The Effect of Subsequent Pregnancy and Childbirth on Stress Urinary Incontinence Recurrence Following Mid-Urethral Sling procedure: A Meta-Analysis

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The Effect of Subsequent Pregnancy and Childbirth on Stress Urinary 1 **Incontinence Recurrence Following Mid-Urethral Sling procedure:** 2 A Meta-Analysis 3 4 Chen Nahshon MD^{1,2}, Yoram Abramov MD^{1,2}, Nir Kugelman MD^{1,2}, Nadav Cohen 5 MD^{1,2}, Ofer Lavie MD^{1,2}, Ariel Zilberlicht MD^{1,2} 6 ¹Department of Obstetrics and Gynecology, Lady Davis Carmel Medical Center, 7 Haifa, Israel. 8 ² Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, 9 Israel. 10 11 Funding: The authors did not receive funding for this study. 12 Conflict of interest: The authors declare no conflict of interest. 13 14 Study protocol can be assessed at PROSPERO International prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO, registration number 15 CRD42022346236). Registered prospectively on July 24th, 2022. 16 17 Corresponding Author: Chen Nahshon, MD 18 Department of Obstetrics and Gynecology 19 Lady Davis Carmel Medical Center 20 21 7 Michal Street Haifa 3436212, Israel Tel: +97248250336, Fax: +97248250068 22 E-mail: csarshalom@gmail.com 23 https://orcid.org/0000-0003-0786-6934 24

Word count: Abstract - 317 Main Text - 2151

26	Tweetable Statement: Pregnancy and childbirth following a mid-urethral sling
27	procedure does not increase the risk for stress urinary incontinence recurrence or
28	reoperation.
29	
30	Short title: SUI Recurrence following a MUS and subsequent childbirth.
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32	AJOG at a glance:
33	☐ A. Why was this study conducted?
34	To assess the risk for stress urinary incontinence (SUI) recurrence following
35	pregnancy and childbirth in women who had already undergone a mid-urethral sling
36	procedure for SUI and to assess the effect of delivery mode on this risk.
37	☐ B. What are the key findings?
38	Subsequent childbirth did not seem to carry an increased risk for SUI recurrence or
39	reoperation. Furthermore, the mode of delivery (vaginal versus cesarean) did not
40	seem to affect this risk.
41	□ C. What does this study add to what is already known?
42	This is the first study to integrate all published data regarding the effect of
43	subsequent pregnancy and childbirth on the risk of SUI recurrence following a mid-
44	urethral sling procedure.

45 **Abstract**

Objective: To assess the risk for stress urinary incontinence (SUI) recurrence and 46 47 reoperation following a midurethral sling (MUS) procedure in women with a subsequent childbirth and to assess the effect of delivery mode on this risk. 48 Data sources: We performed an electronic database search using MEDLINE with 49 the OvidSP interface and PUBMED, Embase, Web of Science and Cochrane Library 50 up to September 20th, 2023. 51 Study eligibility criteria: We included experimental and non-experimental studies, 52 comprising of randomized controlled and observational (case-control, cohort, cross-53 sectional) studies assessing risk factors for SUI recurrence and reoperation following 54 55 childbirth in women who had previously undergone a MUS procedure for SUI. Study appraisal and synthesis method: Analysis was conducted using RevMan 56 5.3 (Cochrane Collaboration, Oxford, UK). Quantitative synthesis was utilized if the 57 58 included studies were sufficient in numbers and homogeneity. The overall certainty of the evidence was assessed using criteria recommended by the Grading of 59 60 Recommendations Assessment, Development and Evaluation Working Group 61 (GRADE). 62 **Results**: A total of 2,001 studies were identified of which six were eligible for analysis, comprising 381 patients who had at least one childbirth following a MUS 63 procedure (study group), and 860 patients who underwent a MUS without having a 64 65 subsequent childbirth (control group). All included studies were observational, the 66 patients' mean age at the time of the MUS procedure ranged from 34 to 36 years and the mean time from MUS procedure to delivery ranged from 21 to 31 months. 67 No differences in SUI recurrence (RR 0.1.02 [95%CI 0.78-1.33]) or reoperation (RR 68 69 1.37 [95% CI 0.87-2.17]) were found between the study and control groups. The

- average follow-up time among the included studies of this comparison was 9.8 years
 (range 2-18 years). Furthermore, the mode of delivery (vaginal versus cesarean) did
 not seem to affect the risk for SUI recurrence.

