Int Urogynecol J (2018) 29:13–21
DOI 10.1007/s00192-017-3475-4

REVIEW ARTICLE

Risk factors for prolapse recurrence: systematic review and meta-analysis

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Received: 23 May 2017 / Accepted: 29 August 2017 / Published online: 18 September 2017

Abstract
Introduction and hypothesis Female pelvic organ prolapse (POP) is a common condition, with a lifetime risk for surgery of 10–20%. Prolapse procedures are known to have a high reoperation rate. It is assumed that etiological factors for POP may also be risk factors for POP recurrence after surgery. There are few reviews available evaluating risk factors for prolapse and recurrence or recently updated meta-analysis on this topic. Our aim was to perform a systematic review and quantitative meta-analysis to determine risk factors for prolapse recurrence after reconstructive surgery.
Methods Four electronic databases (MEDLINE, PubMed, EMBASE, and Google Scholar) were searched between 1995 and 1 January 2017, with no language restrictions.
Results Twenty-five studies met inclusion criteria for a total of 5082 patients with an average recurrence rate of 36%. Variables on which a meta-analysis could be performed were body mass index (BMI) (n = 12), age (n = 11), preoperative stage (n = 9), levator avulsion (n = 8), parity (n = 8), constipation/straining (n = 6), number of compartments involved (n = 4), prior hysterectomy (n = 4), familiy history (n = 3), and several other predictors evaluated in only three studies. The following meta- analyses identified significant predictors: levator avulsion [odds ratio (OR) 2.76, $P < 0.01$], preoperative stage 3–4 (OR 2.11, $P < 0.001$), family history (OR 1.84, P = 0.006), and hiatal area (OR 1.06/cm^2, P = 0.003).
Conclusions Levator avulsion, prolapse stage, and family history are significant risk factors for prolapse recurrence.

Keywords Avulsion · Meta-analysis · Pelvic organ prolapse · Recurrence · Risk factors · Surgery

Introduction

Female pelvic organ prolapse (POP) is a common condition with a multifactorial etiology [1] that varies between patients [2]. It is associated with a significant impairment in overall quality of life (QoL) [3]. The lifetime risk for prolapse surgery has been documented as being 10–20% [4, 5]. Reconstructive surgery is known to have a high reoperation rate (8.5–58%) [4, 6–8]. To date, little is known about factors associated with surgical failure; however, it is assumed that factors that play a role in POP etiology and pathogenesis may also be risk factors for recurrence [9–14]. It is clearly important to identify risk factors for recurrence to provide preoperative consultation and realistic patient expectations after tailoring their most appropriate treatment methodology: conservative or surgical. This is also importat for clinical research, as novel treatment approaches should first be tested in women likely to fail conventional treatment, limiting certain, more invasive, treatment approaches to those at high risk of recurrence.

It is assumed that POP recurrence may be associated with a combination of predisposing, inciting, and intervening factors, but to date, it has not been possible to weigh the importance of risk factors reported in the literature [9]. Several systematic reviews evaluate risk factors for prolapse and recurrence [7, 10, 15–18]; however, we found no recent meta-analysis on this issue.

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Methods

Study protocol

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [19] and searched MEDLINE, PubMed, Google Scholar, and EMBASE to 1 January 2017 to identify relevant articles. Our search items included Pelvic Organ Prolapse OR Female pelvic organ prolapse OR genital prolapse OR Urogenital prolapse OR Cystocele OR Bladder Prolapse AND Recurrence OR Relapse OR Reoperation AND Risk factors OR predictors OR Epidemiology. The reference lists of relevant articles were searched for appropriate studies. No language restrictions were used, and a search for unpublished literature was performed.

Study selection

We selected studies that met the following criteria: risk factors for recurrence of prolapse; (risk-point estimate reported as odds ratio (OR) or data presented such that an OR could be calculated; 95% confidence interval (CI) or data presented such that the CI could be calculated; (internal comparison when calculating risk estimate.

Data extraction

The data extraction was performed using a standardized data extraction form with information on publication year, study design, number of cases, number of controls, total sample size, temporal direction, population type, country, continent, economic development, case–control matching, mean age, number of adjusted variables, risk estimates or data used to calculate risk estimates, and CIs or data used to calculate CIs. Study quality was not assessed. Several authors were contacted for missing data. Adjusted ratios were extracted in preference to nonadjusted ratios; however, where adjusted ratios were not provided, unadjusted ORs and CIs were calculated. Where more than one adjusted ratio was reported, we chose the ratio with the highest number of adjusted variables. Where multiple risk estimates were available in the same study, for example due to the use of different comparator groups, they were included as separate risk estimates.

