Anti-Sperm Antibody Positivity Results A Decrease In Sperm Penetration Rate Both In Vivo And In Vitro: A Systematic Review And Meta-Analysis

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Conceptualization: LS, LY, YL, YJH, NTX, LW. Data curation: LS, LY, FYM, DYY, HF, DMM, ZY. Methodology: LS, LY. Investigation: LS, LY. Writing-review: LS, LY. Validation: DYY, HF, DMM. Review: NTX, LW.

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1. Abstract

1.1. Background: Anti-sperm antibodies (ASA) that bind to sperm have been associated with infertility, but most of the available studies have conflicting results.

1.2. Objectives: We carried out a meta-analysis to evaluate whether female/male ASA-positiveness would have an impact on sperm penetration through the cervical mucus in these patients.

1.3. Materials and Methods: A systematic search of the target literature was conducted using PubMed, EMBASE, and Cochrane Library. Review Manager 5.4 software was used to analyze data. Relative risk (RR) with the corresponding 95% confidence intervals (95% CIs) were implemented as a measure of effect size to assess the value of post-coital test (PCT) and sperm-cervical mucus penetration test (SCMPT) between ASA-positive patients and control groups.

1.4. Results: A meta-analysis of the negative rate of PCT was performed in 10 controlled studies. There was a significant association between ASA and PCT negative rate (RR = 1,63, 95% CI = 1.37 to 1.95, p <0.01). Another meta-analysis of the positive rate of SCMPT was performed in 8 controlled studies. There was a significant difference in the SCMPT positive rate (RR = 0.65, 95% CI = 0.56 to 0.77, p <0.01).

1.5. Discussion: Compared with the control group, the sperm penetration rate in the ASA positive group was lower. Clinicians working on reproductive health and infertility should be aware of this issue in order to evaluate and treat patients in order to improve their pregnancy rate. It is recommended that infertile couples undergo routine ASA testing and propose targeted treatment strategies to help improve the success rate of reproductive therapy.

1.6. Conclusions: Both in vivo and in vitro experiments reflected decreased sperm penetration through the cervical mucus in ASA-positive patients.

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2. Keywords:

Anti-sperm antibodies; Sperm penetration; PCT; SCMPT; Infertility

3. Introduction

Anti-sperm antibody (ASA), which can bind to sperm, has been detected in serum and seminal plasma and has been linked to infertility in a number of studies[1,2]. High-titer anti-sperm antibodies are typically indicative of unsuccessful fertilization when they are discovered in seminal plasma. A high level of ASA is present in males with a clinical history of testicular torsion, testicular cancer, epididymitis, bilateral orchitis associated with extensive destruction of seminiferous tubules, semen infection, varicocele and genital infection, as well as inflammation brought on by vasectomy[3-5]. Just 1-2%[6] of fertile males have significant levels of ASA in their semen, compared to 5-15%[7] of infertile men. In 1922, S. R. Meaker was the first to note the occurrence of ASA in females[8]. According to reports, the ASA of women was frequently significantly correlated with that of their male spouses. In their study, [9] Witkin and Chaudhry analyzed data from more than 600 couples and found that 12.4% of men had sperm surface antibodies and their wives had anti-sperm antibodies in their serum. A study showed that 29.6% of 459 infertile women had been detected ASA in serum[10]. Women who had ASA found in their serum samples tended to have it found more frequently in their cervical mucus samples. Presence of ASA in female partner serum may also increase the risk of miscarriage[11]. The impairment of sperm function is associated with the presence of ASA in male and/or female partners. According to one study, sperm concentration and motility were both inversely linked with ASA[12]. According to MElstein [13], the rate of sperm passage was significantly decreased when the cervical mucus protein concentration surpassed 12.5ug/mg, particularly when antibodies were present. Human sperm treated with specific antibodies have a decreased ability to penetrate the cervical mucus and also develop sperm agglutination and immobilization [14]. ASA levels are associated with seminal leukocyte concentrations [13,15], which can produce reactive oxygen species (ROS) that lead to sperm dysfunction and sperm DNA damage, but a prospective study [12] did not reveal sperm DNA damage. ASA may also mediate sperm apoptosis, which leads to a decrease in sperm numbers [1]. Sperm function impairment and sperm deficiency may affect sperm's ability to pass through cervical mucus, which may affect fertilization and make it challenging for sperm to reach the vicinity of the oocyte and interfere the process of sperm and oocyte binding. The detection method of sperm through cervical mucus mainly includes postcoital tests (PCT) and the sperm-cervical mucus penetration technique (SCMPT). Therefore, the objective of this research is to gather factual information from widely quoted literature to demonstrate if ASA can impact the capacity of sperm to travel through cervical mucus.

