value of TPUS in identifying the right ring pessary size for an individual woman: we showed that the minimal ring pessary size that has a higher chance of staying in place can be estimated based on the Valsalva HARP-ratio. Measuring Valsalva HARP-ratio could allow for a faster selection of the successful size, thus reducing the need of extra visits for pessary refitting and the discomfort due to multiple fitting trials. After the disappointment of one or more unsuccessful trials, some women refuse to undergo an additional one, thus missing the chance of a successful fitting. In these cases, a faster selection of the successful size could increase pessary fitting success rate by reducing the number of unsuccessful trials.

Failure to relieve POP symptoms

Women with solitary predominant posterior compartment POP have a higher risk of unsuccessful fitting due to failure to relieve POP symptoms. Previous literature proved the association of posterior compartment prolapse [25] and higher Colorectal-Anal Distress Inventory-8 scores (which assess colorectal symptoms) [26] with unsuccessful fitting. We showed that the link between posterior compartment POP and unsuccessful fitting is pessary failure to relieve symptoms. In Chapter 4, we observed that unsuccessful trials due to failure to relieve POP symptoms have a bigger HARP-ratio compared to successful trials; hence, it would be interesting in future research to assess the effect of different ring pessary sizes on symptoms of posterior compartment POP.

Pain/discomfort

Some unsuccessful pessary fittings are associated with pain/discomfort and our hypothesis was that pain/discomfort might be due to a big pessary with respect to the levator hiatal dimension. However, in Chapter 3 and Chapter 4 we could not identify any parameter associated with this reason for pessary fitting failure. It might be that the group that was unsuccessful because of pain/discomfort was too small in our study to allow for the detection of a statistically significant association. Another possible explanation is that parameters that might be relevant for pain/discomfort (i.e., vaginal atrophy, fornix posterior width, and pessary dimension with respect to the vaginal space) were not assessed in our study. Vaginal atrophy can only be assessed clinically and can

be quantified with a specific index [27]. However, this index is not used in the clinical practice. Fornix posterior width is clinically assessed during pessary fitting but it is difficult to objectively quantify. Imaging techniques might be used for this purpose. However, the resolution of TPUS becomes very poor at the level of the fornix posterior, which is generally located 10 cm away from the transducer. Even if the resolution was higher, an additional limitation is that the vaginal walls are elastic. Therefore, simply acquiring an image of this region without exerting tension would not provide enough information for an objective quantification of fornix posterior width. This also limits the estimation of the maximum pessary size a woman can be fitted with (without causing complications such as pain/discomfort or vaginal bleeding due to ulceration), based on a quantitative assessment of the vaginal space.

TPUS and pessary use

Beyond fitting process, long-term pessary use has to be successful too for vaginal pessaries to be a valuable treatment option for symptomatic POP. Lone and co-workers [28] reported that 86.1% of the women who are successful at four weeks after pessary insertion, are still successful at five year follow-up. In our meta-analysis we also observed that the success rate remains substantially stable after four weeks. Therefore, planning at four weeks the follow-up in which pessary fitting success is assessed would ensure the vast majority of the unsuccessful fittings to be identified. In addition, the majority of the women who are successful at four weeks would have a long-term pessary use.

After pessary fitting success assessment, the following visit for pessary management is generally scheduled at three months. Considering that vaginal pessaries, by supporting POP, might relieve the LAM from the abnormal pressure exerted by POP, our hypothesis was that LAM function changes during pessary use. Around three months after successful pessary fitting, we observed an increase in HA at rest in women without complete avulsion and an increase in displacement in contraction (i.e., relative difference between HA at rest and HA on maximal contraction). These results suggest that puborectalis muscle (PRM) function (the PRM being the LAM subdivision surrounding the levator hiatus) changes during pessary treatment. There are two possible explanations of these results. Women with POP try to relieve their POP symptoms by contracting the PRM. Vaginal pessaries, by supporting POP, could reduce the need for this continuous contraction, allowing the PRM to relax. Alternatively, a progressive relaxation of the resting tone occurs in women with POP undergoing pessary treatment, which can be clinically experienced by the need of a bigger pessary size after some time of pessary use.