Statistical analysis

Pooled ORs and 95% CIs were calculated for the effect of body mass index (BMI), age, preoperative prolapse stage, levator avulsion, parity, constipation/ obstructed defecation, number of involved compartments, prior hysterectomy, and family history of prolapse on the risk of prolapse recurrence using a random effects model [20]. We tested heterogeneity with Cochran's Q statistic, with $P < 0.10$ indicating heterogeneity, and quantified the degree of heterogeneity using the I^2 statistic, which represents the percentage of total heterogeneity variability across studies. I^2 values of 25, 50, and 75% corresponded to low, moderate, and high degrees of heterogeneity, respectively [21]. We quantified publication bias using Egger's regression model [22], with the effect of bias assessed using the fail-safe number method. The fail-safe number was the number of missed studies necessary to nullify our observed results to statistical nonsignificance at the $p < 0.05$ level. Publication bias is generally regarded as a concern if the fail-safe number is N $5n + 10$, with n being the number of studies in the meta-analysis [23]. All analyses were performed with Comprehensive Meta-analysis, version 3.0 (Biostat, Englewood, NJ , USA).

Results

From 3548 citations screened by our search, we identified 25 studies that met inclusion criteria (Fig. 1). Table 1 shows selected characteristics of these studies, with 5082 patients and an average recurrence rate of 36%. Seven studies were conducted in Europe, 12 in the USA, one in Asia, and five in Australia. Cited and retrieved categories were publication year, study type, continent, number of patients included, recurrent percentage, follow-up period, definition of prolapse recurrence, and inclusion criteria for each study, as different studies used different definitions for recurrence: e.g., need for reoperation [even for stress urinary incontinence (SUI) after prolapse surgery], stage ≥ 2 prolapse, Bp > 0, etc (Table 1). Evaluated risk factors—either provided or calculated—were BMI (12 studies), age (11 studies), preoperative stage (9

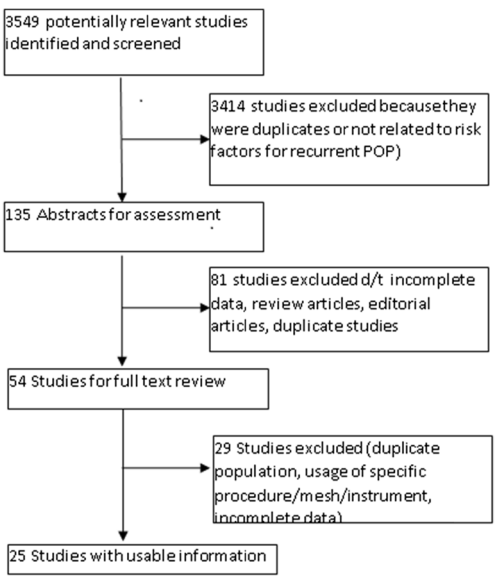

Fig. 1 Study selection flowchart

Table 1 Studies in this systematic review and meta-analysis, and factors evaluated for prolapse recurrence