 Conclusions: Subsequent pregnancy and childbirth do not seem to increase the risk
 for SUI recurrence or reoperation following a MUS procedure.
- 76 **Keywords:** childbirth; delivery; midurethral sling; pregnancy; recurrence;
- 77 reoperation; Tension-free vaginal tape

Introduction

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Stress urinary incontinence (SUI) is a bothersome condition which adversely affects women's quality of life worldwide. The estimated prevalence of SUI in the general population is 20-25%, while in younger women the rates range from 4 to 23% $^{1-3}$. The mid-urethral sling (MUS) procedure is considered to be the gold standard treatment for SUI with success rates of up to 85% 4. A unique group of women who have not yet completed their family planning and seek surgical treatment for SUI, pose a clinical dilemma as for the potential determinantal effect of additional pregnancy and childbirth on their surgical outcome. Many clinicians recommend postponing surgical treatment for SUI until completion of childbearing due to concern regarding SUI recurrence following subsequent pregnancy and childbirth 5,6. Furthermore, many advocate cesarean rather than vaginal delivery following a previous MUS procedure 6. These policies are based upon the fact that pregnancy and childbirth have been shown to be major risk factors for SUI. Nonetheless, whether they affect the risk for recurrent SUI following a MUS procedure is yet unclear, as only few studies have addressed this question with conflicting results 5,7-11. The primary goal of the current study was to perform a comprehensive metaanalysis based on currently available data regarding the effect of subsequent pregnancy and childbirth on the risk for SUI recurrence and reoperation following a MUS procedure. A secondary goal was to assess the effect of the mode of delivery (vaginal versus cesarean) on the risk for SUI recurrence and reoperation following a MUS procedure.

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Methods

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Search strategy and selection criteria 104 105 This meta-analysis was conducted by the Cochrane Handbook for Systematic Reviews of Interventions ¹² .Study protocol can be assessed at PROSPERO 106 107 International prospective register of systematic reviews 108 (http://www.crd.york.ac.uk/PROSPERO, registration number CRD42022346236). Searches were conducted by an experienced research librarian using the following 109 databases: MEDLINE using the OvidSP interface and PUBMED, Empase, Web of 110 Science and Cochrane Library up to September 20th, 2023. Search strategies are 111 detailed in Supplementary Document 1. No restrictions were imposed regarding the 112 113 year of publication. Only manuscripts in the English language were included. We included experimental and non-experimental studies, comprising of randomized 114 controlled as well as observational (case-control, cohort, cross-sectional) studies 115 116 assessing the effect of subsequent pregnancy and childbirth on the risk for SUI recurrence and reoperation following a MUS procedure, as compared to women who 117 118 had undergone a MUS procedure without subsequent childbirth. We also included studies assessing the effect of delivery mode (vaginal versus cesarean) on this risk. 119 120 Case reports, reviews, editorials, and non-human studies were excluded. Abstracts of studies were excluded if the entire article was not published as well. If two 121 publications seemed identical (duplicate publication), only one of the studies was 122 123 included. Screening of titles, abstracts and full texts was conducted independently by 124 two reviewers; disagreements were resolved by discussion. If needed due to a disagreement, a third reviewer was added to the discussion. A detailed list of study 125 characteristics related to patients' demographics, clinical data and study 126 127 methodology was created for all studies included in this meta-analysis.