The results presented in Chapter 3 and 4 suggest that the support of the LAM is necessary to hold ring pessaries comfortably in place. Therefore, a change of PRM function during pessary treatment might influence the success of ring pessaries use over time.

New developments

- Automatic identification of the plane of minimal hiatal dimensions and automatic segmentation of levator HA.
  In Chapter 6, we showed that automatic identification of the plane of minimal hiatal dimensions and automatic segmentation of levator HA and levator diameters are feasible. These results are very promising for the future of TPUS because of the following potential benefits. First, TPUS training would become easier: the clinician would just need to learn how to perform the TPUS, while the analyses would be performed automatically. Second, the analyses performed automatically are much faster. Third, automatic analyses reduce the interobserver variability of the measurements. In The Netherlands TPUS is mostly used in tertiary centres and very often in research settings. The three benefits mentioned above (particularly the first two) could make the implementation of TPUS in the clinical setting easier, thus making TPUS more widespread.
- The appearance of LAM subdivisions on 3D TPUS.
  In Chapter 7, we showed that the separate LAM muscle subdivisions can be identified in 3D TPUS images of vaginally nulliparous women. This result is an important step in the direction of in vivo 3D biomechanical analysis, which could allow for a reliable quantitative assessment of the pelvic floor function to be used for diagnostic purposes and for the assessment of functional changes over time (e.g., during treatment).

Strengths and limitations

Our original studies have several strengths. First, a prospective design was used which reduces the risk of selection bias. Second, all scans and TPUS assessments were performed by the same clinician, thus reducing a potential source of variability. Third, the assessor was blinded to all clinical data and intra-observer variability is not expected to introduce a bias in levator HA measurements, as their repeatability has been proven very high [29,30]. However, some limitations have to be acknowledged. The analyses performed in our studies were new: no previous published study assessed the association between specific reasons for pessary fitting failure and different predictive parameters; the parameter HARP-ratio has not been reported in the literature before; change in PRM function during pessary use has never been assessed before with TPUS. Therefore, a sample size could not be calculated and ours should be considered exploratory studies, which still need external validation. In addition, the generalizability of our findings to the first line care cannot be guaranteed, considering that our data were collected in a urogynecological center, where primary care is not provided. Our results suggest that TPUS can be of added value in pessary fitting process. However, the availability of clinicians with the necessary expertise is still quite limited, as well as the availability of the required 3D/4D ultrasound machines. Therefore, a widespread clinical applicability of TPUS in pessary fitting process is unlikely in the near future.

Future perspectives

We think that personalized 3D printing is the future of pessary design, especially for those women who cannot be fitted with the commercial pessaries currently available. In this thesis, we have shown that TPUS enables the identification of anatomical characteristics that reduce the probability of pessary fitting success. This can be considered a first step in the direction of personalized 3D printed pessaries that better suit the anatomical characteristics of an individual woman. As an example, we already mentioned that women with LAM avulsion have a higher risk of pessary dislodgment. These women might benefit from a personalized pessary (e.g., an asymmetrical pessary in the case of unilateral avulsion). Research on personalized 3D printing for medical use is attracting increasing interest, and the first clinical applications are already available [31-33]. An example is personalized 3D-printed implants in the field of orthopaedics. The process starts with a CT scan and the implant is designed to fill the bone defect and achieve adequate stability and fixation [32]. A fundamental difference between 3D-printed implant in orthopaedics and 3D-printed pessaries in urogynaecology is that the bones are rigid, while the vagina is an elastic structure and at rest the vaginal walls are in apposition. Therefore, an image of the vagina acquired at rest does not seem to provide the information needed to design a personalized pessary that suits at best the anatomy of the patient. This is one of the limitations that should be overcome to make personalized 3D pessary printing clinically available, which implies that their clinical availability cannot be expected in the near future. However, we think that personalized 3D printing is a very promising technology that will be applied to the future of pessaries design.