Author	Publication Year	Study type	Continent	Total number	%Recurrence	f/u years	Definition of recurrence	Population (women who…)	Type of past surgeries	BMI
K Kenton [24]	1999	Retrospective case control	USA	181	43	N/A	> 1 operation	Underwent surgery for POP	1,2,4,5,6,7,8,9,10	
R P Goldberg [25]	2001	Prospective cohort	USA	143	34	1	Stage 2 POP-Q	Were planning to undergo reconstructive surgery who had POP-Q > 1.	3,4,5,6,7,9,12	
Clark AL [26]	2003	Prospective cohort	USA	376	30	5	> 1 operation	Underwent surgery for POP	1,2,4,5,6,7,9, 10,11, 12	†
G Tegerstedt [27]	2004	Retrospective cohort	Europe	128	44	11	Stage 2 POP-Q	Underwent surgery for POP	3,4,5,6,8	†
J L Whiteside [11]	2004	Prospective cohort	USA	176	58	1	Stage 2 POP-Q	Underwent surgery for POP/ui	3,4,5,6,7,9,10,12	
B Vakili [28]	2005	Retrospective cohort	USA	292	35	0.42	Stage > 0 POP-Q	Underwent surgery for POP	3,4,5,7,8,9,10, 11,12	
I Diez-Itza [13]	2007	Retrospective cohort	Europe	134	31	5	Stage 2 POP-Q	Underwent surgery for POP	3,4,5	
S Salvatore [12]	2008	Prospective cohort	Europe	360	10	2.2	Stage 2 POP-Q of the same compartment	Were planning to undergo reconstructive surgery who had POP-Q > 1.	3,4,5	†
M Fialkow [29]	2008	Retrospective cohort	USA	142	25	10	Grade 1 Oslen's classification	Underwent surgery for POP	3,4,5,6,7,8,13	†
M A Denman [8]	2008	Prospective cohort	USA	374	17	10	> 1 operation	Underwent surgery for POP/ui	10,12, 14	†
M J Jeon [14]	2008	Retrospective cohort	Asia	212	17	2	Stage 2 POP-Q	Underwent surgery for POP	3,4,5,7,8,9,10,12	
HP Dietz [30]	2010	Retrospective cohort	Australia	83	40	4.5	Stage 2 POP-Q	Underwent surgery for POP (Ant.)	3,4,5, 12	
A N Model [31]	2010	Retrospective	Australia	727	51	N/A	Stage 2 POP-Q	Represented with pelvic floor dysfunction	3,4,10, 14	
Morgan [32]	2011	Retrospective cohort	USA	83	N/A	0.12	Stage 2 POP-Q	Underwent surgery for POP and returned for f/u	3,4,5,8,9,12	
M Weemhoff [33]	2012	Prospective cohort	Europe	156	51	2	Stage 2 POP-Q	Underwent surgery for POP	3,4,5,7	†
V Wong [34]	2013	Retrospective cohort	Australia	209	33	2.2	Stage 2 POP-Q	Underwent surgery for POP	11	
Kawasaki [35]	2013	Retrospective cohort	USA	282	15	0.17	N/A	Underwent surgery for POP	Only 4	†
A L Edenfield [36]	2013	Retrospective cohort	USA	219	25	1.17	Stage 2 POP-Q	Underwent uterosacral ligament suspension	7,4,5, 15	†

Table 1 (continued)

Author	Publication Year	Study type	Continent	Total number	%Recurrence	f/u years	Definition of recurrence	Population (women who…)	Type of past surgeries	BMI
E C Crosby [37]	2014	Prospective cohort	USA	42	N/A	6.6	Stage 2 POP-Q	Were planning to undergo reconstructive surgery for the first time	3,4,5,7,8	
Rodrigo [38]	2014	Retrospective cohort	Australia	334	42	2.5	Stage 2 POP-Q ba>/= − 1	Underwent surgery for POP stage 2 and above and returned for f/u in 4 clinical audits	4,11, 3,15	†
TFM Vergeldt [39]	2015	Prospective cohort	Europe	139	55	1	Stage 2 POP-Q	Were planning to undergo anterior colporrhaphy	4,14	†
Vergeldt [40]	2016	Combined (prospective cohorts)	Europe	287	52	1 or 2	Stage 2 POP-Q	Combined Weemhoff 2012 & Vergeldt 2015	4+/− others no mesh	
SSA Jalil [41]	2016	Retrospective cohort	Australia	207	46	1.3	Stage 2 POP-Q	Underwent surgery for POP and had f/u	3,4,5,7,11,12	
C Rappa [42]	2016	Retrospective cohort	Europe	360	20	> 0.5	Stage 2 POP-Q	Underwent uterosacral ligament suspension	3 + 7, 4,5,15	†
L Turner [43]	2016	Retrospective cohort	USA	126	33	1	Stage 2 POP-Q	Underwent lap/robotic sacrocolpopex	8,3,12	†

Author	Age	Stage preop	Levator avulsion	Parity	Obst. defecation	No of comp	Hysterectomy	Family hystory	Hiatal area
K Kenton [24]					†				
R P Goldberg [25]									
Clark AL [26]	†	†		†					
G Tegerstedt [27]	†	†			†				
J L Whiteside [11]	†	†				†	†		
B Vakili [28]									
I Diez-Itza [13]	†	†		†	†			†	
S Salvatore [12]		†			†		†		
M Fialkow [29]	†	†		†		†			
M A Denman [8]	†			†		†	†		
M J Jeon [14]	†	†		†	†			†	
HP Dietz [30]			†						
A N Model [31]			†						
Morgan [32]		†	†						