4. Materials and methods

This systematic review was developed rested upon the recommendations

from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements[16]. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. The protocol is registered in the PROSPERO registry (CRD42022342206, http://www.crd.york.ac.uk/ PROSPERO).

4.1 Search strategy

To find all pertinent studies without regard to language restrictions, we carried out an organized search across three accessible databases (PubMed, EMBASE, and Cochrane Library). In addition, pertinent supplementary studies found in the primary and event studies' reference lists were examined. The following search phrases were entered into PubMed: ((((((((antisperm antibodies) OR (ASA)) OR (sperm antibodies))) OR (spermatozoa antibodies)) OR (spermatozoon antibodies)) OR (immunological infertility)) OR (autoantibodies)) OR (immunoglobulins)) AND (((((((sperm-mucus interaction) OR (cervix mucus)) OR (mucus, cervix)) OR (cervical mucus)) OR (mucus, cervical)) OR (cervical mucus analysis)) OR (postcoital test)) OR (sperm-cervical mucus penetration test)). This same combination of words was used to search in Cochrane Library. The following search phrases were entered into EMBASE: ('sperm antibody'/exp OR 'antisperm antibodies':ti,ab OR 'sperm antibodies':ti,ab OR 'spermatozoa antibodies':ti,ab OR 'spermatozoon antibodies':ti,ab OR 'autoantibody'/exp OR 'autoantibodies':ti,ab OR 'immunoglobulin':ti,ab OR 'immunological infertility':ti,ab) AND ('uterine cervix mucus'/exp OR 'uterine cervical mucus':ti,ab OR 'spermmucus interaction':ti,ab OR 'cervical mucus analysis'/exp OR 'postcoital test':ti,ab OR 'sperm-cervical mucus penetration test':ti,ab).

4.2. Eligibility criteria

The inclusion criteria for this study were as follows: a) studies measuring ASA in infertile couples; b) studies reporting value of PCT or SCMPT; PCT: The average motile sperm count in cervical mucus was examined 6 to 12 hours after coitus under high (×400) magnification. An PCTnegative result is suggested that sperm have a strong ability to pass through cervical mucus SCMPT: This test is an in vitro test for sperm penetration into cervical mucus. Sperm were incubated for 30 minutes at 37°C, and then they were inspected under a microscope (50 to $100 \times$). Based on the greatest distance that a minimum of five motile sperm could travel, penetration was calculated. SCMPT-positive result is suggested that sperm have a strong ability to pass through cervical mucus. c) observational studies (cross-sectional, case-control, or cohort). Included studies were required to meet all of the above criteria. We excluded articles a) utilized unspecified additional techniques to evaluate sperm penetration; b) that were case reports; c) the content of the study does not include ASA; d) that could not get meaningful data for this review even after we contacted the authors via e-mail.

4.3. Study selection, data extraction, and quality of evidence

Read the titles of each article that the database search turned up, searched

all research that might be included in this review, regardless of population size, source, or age, and examined the abstracts of pertinent articles on the correlation between the surveys. Two scholars looked over the included articles, gathered information that was relevant to the study's objectives and used consensus to settle disagreements. All closely related literature, meta-analysis, and review articles were also reviewed for their reference lists to identify additional published work not indexed by above-mentioned databases. A third reviewer dealt with disputes over whether a study should be included. The data collected were as follows: authors and publication year, type of study, country, sample size, age, PCT negative rate, and SCMPT positive rate. Other information was obtained by contacting authors via e-mail. We used Newcastle Ottawa Scale (NOS) [17] to evaluate the quality of included cohort and case-control studies. The highest score for NOS was 9 points. Studies with an NOS score between 5 and 7 and greater than 7 were considered "medium"-quality studies and "high"-quality studies, respectively. On the contrary, studies with NOS score lower than 5 points were considered "low"-quality studies. We also analyzed the impact of possible conflicts of interest and whether the research was ethically approved [18].

4.4. Statistical analysis

Statistical analyses were conducted using REVMAN Review Manager 5.4 software. To assess the efficacy of PCT and SCMPT between two groups, we utilized relative risk (RR) and the corresponding 95% confidence interval (CI) as a measure of effect magnitude. The X² test was applied to assess statistical significance, and a pooled effect was deemed significant when P <0 .05. The percentage of variability across studies attributable to heterogeneity was estimated using the I² test, which was considered to be a significant difference when P <0.05. Low, medium, and high degrees of heterogeneity were clarified by I² values of 25%, 50%, and 90%, respectively. Due to excessive heterogeneity the random effects model

was used to merge data. Subgroup and sensitivity analyses were also carried out to investigate the sources of heterogeneity between studies. We observed the funnel plot to see if there was any publication bias.