Besides (or together with) personalized 3D pessary printing, future research with TPUS should further focus on3D biomechanical analyses of the LAM. In Chapter 7, we have shown that the 3D segmentation of the LAM subdivisions is feasible, which, as aforementioned, is an important step in the direction of 3D biomechanical analyses. In Chapter 5, we observed in 2D that the PRM function changes some months after pessary use. Long-term studies should assess PRM function changes during pessary treatment and 3D analyses should be applied in order to have a better dimensional representation of the muscle. Strain analysis is an example of functional 3D analysis, which enables the measurement of active deformation of tissues [35]. Future studies on strain analysis of the pelvic floor should assess its diagnostic value (e.g., for the diagnosis of LAM avulsion) and its accuracy in detecting functional changes over time (e.g., during pessary treatment or pelvic floor muscle treatment). If proven successful, strain analysis could allow for a reliable quantitative assessment of the pelvic floor function, thus providing physicians with a valuable tool to be applied in their clinical practice.

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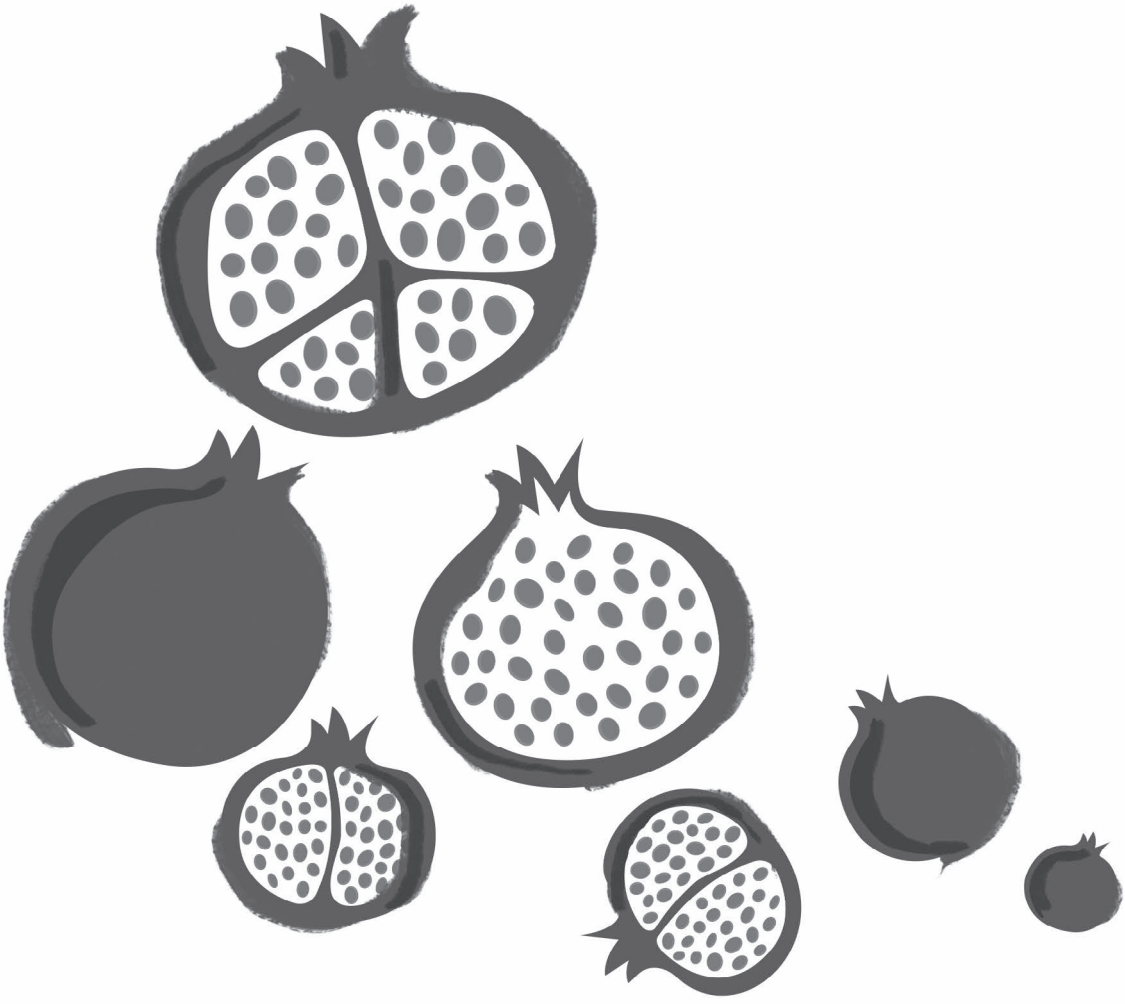