Table 1 (continued)

Author	Age	Stage preop	Levator avulsion	Parity	Obst. defecation	No of comp	Hysterectomy	Family hystory	Hiatal area
M Weemhoff [33]	†	†	†	†	†	†		†	
V Wong [34]			†						
Kawasaki [35]									
A L Edenfield [36]									
E C Crosby [37]			†						
Rodrigo [38]	†		†				†		†
TFM Vergeldt [39]	†	†	†	†					†
Vergeldt [40]		†	†			†			†
SSA Jalil [41]			†						
C Rappa [42]									
L Turner [43]	†	†		†					

POP pelvic organ prolapse, *POP-Q* Pelvic Organ Prolapse Quantification System, *N/A* not available, *USI* urinary stress incontinence

[1] Hysterectomy

[2] Hysterectomy for prolapse

[3] Any hysterectomy (including total abdominal hysterectomy; laparoscopic assisted vaginal hysterectomy/Manchester

[4] Anterior repair

[5] Posterior repair

[6] Enterocele repair

[7] Uterosacral/sacrospinous ligament suspension

[8] Sacrocolpopexy

[9] Retropubic urethropexy

[10] Needle suspension/colposuspension

[11] Anterior repair with mesh (Perigee, Ant Elevate, Uphold, Prolift)

[12] Suburethral sling

[13] Colpocleisis

[14] Any POP surgery

[15] Any USI surgery

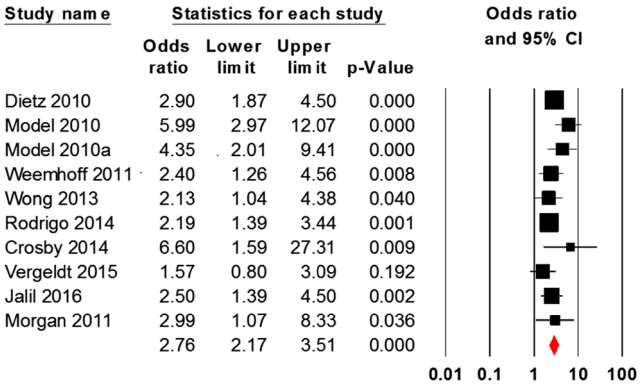

Fig. 2 Meta-analysis of association between levator muscle avulsion and pelvic organ prolapse (POP) recurrence. Test for heterogeneity $I^2 = 24.96$, $P = 0.21$. Odds ratio estimates with the corresponding 95% confidence intervals

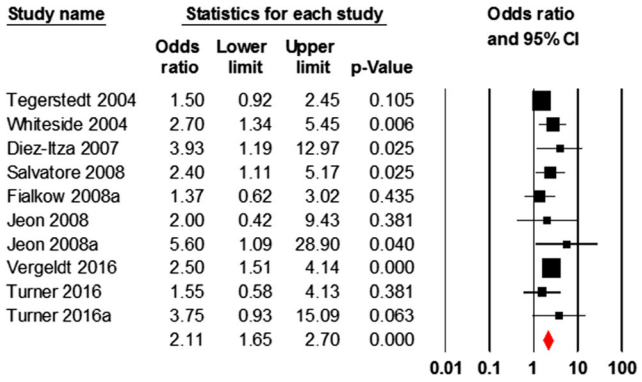

Fig. 4 Meta-analysis of the association between preoperative stage 3–4 and pelvic organ prolapse (POP) recurrence. Test for heterogeneity $I^2 = 0.00$, $P = 0.59$. Each study is shown by an odds ratio estimate with the corresponding 95% confidence interval

studies), levator avulsion and parity (8 studies each), constipation/ obstructed defecation (6 studies), number of involved compartments and prior hysterectomy (4 studies each), family history of prolapse (3 studies), and hiatal area, levator contractility, genital hiatus length, presence of urge urinary incontinence (UUI), and surgeon experience (2 studies each). Several parameters were evaluated once: assisted vaginal delivery, sling operation, weight, past macrosomic baby, urinary incontinence (UI), fecal incontinence (FI), need to splint, stress urinary incontinence (SUI), and urinary retention. Factors evaluated as being associated with prolapse are limited by currently used assessment techniques. Several potential mechanical factors could not be assessed because such measurements were not done prior to surgery in the literature. For example, no study investigated the mechanical properties of apical ligaments or the force generated by a levator ani muscle contraction.