128	Outcomes
129	Primary outcome:
130	SUI recurrence following childbirth.
131	2. Reoperation for SUI recurrence following childbirth.
132	Secondary outcome:
133	1. The effect of delivery mode (vaginal birth versus cesarean section) on SUI
134	recurrence.
135	2. The effect of delivery mode (vaginal birth versus cesarean section) on
136	reoperation rates for SUI.
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138	Strategy for data synthesis
139	Analysis was conducted using RevMan 5.3 (Cochrane Collaboration, Oxford, UK).
140	We complied with the methods and techniques introduced and explained in chapter
141	10 of the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy
142	¹² . The results were measured by risk ratio (RR), presenting the confidence interval
143	(CI) and p-value and I² for heterogenicity assessment. A two-tailed P<0.05 was
144	considered statistically significant for all comparisons. Heterogeneity across studies
145	was assessed using the I^2 statistic tool. An I^2 < 25% was considered to represent a
146	low level of heterogeneity, while an I² statistic of 25% to 50% a moderate level and I²
147	> 50% a high level of heterogenicity. Pooling of the results was performed using
148	either the Mantel-Haenszel fixed effects model or the Der Simonian-Laird random-
149	effects model. The random-effects model was used if the I² test indicated significant
150	heterogeneity between the studies. In contrast, the results were interpreted using the

fixed-effects model in cases of low statistical heterogeneity. According to the

Cochrane Handbook for Systematic Reviews of Interventions ¹², tests for funnel plot

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asymmetry should be used only when at least ten studies are included in the metaanalysis since when there are fewer studies, the power of the tests is too low to distinguish the chance from real asymmetry. In our meta-analysis, only six studies were included. Therefore, publication bias was not assessed. Sensitivity analyses were conducted by omitting studies with the highest weight, removal of outliers, and by skipping one study at a time to evaluate whether the results could have been affected markedly by a single study. Quantitative synthesis was utilized if the included studies were sufficient in numbers and homogeneity. Risk of bias (quality) assessment Cochrane Collaboration's Risk of Bias tool would be used to evaluate the quality of randomized controlled trials. Methodological quality assessment of observational studies was conducted using the Newcastle-Ottawa Quality Assessment Scale 13. The overall certainty of the evidence was assessed using criteria recommended by the Grading of Recommendations Assessment, Development and Evaluation Working Group (GRADE) 14. This meta-analysis was reported according to the Meta-analysis of Observational

Studies in Epidemiology (MOOSE) statement 15.

Results 170 Study selection and characteristics 171 172 A total of 2,001 studies were identified through database searching, with 389 173 duplicates removed. Fig. 1 describes the data collection and selection process. Finally, we included six studies ^{16–21} comprising 381 patients who had at least one 174 childbirth following a MUS procedure (study group) as well as 860 patients who had 175 a MUS procedure without a subsequent childbirth (control group). Among patients in 176 the study group 182 had a vaginal birth, 195 had a cesarean delivery and four 177 patients had both vaginal and cesarean deliveries. No instrumental deliveries were 178 recorded in any of the studies. Tables 1 and 2 summarize the studies' main 179 characteristics. Three studies were population register-based and four were 180 retrospective. SUI recurrence was defined subjectively in all studies. Patients' 181 average age at the time of the MUS procedure ranged from 34 to 36 years. The 182 183 average time from MUS procedure to delivery ranged from 21 to 31 months (Tables 1 and 2). The average follow-up time among the included studies of this comparison 184 185 was 9.8 years (range 2-18 years). 186 The methodological quality assessment summary according to the Newcastle-Ottawa Quality Assessment Scale ¹³ is presented in Supplementary Table 2, studies 187 ranged from low to medium quality. 188 Synthesis of results 189 190 Primary outcome measure The forest plots for the effect of childbirth on SUI recurrence and re-operation rates 191 are presented in Fig. 2. No differences in the risk for SUI recurrence (17-24% vs. 15-192 22% respectively, RR 1.02 [95%Cl 0.78-1.33], P=0.90, l²=46%) or re-operation (3-193