CHAPTER 9

Summary
Nederlandse samenvatting

Summary

In this thesis we assess the added value of transperineal ultrasound (TPUS) in pessary treatment for pelvic organ prolapse (POP) and set out to improve the anatomical and functional assessment of the levator ani muscle (LAM) using TPUS.

In Chapter 1, we report prevalence, risk factors and clinical manifestations of POP. In addition, we describe how POP is assessed and treated with focus on pessary treatment. Furthermore, LAM anatomy and the technique for LAM avulsion and levator hiatal area (HA) assessment with TPUS are described.

In Chapter 2, we present a systematic review and meta-analysis of the predictive parameters for unsuccessful pessary fitting for POP up to three months follow-up. We observe that younger age, higher BMI, pre-menopausal status, de novo stress urinary incontinence, prior surgery (i.e., hysterectomy, POP surgery, pelvic surgery, or incontinence surgery), solitary predominant posterior compartment POP, presence of colorectal symptoms, shorter total vaginal length, wide introitus, LAM avulsion and larger HA on maximum Valsalva are associated with unsuccessful pessary fitting. Furthermore, we conclude that more research is needed to investigate the association of anatomical parameters with specific reasons for unsuccessful pessary fitting and that the added value of TPUS in pessary fitting process has to be further investigated.

In Chapter 3, we assess the association of clinical, demographical and TPUS parameters with specific reasons for unsuccessful pessary fitting. We observe that complete LAM avulsion and a small ring pessary with respect to the levator HA in Valsalva are predictors of pessary dislodgment, while solitary predominant posterior compartment POP is a predictor of failure to relieve POP symptoms.

In Chapter 4, TPUS is used to predict the right ring pessary size based on the levator HA. We conclude that a ring pessary size that produces a Valsalva HARP-ratio (i.e., levator HA in Valsalva divided by the ring pessary size) > 5.00 has a higher risk of dislodgment/failure to relieve POP symptoms.

In Chapter 5, we assess the functional changes of the puborectalis muscle (PRM) three months after successful pessary fitting. In the entire sample the relative difference between levator HA at rest and in contraction (i.e., displacement in contraction) increases by 2.1% (p=0.017). In women without complete LAM avulsion levator HA at rest increases by 4.1% (p=0.016) and displacement in contraction increases by 2.7% (p=0.016). We conclude that PRM function changes three months after successful pessary fitting and that these changes occur mainly in women without complete avulsion.

In Chapter 6, we use deep learning to automatically identify the plane of minimal hiatal dimensions and automatically segment levator HA and levator diameters with interclass correlation coefficients (ICC) of 0.94 (0.87-0.97), 0.92 (0.78-0.97), and 0.82 (0.66-0.91) for levator HA, anteroposterior diameter and coronal diameter, respectively.