For each parameter investigated in at least 2 studies, a meta-analysis was attempted. However, due to differences in definitions, we could not include all identified papers. For instance, a number of studies compared BMI > 30 to normal, some compared BMI > 25 to normal, and in some, the definition was not clear. Similar issues arose with age as a predictor of recurrence. In such situations, we used the most common definition. Meta-analysis was performed for levator muscle avulsion, (9 studies, Fig. 2), family history of prolapse (3 studies, Fig. 3), preoperative prolapse staging (8 studies, Fig. 4), prior hysterectomy (4 studies, Fig. 5), hiatal area on Valsalva (2 studies, Fig. 6), obstructed defecation (6 studies, Fig. 7), and obesity and overweight (6 studies, Fig. 8).

Significant OR and CI were found for levator avulsion (2.76, 95% CI 2.17–3.51, $P < 0.01$), preoperative staging 3–4 (2.11, 95% CI 1.65–2.70, $P < 0.001$), family history (1.84, 95% CI 1.19–2.86, $P = 0.006$), and hiatal area (1.06/cm^2, 95% CI 1.02–1.10, $P = 0.003$). There was no evidence of publication bias based of Egger's regression analysis for any of the risk factors assessed: avulsion ($P = 0.26$; Fig. 9), family history ($P = 0.16$), preoperative prolapse staging ($P = 0.18$), prior hysterectomy ($P = 0.20$), hiatal area (insufficient data), obstructed defecation ($P = 0.73$), and obesity and overweight ($P = 0.06$).

Discussion

This systematic review and meta-analysis evaluated 25 studies in which > 5000 women with POP were assessed for recurrence following primary surgical treatment, with a follow-up period of 0.11–10 years. Most studies defined recurrence as

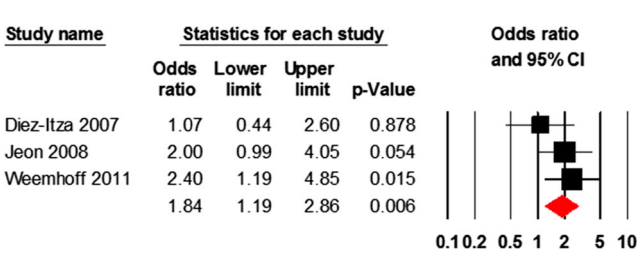

Fig. 3 Meta-analysis of association between family history of pelvic organ prolapse (POP) and POP recurrence. Test for heterogeneity $I^2 = 1.29$, $P = 0.36$. Each study is shown by an odds ratio estimate with the corresponding 95% confidence interval

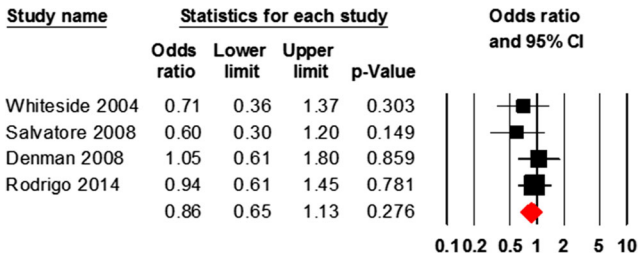

Fig. 5 Meta-analysis of the association between hysterectomy and pelvic organ prolapse (POP) recurrence. Test for heterogeneity $I^2 = 33.10$, $P = 0.15$. Each study is shown by an odds ratio estimate with the corresponding 95% confidence interval

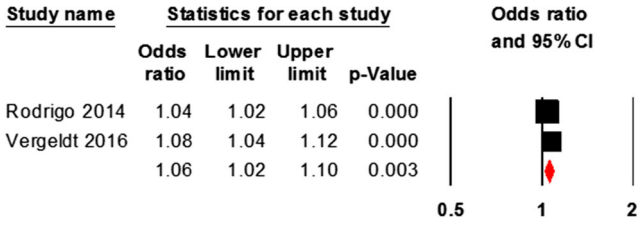

Fig. 6 Meta-analysis of the association between hiatal area and pelvic organ prolapse (POP) recurrence. Test for heterogeneity $I^2 = 68.27$, $P = 0.08$. Each study is shown by an odds ratio estimate with the corresponding 95% confidence interval