12% vs. 3-7% respectively, RR 1.37 [95% CI 0.87-2.17], P=0.17, I²=9%), were found

195	between patients with and without a childbirth following the MUS procedure.
196	Secondary outcome measures
197	The forest plots for the effect of delivery mode on SUI recurrence and re-operation
198	rates are presented in Fig. 3. No differences in the risk for SUI recurrence (RR 1.81
199	[95%CI 0.48-6.80], P=0.38, I ² =0%) or re-operation (RR 1.43 [95% CI 0.70-2.92],
200	P=0.33, I²=0%), were found between patients who had a vaginal versus a cesarean
201	delivery.
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203	Sensitivity analyses showed that none of the results were significantly affected by a
204	single study. Using the GRADE criteria 14, the overall certainty of the existing
205	evidence was determined as low considering data acquisition from observational
206	studies. Due to low heterogeneity, high consistency between studies, and direct
207	evidence, the final grading was not changed.

Comment

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Principal Findings The current meta-analysis found that subsequent labor and delivery were not associated with an increased risk for SUI recurrence or reoperation following a mean follow up period of 9.8 years from a MUS procedure. Furthermore, this risk was not affected by the mode of delivery (vaginal versus cesarean). Risk of SUI recurrence following a MUS procedure was found to range from 15% to 24%, with or without subsequent childbirth and risk for SUI reoperation following a MUS procedure was found to range from 3% to 12%. Comparison with Existing Literature Stress urinary incontinence is a common disorder with an increasing incidence in postmenopausal and elderly women. A relatively small proportion of women are diagnosed with SUI at a younger age when future childbearing may still be desired. In cases where surgical treatment is considered the clinician may face questions regarding the potential effect of future childbearing on the surgical outcome of this procedure, as well as the potential effect of a MUS on future pregnarcies and deliveries. Furthermore, the preferred mode of delivery following a MUS (vaginal versus cesarean) may also require patient consultation ^{5,6}. Currently, there is paucity of evidenced-based data regarding the effect of subsequent pregnancy and delivery on the risk for SUI recurrence following a MUS procedure. Since both pregnancy and delivery are independent risk factors for pelvic floor disorders ²² many clinicians advocate postponing the MUS procedure until the completion of childbearing ^{23,24}. In a survey among members of the American

Urogynecologic Society (AUGS) 25 nearly 15% of respondents stated they would not

perform an anti-incontinence surgery on patients who desire future pregnancy, and 40% said they would advocate a cesarean rather than a vaginal delivery for patients who had undergone surgery for SUI. Another survey from the United Kingdom found that although 78% of clinicians would perform an anti-incontinence procedure on patients who have not yet completed childbearing, 60% would advise a cesarean delivery in subsequent pregnancies ⁶. Currently, AUGS states that existing data are insufficient to establish whether recurrent SUI rates differ between vaginal and cesarean delivery 26. In view of the current meta-analysis it seems that subsequent childbearing does not increase the risk of SUI recurrence or re-operation following a MUS procedure. Thus, women may not need to wait until completion of childbearing before undergoing a MUS procedure. Furthermore, women may be advised that elective cesarean delivery may not be required as vaginal birth was not associated with an increased risk for SUI recurrence. Moreover, if a patient becomes incontinent following a MUS procedure and subsequent childbirth, a repeated MUS may be offered in the future. In accordance with our results, the reported reoperation rate for MUS has been reported to range between 3.5 and 14.5% 27.28. Such a procedure has been found to be safe and efficient. A meta-analysis reported cure rates for recurrent SUI of 73% which is slightly lower than that for primary MUS ²⁹. Regarding pregnancy safety following a MUS procedure, studies have found that major perinatal complications due to a previous MUS procedure are extremely rare, such as complete urinary obstruction ^{9,30}. Minor complications included voiding difficulties, sling displacement, bladder irritations, and urinary tract infections ^{9,30}. Though rare, these complications need to be discussed with patients planning to perform a MUS procedure between or before planned pregnancies.