In Chapter 7, we identify and describe the appearance of the LAM subdivisions on TPUS, which has not been reported in literature before. This work is the first step in the direction of static analyses of the LAM in 3D and of in vivo 3D biomechanical analyses of LAM function.

In Chapter 8, we discuss our main results and their clinical implication. Lastly, we report strength and limitations of our original studies and delineate future applications of TPUS to pessary treatment.

Nederlandse samenvatting

In dit proefschrift ligt de focus op de toegevoegde waarde van transperineal ultrasound (TPUS) bij pessariumtherapie voor prolaps (POP). Bovendien onderzoeken wij methodes om de anatomische en functionele beoordeling van de levator ani spier (LAM) door middel van TPUS te verbeteren.

In hoofdstuk 1 rapporteren wij prevalentie, risicofactoren en klinische manifestatie van POP. Bovendien, beschrijven wij hoe POP beoordeeld en behandeld wordt met focus op pessariumtherapie. Wij beschrijven verder de anatomie van de levator ani muscle (LAM) en de techniek waarmee LAM avulsie en levator hiatal area (HA) beoordeeld worden door middel van TPUS.

Middels een systematic review en meta-analyse worden de voorspellende parameters voor een niet succesvol pessarium pas proces bij verzakking beschreven in hoofdstuk 2. Wij stellen vast dat jongere leeftijd, hogere BMI, premenopauzale status, de novo stress urine-incontinentie, chirurgie in voorgeschiedenis (i.e., hysterectomie, POP chirurgie, pelvische chirurgie, of incontinentie chirurgie), het hoogste POP stadium in het achterste compartiment, colorectale klachten, kortere totale vaginale lengte, wijde introïtus, LAM avulsie en grotere HA op maximale Valsava geassocieerd zijn met niet succesvol pessarium pas proces. Bovendien, concluderen wij dat meer onderzoek gedaan moet worden naar de associatie tussen anatomische parameters en specifieke redenen van niet succesvol pessarium pas proces en dat de toegevoegde waarde van TPUS in het pessarium pas proces verder onderzocht moet worden.

In hoofdstuk 3 bepalen we de associatie van klinische, demografische en TPUS-parameters met verschillende redenen voor niet succesvol pessarium pas proces. Complete LAM avulsie en een klein ring pessarium ten opzichte van de levator HA in Valsalva zijn predictoren voor het niet op de juiste plaats blijven zitten van het pessarium. Het hebben van voornamelijk een achterste compartiment verzakking is een predictor voor een niet succesvol pessarium pas proces op basis van het niet verlichten van de verzakkingssymptomen.

In hoofdstuk 4 wordt TPUS gebruikt om de juiste maat ring pessarium te voorspellen op basis van de levator HA. Wij concluderen dat een ring pessarium met een Valsalva HARP-ratio (i.e., levator HA in Valsalva gedeeld door de maat van het ring pessarium) > 5.00, een hoger risico op falen geeft (op basis van niet goed blijven zitten van het pessarium of persisteren van de symptomen).