5. Results

5.1 Included studies

The search strategy identified a total of 1025 studies, of which 37 studies with titles and abstracts met the inclusion criteria. After excluded 21 studies those used different outcome variables or had no ASA testing data, there were finally 16 articles included in the scope of the analysis (Figure 1). Two studies conducted in Japan [19-20]; 5 studies in America [21-25]; 1 study in Italy[26]; 2 studies in German[27-28]; 3 studies in England[13, 29-30]; 1 study in France[31]; 1 study in Malaysia [32]; and 1 study in Sweden [33]. ASA detection methods include TAT[21-22,25,28,32-33], SIT[19,21-22,33], IBT[20,24,31], MAR[26-27] and immunolabeling[28,30,32]. Some studies[20,23-24,26-27,30-31] tested ASA from semen samples of men, some[13,21-22,25,28] from cervical mucus samples of women, and others[19,21-22,25,28-29,33] from serum samples of one spouse. In addition, some studies[19-20,23-24,26-28,30,32-33] assessed sperm penetration at cervical mucus using an in vivo assay - PCT, while others[13,21-22,25,27-29,31,33] used an in vitro assay - SCMPT.

5.2 Sperm penetration rate of ASA-positive patients

According to studies, the sperm penetration rate of ASA-positive patients was lower. For most studies, there were significant differences in characteristics between ASA-positive and ASA-negative patients (Table 1). The PCT-negative rate of ASA-positive patients ranged from 50.0% to 100.0%, while the negative patients were only 13.0% to 75.0%. The SCMPT positive rate of ASA-positive patients ranged from 2.9% to 68.8%, compared with 55.3%-95.0% of negative patients.

Table 1: Characteristics of the controlled studies on sperm penetration through the cervical mucus in ASA-positive and ASA-negative men in the systematic review

N	Auth	Cou	Study	Quality	Conflict	Ethicscom mittee	Group	ASA detection	ASA titer	ASA sam	ASA sam	Sampl size AS	e AS	PCT rate	negative	Р	SCMP semi-qu titative a	an malysis	P	SCMPT] rate	positive	- P
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							ASA(+)													35(2	190	
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							vs ASA	MAR	30%	semen	male	28	162	8.6	8.8							
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							vs ASA	MAR	30%	semen	male	17	173	6.5	0.9							
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15	Fjallb rantet	Swe	Cabart	0	No	Vac	A'SA(+) vs ASA (-)	TAT	32-64	serum	male	14	8	11(7 8.6 %)	4(50 .0%)	0.50±	1.60 ± 0.68	2.3 e-4			
15	al. (1968)	den	Conort	9	NO	ies	A'SA(+) vsASA	SIT	6h	serum	male	16	20						6(37 .5%)	18(9 0.0 %)	
							A'SA(+) vs ASA (-)	SIT	6h	serum	male	16	20			0.50 ±0.73	1.25 ± 0.64	3.3 e-3	5(31 .3%)	19(9 5.0 %)	
							A'SA(+) vs ASA (-)	SIT	6h	serum	male	13	9	11(8 4.6 %)	4(44 .4%)					7	
16	Elstein et al. (1970)	Eng la nd	Cohort	6	No	Yes	ASA(+) vs ASA (-)	-	-	СМ	female	16	3			0.38 ±0.62	1.70 ± 0.57	9.3 e-6	11(6 8.8 %)	2(66 .7%)	

ASA, anti-sperm antibodies; SIT, sperm immobilization test; TAT, tray agglutination test; MAR, mixed antiglobulin reaction; IBT, immunobead binding test; CM, cervical mucus; PCT, postcoital test; SCMPT, sperm-cervical mucus penetration technique.