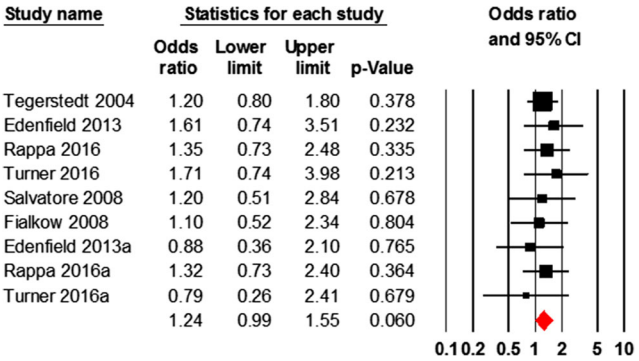

Fig. 8 Meta-analysis of the association between obesity & overweight (BMI > 25) and pelvic organ prolapse (POP) recurrence. Test for heterogeneity $I^2 = 0.00$, $P = 0.96$. Each study is shown by an odds ratio estimate with the corresponding 95% confidence interval

Pelvic Organ Quantification (POP-Q) system stage > 2 for any compartment; however, there were also other definitions, such as a second operation or POP-Q stage 2 for the operated compartment (Table 1). Our review provides an overview of investigated risk factors and their contribution (OR, CI) to prolapse recurrence; significance found for the following risk factors: levator avulsion, preoperative staging 3–4, familial history, and levator hiatal area measured on Valsalva. Although these risk factors have been identified in several studies, our analysis did not always reach statistical significance. The power of any meta-analysis lies in its ability to overcome power issues commonly inherent in published studies, and in this regard, we believe we reached valid and plausible conclusions.

Studies show that pelvic reconstructive surgery has a high reoperation rate [4, 6–8, 11]. Prolapse recurrence is becoming increasingly topical, not least due to the mounting availability of surgical options, such as traditional approaches (vaginal or abdominal) alongside more recently developed laparoscopic and robotic procedures, with or without the use of synthetic or biological implants. Little is known about factors associated with surgical failure, few published systematic reviews evaluate risk factors for prolapse and recurrence, and we found no recent meta-analysis on this topic. Hence, we believe this work substantially adds to the information currently available in the literature regarding risk factors for prolapse recurrence.

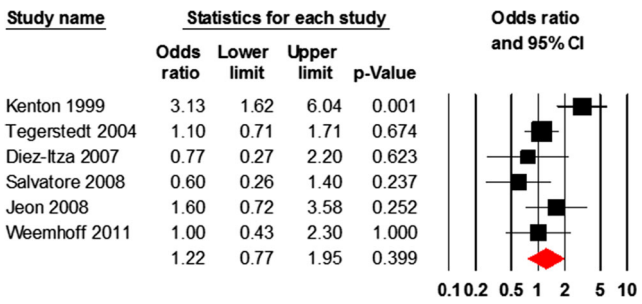

Fig. 7 Meta-analysis of the association between obstructed defecation and pelvic organ prolapse (POP) recurrence. Test for heterogeneity $I^2 = 58.58$, $P = 0.03$. Each study is shown by an odds ratio estimate with the corresponding 95% confidence interval

Strengths and limitations

The strengths of this study include its thorough and systematic review, the large population size (25 studies published over 17 years from four continents, and > 5000 patients. On the other hand, it is well known that systematic reviews of prognostic studies are complicated by several issues [44]. In our meta-analysis, the difference in recurrent prolapse definition and inclusion criteria for each study, as well as the huge diversity in risk-factor definitions, narrowed our ability to compare and use all available information in our statistical analysis. As noted by others [45], uniformly accepted criteria for prolapse recurrence are lacking. A widely accepted consensus regarding the definition of recurrent prolapse and risk factors will benefit future iterations of our work. In addition, data was largely obtained from retrospective studies, and surgical treatment type varied widely between simple and complicated procedures, between vaginal, abdominal, and laparoscopic approaches, and few studies included mesh surgery. However, population heterogeneity and included procedures may be seen as an advantage, representing universally applicable results, and the overall recurrence rate of 36% is plausible in many different settings. Also, that most studies were done in developed countries with similar population profiles is clearly an additional limitation, especially considering emerging data on interethnic variations in pelvic organ support in general and POP in particular [46, 47]. Combining adjusted and unadjusted OR is another limitation that overemphasizes results gleaned from the unadjusted ratios alone, which are typically larger than adjusted values. Risk factors identified by us are unlikely to be independent: Hiatal area is clearly associated with avulsion [48–50] and prolapse stage [51]. A congenital component is likely, as indicated by family history, but any genetic predisposition may, in turn, affect levator hiatus distensibility and/or the likelihood of major levator trauma during childbirth. Finally, it is increasingly apparent that both etiology and pathophysiology may vary considerably from