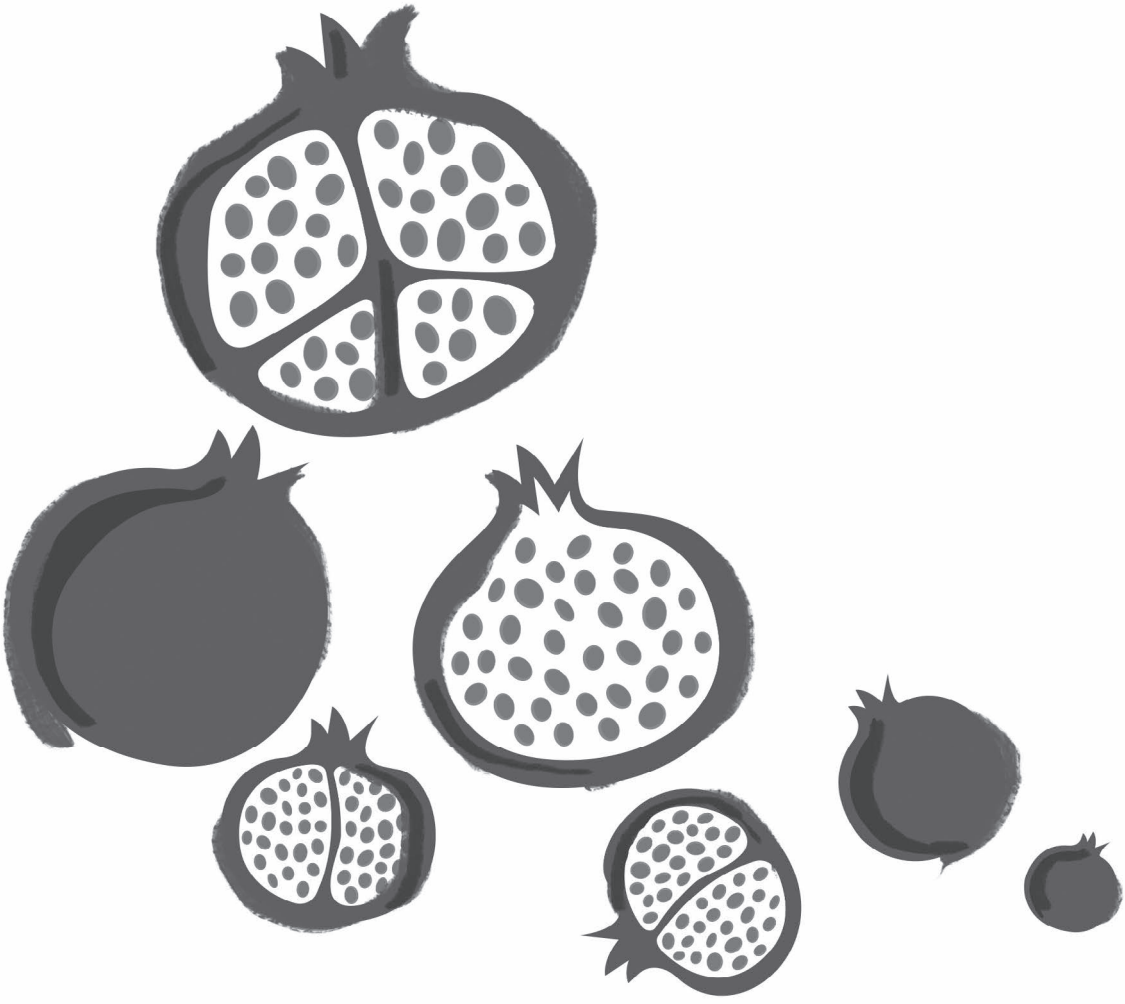
In hoofdstuk 5 bepalen wij de functionele verandering van de puborectalis spier (PRM) drie maanden na succesvol pessarium pas proces. In de hele groep neemt het relatieve verschil tussen levator HA is rust en in contractie (i.e., verplaatsing tijdens contractie) toe met 2.1% (p=0.017). In de groep vrouwen zonder complete LAM avulsie neemt de levator HA in rust toe met 4.1% (p=0.016) en de verplaatsing tijdens contractie neemt toe met

2.7% (p=0.016). Wij concluderen dat de functie van de PRM drie maanden na succesvol pessarium pas proces verandert en dat deze verandering voornamelijk optreedt bij vrouwen zonder complete LAM avulsie.

In hoofdstuk 6 gebruiken wij deep learning om automatisch het vlak van minimale hiatale dimensie te identificeren en om automatisch levator HA en levator diameters te segmenteren met interclass correlation coefficients (ICC) van 0.94 (0.87-0.97), 0.92 (0.78-0.97) en 0.82 (0.66-0.91) voor levator HA, anteroposteriore diameter en coronale diameter.