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Strengths and Limitations

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This is the first published meta-analysis regarding the effect of subsequent childbirth on the risk for SUI recurrence and re-operation following a MUS procedure. We utilized major clinical literature databases from which data were extracted and analyzed using robust statistical methodologies. Limitations of this meta-analysis include lack of information on confounders that may influence the results as well as insufficient data regarding characteristics of the study participants such as the number of deliveries before and after the MUS procedure, birthweight, instrumental deliveries, patients BMI, the specific type of MUS performed for each woman and whether the sling was synthetic or biologic. The final number of studies included and analyzed in this meta-analysis was small (6 studies) as most studies screened were of low quality or did not comply with our inclusion criteria, and analyses included only three studies per comparison. In addition, the three population-basec studies included in this meta-analysis are from a selected population in Scandinavia, thus generalization of the results to other countries may be inaccurate. Adjustments of the data presented to the local population should be taken into consideration. Last, the language restriction used in this meta-analysis might have introduced selection bias.

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Conclusions and Implications

This is the first meta-analysis to evaluate the effect of subsequent childbirth on the risk for recurrence and reoperation among women who had undergone a MUS procedure for SUI. The study results indicate that subsequent pregnancy and delivery do not necessarily increase the risk for SUI recurrence or reoperation following a MUS procedure. Furthermore, the mode of delivery did not seem to affect this risk. Nonetheless, due to the unavoidable confounding effect associated with

283	observational studies, these conclusions should be taken with a grain of salt. Well-
284	designed prospective randomized studies are still needed in order to support or
285	negate these findings.
286	
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291	Conflict of interest: All authors declare no conflict of interest.
292	Author's contribution:
293	Chen Nahshon: Data collection, Statistical analysis, Writing - Origina draft,
294	Methodology, Investigation.
295	Yoram Abramov: Writing- Review and Editing, Validation, Review.
296	Nir Kugelman: Validation, Review.
297	Nadav Cohen: Validation, Review.
298	Ofer Lavie: Validation, Review.
299	Ariel Zilberlicht: Conceptualization, Writing- Review and Editing, Methodology,
300	Investigation, Supervision.
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426 **Legends**:

- Figure 1: Flow chart of database searching and study selection.
- Figure 2: Forest plots for risk following childbirth; A: Risk for SUI recurrence. B: Risk
- 429 for MUS re-operation.
- Figure 3: Forest plots for risk according to delivery method; A: Risk for SUI
- recurrence. B: Risk for MUS re-operation.

Table 1: Characteristics of population-based studies

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Mean	follow- up	9 years (range 2-15)	120 months (range 22-215)	10.7 years (IQR 7.2- 13.9)
Repeat MUS- n (%)	with without delivery delivery	28 (8%)	5 (3%)	17 (5%)
Repeat I	with	20 (12%)	4 (6%)	3 (3%)
SUI	by by SUI recurrence vaginal cesarean following without purth a section delivery delivery north delivery (%) (%) delivery	20 95 (61%) 36 (22%) 63 (17%) (12%)	33 (6%) 12 (17%) 37 (24%) 4 (6%)	40 (43%) 14 (61%) 57 (66%) 3 (3%)
	by SUI recurrer cesarean following without retton- delivery delivery no (%) (%)	36 (22%)	12 (17%)	14 (61%)
Delivery Delivery	by cesarean section- n (%)	95 (61%)	33 (46%)	40 (43%)
Delivery	by vaginal birth – n (%)	64 (39%)	39 (54%)	54 (57%)
Time		N/A	27 months (range 10-116)	2.C years 54 (1.6-4.6) (57%)
e at or SUI	With Without delivery delivery	N/A	34 years 38 years months (range (range 24-44) 28-44) 10-116)	3.5 years 3.5 years 2.6 (range (range yea 32-38) 33-38) (1.6
Mean age at surgery for SUI	With delivery	N/A	34 years (range 24-44)	32-38)
	Type of MUS	374 retropubic/transobtoratorN/A	156 TVT/TOT/TVT-0/AJUST	36 year (range 330 retropubic/transobtorator
	MUS, no following delivery	374	156	330
u	with MUS, no following following delivery	163	72	94
		population- based cohort study	population- based cohort study	register- based case- control study
	Country Design	popul based cohor Sweden study	popul based cohor Norway study	registe based contro Finland study
	Study	Bergman 2018	Dyrkorn 2020	Tolukas 2020