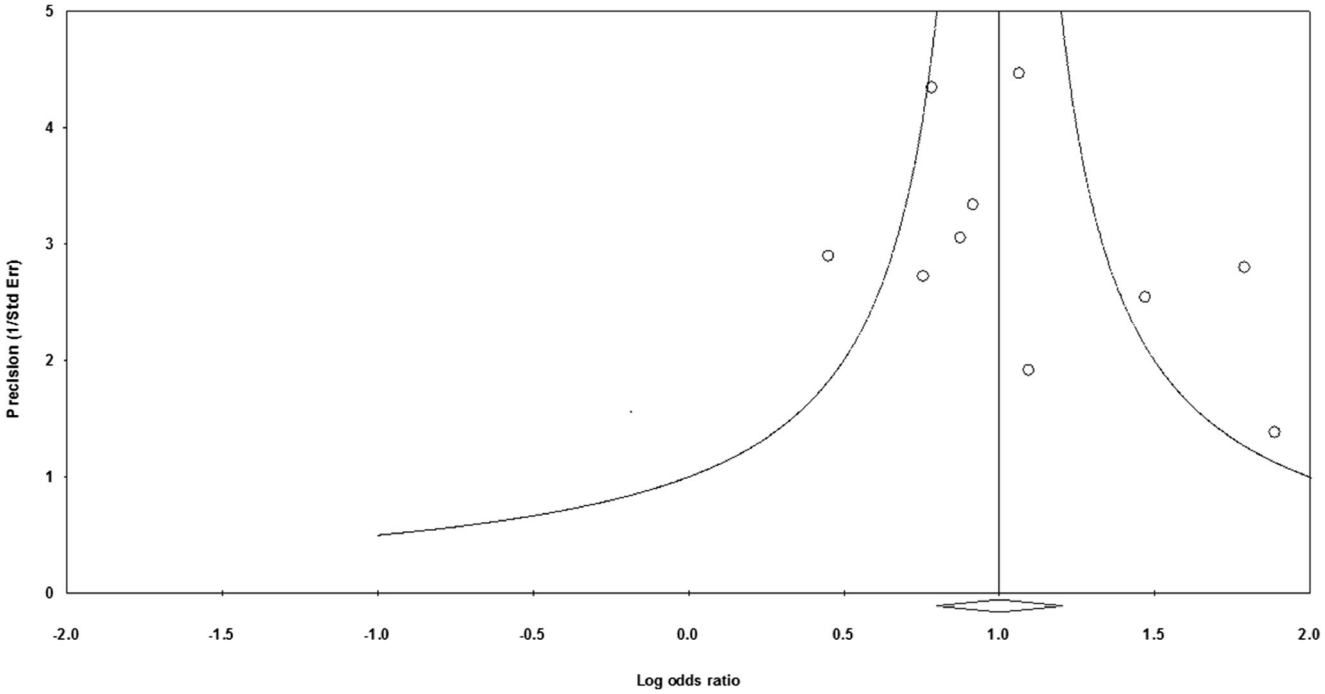

Fig. 9 No evidence of publication bias for the avulsion risk factor ($P = 0.26$)

one compartment to the other. This is certainly the case for levator trauma [51]. The role of obesity is another example, as it may affect the posterior compartment much more than the anterior or central compartments [52]. Hence, future work in this field should consider prolapse recurrence separately for different compartments.

In conclusion, our meta-analysis demonstrates that levator muscle avulsion, preoperative prolapse stage, family history of prolapse, and levator hiatal area are significant risk factor for prolapse recurrence. To facilitate future work in this field, definitions for recurrent prolapse and risk factors need to be standardized. For the time being, risk factors identified in this meta-analysis may serve to help physicians inform patients, select surgical treatment, and design and plan surgical intervention trials.

Funding This study was unfunded.

Compliance with ethical standards

Conflicts of interest H.P. Dietz has received unrestricted educational grants from GE Medical. T. Friedman and G.D. Eslick have no conflict of interest to declare.

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