In hoofdstuk 7 beschrijven wij hoe de LAM subdivisies eruitzien op TPUS, wat in de literatuur nog niet beschreven was. Dit werk is de eerste stap in de richting van statische analyses van de LAM in 3D en van in vivo biomechanische analyses van de functie van de LAM.

In hoofdstuk 8 bespreken wij onze belangrijkste resultaten en hun klinische implicaties. Als laatste, rapporteren wij de sterktes en zwaktes van onze originele studies en schetsen toekomstige applicaties van TPUS op pessariumtherapie.



CHAPTER 10

Review committee
List of publications
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Acknowledgments

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List of publications

C. Manzini, T. Friedman, F. Turel, H.P. Dietz. Vaginal laxity: which measure of levator ani distensibility is most predictive? Ultrasound Obstet Gynecol. 2020 May;55(5):683-687. doi: 10.1002/uog.21873.

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About the author

Claudia Manzini was born on June 29th 1989 in Monza (Italy) and grew up with two sisters and one brother. After attending high school at Liceo Classico B. Zucchi in Monza, she was admitted to medical school at Vita-Salute San Raffaele University, Milan. During her studies Claudia discovered her interest for Obstetrics and Gynaecology and Psychiatry. She did her master thesis project at the Mood Disorder Unit of the San Raffaele Turro Hospital, Milan.

In 2015, after having obtained her medical school degree, a mix of love and personal ambition brought her to Utrecht, the Netherlands. She learned Dutch and after a few months she followed a stage at the Department of Obstetrics and Gynecology of the Meander Medical Centre in Amersfoort, through which she developed her passion for this field. Between June 2016 and September 2017, Claudia worked as a clinical resident at the Groene Hart Ziekenhuis in Gouda. This experience made her realize how much she enjoys working independently, as well as together with a great team (professionally and personally).

In October 2017 Claudia started her PhD at the Department of Gynecology of the University Medical Center Utrecht under the supervision of Prof. dr van der Vaart, Dr. M.I.J. Withagen and (after a few years) Dr. A.T.M. Grob. Between November and December 2017, she was visiting scholar at the Nepean Clinical School and Hospital (NSW, Australia) under the supervision of Prof. Dietz. There, she was trained in pelvic floor ultrasonography and did a research project which led to her first publication. During her PhD Claudia discovered her passion for clinical research. She particularly enjoyed the creativity that research allows (e.g., thinking about a new research question and how to answer it) and the excitement that interesting results can produce. In addition, she further developed her ultrasound skills, hence becoming one of the expert of pelvic floor ultrasonography at the Bergman Clinics Vrouw Hilversum.

After having dedicated four years primarily to research, Claudia worked as a clinical resident at the Department of Obstetrics and Gynecology of the Meander Medical Centre in Amersfoort until July 2022, when she started working at the Diakonessenhuis in Utrecht. Her ambition is to pursue a career in this field combining research and clinical practice.

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"Passerà questa pioggia sottile come passa il dolore
....

Ma se ti svegli e hai ancora paura ridammi la mano" (Fabrizio de André, Hotel Supramonte).
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In questo si attua il gesto simbolico di riconoscimento del figlio da parte del *padre* di cui parla Massimo Recalcati: "È solo il Nome del Padre che fonda la possibilità di ricevere un nome, di essere nominato in quanto figlio. La paternità implica sempre un atto di parola, un atto di responsabilità, l'atto di una adozione simbolica del figlio. Non esiste paternità naturale, perché la paternità è sempre un evento di linguaggio". Questo tuo interesse ti ha permesso di vivere tramite i tuoi figli tante vite diverse, tutte con le proprie specificità, i propri momenti difficili e i tanti momenti belli. Grazie per il sostegno che mi hai sempre dato. Grazie perché so che sei fiero di me e questo mi ha dato la fiducia necessaria per realizzare tutto ciò che ritengo importante nella mia vita.

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