Additional 4 patients had both vaginal birth and cesarean section.

MUS- Midurethral sling; SUI- stress urinary incontinence; TVT- tension free vaginal tape; TOT- transobtorator tape, TVT-O- tension free vaginal tape obturator; AJUST – adjustable sling-incision sling.

Table 2: Characteristics of retrospective studies

							Delivery					
					Mean		þý					Mean
					age at	Time from	vaginal	Delivery by	SUI	SUI	Repeat	follow-up
					surgery	MUS to	birth – n	cesarean	following	following	MUS- n	
Study	Country	Design	c	Type of MUS	for SUI	pregnancy	(%)	section- n (%)	VD – n (%)	CS -n (%)	(%)	(range)
			_		33.9	21.6						
					years	months						
Panel			19		(range	(range 3-	10					
2007	France	retrospective	*	TVT/TOT	20-42)	(23)	(23%)	9 (47%)	2 (20%)	1 (12.5%)	1 (5%)	13.8 (1-52)
					33.1	30.2		2				
					years	months		9				
Cavkaytar					(range	(range 13-	(
2014	Turkey	retrospective	12	TVT/TOT	27-40)	26)	5 (42%)	7 (58%)	2 (40%)	0	N/A	52 (30-68)
							0					
					35.4	28.3)					
Adams-					years	months	,					
Piper			21	retropubic/	(range	(range 10-	10					
2016	California	retrospective	* * *	transobtorator	28-48)	(02	(48%)	11 (52%)	0	1 (9%)	1 (5%)	19.8 (1-51)

^{*} Excluding one patient still pregnant during the study.

MUS- Midurethral sling; SUI- stress urinary incontinence; TVT- tension free vaginal tape; TOT- transobtorator tape; N/A- not available.

^{**} to delivery.

^{***} Five patients in original research excluded from analysis due to SUI prior to delivery.

Figure 1: Flow Chart of Database Searching and Study Selection

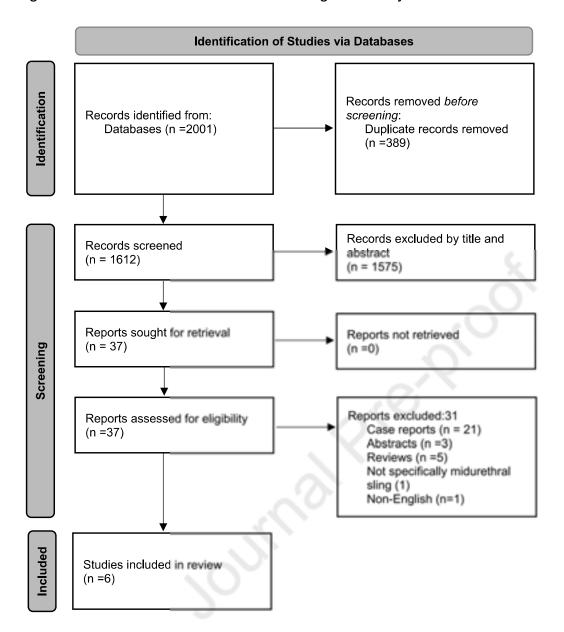
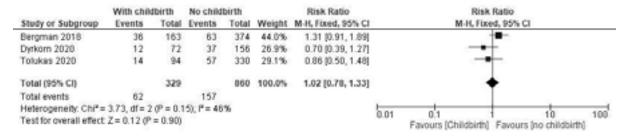


Figure 2: Forest Plots for Risk Following Childbirth

A: Risk for Stress Urinary Incontinence Recurrence



B: Risk for Midurethral Sling Re-operation

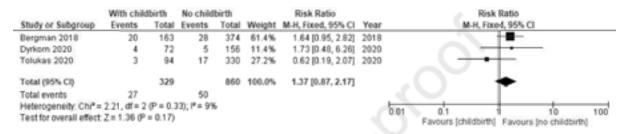
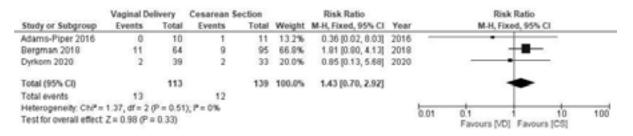


Figure 3: Forest Plots for Risk According to Delivery Mode

A: Risk for Stress Urinary Incontinence Recurrence

	Vaginal De	livery	Cesarean	Section		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Rixed, 95% CI
Panel 2007	2	10	1/	9	36.1%	1.80 [0.19, 16.66]	2007	
Cavkaytar 2014	2	5	0	7	14.7%	6.67 [0.39, 114.78]	2014	
Adams-Piper 2016	0	10	_ (1)	11	49.2%	0.36 [0.02, 8.03]	2016	-
Total (95% CI)		25		27	100.0%	1.81 [0.48, 6.80]		
Total events	4		2					
Heterogeneity: Chi ² =	1.84, df = 2 (P = 0.40	$0.1^{\circ} = 0.96$					0.01 0.1 1 10 100
Test for overall effect	Z = 0.88 (P =	0.38)						0.01 0.1 1 10 100 Favours [vD] Favours [CS]

B: Risk for Midurethral Sling Re-operation



Supplementary Table S1: Reasons for study exclusion at full-text evaluation stage

Reason for non-inclusion	References
Abstracts, Comments, Surveys	(1-3)
Case reports	(4-24)
Reviews	(25-29)
Not specifically midurethral sling	(30)
Non-English papers	(31)

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Supplementary Table S2: Quality Assessment of the Included Studies According to Newcastle–Ottawa Scale.

First author (year)	Selection	Comparability	Outcome/exposure	Total	Quality*
Panel 2007 ¹⁹	2	0	2	4	Low
Cavkaytar 2014 ¹⁷	3	1	3	7	Medium
Adams-Piper 2016 ¹⁶	2	0	2	4	Low
Bergman 2018 ²¹	3	2	2	7	Medium
Dyrkorn 2020 ¹⁸	3	2	2	7	Medium
Tolukas 2020 ²⁰	3	2	2	7	Medium

^{*} Low - up to 5 points, Medium - 6-7 points, High - 8-9 points.

Supplementary Table S3: Inclusion and Exclusion criteria for Included Studies

	Inclusion criteria	Exclusion Criteria
	Women who had undergone a	N/A
	MUS procedure and	
Bergman 2018	afterwards a delivery.	
	Case group- having undergone	Inability to consent to follow-
	one or more childbirths after	up
	MUS surgery.	
	Control – No subsequent birth	
Dyrkorn 2020	following MUS	
	Women who had had a	Hypospadias as indication for
	pregnancy ending in	procedure, Age under 18 at
	delivery after MUS	MUS, more than one MUS
Tolukas 2020		procedure before childbirth
	Pregnancies after treatment of	N/A
Panel 2007	SUI by TVT or TOT	
	Women who has an infant	N/A
	after MUS placement to treat	
Cavkaytar 2014	SUI	
	Cases with the date of a live	N/A
	birth subsequent to the date	
Adams-Piper 2016	of MUS	