5.3 Meta-analysis

Meta-analysis of the negative rate of PCT was performed in 10 controlled studies [19-20,23-24,26-28,30,32-33]. Because of the differences in research methods within each study, we divided it into 19 sub-analysis. The ASA positive group consisted of 550 men, and the ASA negative group consisted of 1,700 people. The results showed that there was a

5.3 Meta-analysis

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Meta-analysis of the positive rate of SCMPT was performed in 8 controlled studies [13,22,25,27-29,31,33]. Because of the differences in research methods within each study, we divided it into 25 sub-analysis. The ASA positive group consisted of 985 men, and the ASA negative group consisted of 3,205 people. There was a significant difference in the SCMPT positive rate (RR = 0.65, 95% CI = 0.56 to 0.77, p <0.01) with a high degree of heterogeneity between studies (I² = 71%, p < 0.01) (Figure 3) and SCMPT semi-quantitative analysis between the two groups (SMD = -2.24, 95% CI = -4.28 to -0.19, p = 0.03) (I² = 99%, p < 0.01) (Figure 4). Fjallbrant et al[33] showed that different ASA and SCMPT assays produced differential results in the two groups (Supplementary Figure 1 A). Eggert-Kruse et al[27] found that different sources of cervical mucus

may have a certain impact on the results (Supplementary Figure 1B).

Figure 1. Flow diagram

3.4 Heterogeneity analysis

Heterogeneity analysis includes subgroup analysis and sensitivity analysis. We conducted subgroup analysis on the results of PCT and SCMPT, and divided ASA patients into male and female groups according to their gender (Figure 2-3);

divided into serum group, semen group and CM group according to the source of ASA samples (Figure 5-6), and divided them into five subgroups including TAT, SIT, MAR, IBT and immunolabeling according to ASA detection methods (Figure 7-8). The results indicated that gender and sample source grouping factors were not sources of heterogeneity, but we found that male factors (PCT, RR=1.71; SCMPT, RR=0.61) were more likely than female factors (PCT, RR=1.47; SCMPT, RR=0.72) to cause a decrease in sperm penetration, and this difference was also reflected in the results of the semen and CM groupings. The detection methods of ASA can be regarded as a source of heterogeneity in the results of both PCT and SCMPT, the most sensitive method in PCT is IBT (RR=3.05), while the RR value of TAT is only 1.19. We also performed a sensitivity analysis of the PCT and SCMPT results and found no significant source of heterogeneity among studies.

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Figure 1. Flow diagram

Figure 2. Results of the meta-analysis for the PCT negative rate

	ASA	+)	ASA	(-)		Risk Ratio			Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% Cl			M-H, Ran	dom. 95% C	a	
1.1.1 male ASA												
10 Koriyama 2013 (1)	6	11	29	140	4.1%	2.63 [1.40, 4.94]					_	
10 Koriyama 2013 (2)	4	8	31	143	3.3%	2.31 [1.08, 4.93]						
12 Wall 1974	26	45	25	70	5.9%	1.62 [1.08, 2.42]						
15 Fjallbrant 1968 (3)	11	14	4	8	3.4%	1.57 [0.75, 3.31]			_	· · ·		
15 Fjallbrant 1968 (6)	11	13	4	9	3.3%	1.90 [0.88, 4.10]					_	
Gilbert 1986	20	22	17	37	6.2%	1.98 [1.36, 2.87]				-		
Barbonetti 2019	55	103	3	17	2.1%	3.03 [1.07, 8.58]					-	_
3 Check 1991	9	13	6	48	2.9%	5.31 [2.32, 12.17]				-		_
Eggert-Kruse 1991 (1)	22	28	79	162	7.3%	1.61 [1.26, 2.07]						
Eggert-Kruse 1991 (2)	13	17	88	173	6.9%	1.50 [1.11, 2.03]						
Eggert-Kruse 1989 (1)	18	34	87	199	6.4%	1.21 [0.85, 1.73]				-		
Eggert-Kruse 1989 (7)	25	50	58	138	6.5%	1.19 [0.85, 1.67]				· ·		
Subtotal (95% CI)		358		1142	58.3%	1.71 [1.43, 2.04]				•		
fotal events	220		431									
1.1.2 female ASA												
14 Wong 1978 (1)	22	26	6	14	4.1%	1.97 [1.06, 3.69]					-	
14 Wong 1978 (2)	13	20	15	20	5.9%	0.87 [0.58, 1.30]			_	+		
14 Wong 1978 (3)	15	21	13	19	5.9%	1.04 [0.69, 1.57]			-	-		
Shibahara 2007 (1)	24	31	28	137	6.1%	3.79 [2.59, 5.55]				-	-	
Shibahara 2007 (2)	10	10	14	21	6.6%	1.45 [1.04, 2.01]						
Eggert-Kruse 1969 (2)	24	42	82	193	6.8%	1.34 [0.99, 1.83]				-		
Eggert-Kruse 1989 (8)	21	42	66	154	6.4%	1.17 [0.82, 1.66]				-		
Subtotal (95% CI)		192		558	41.7%	1.47 [1.03, 2.09]				•		
Total events	129		224									
leterogeneity: Tau* = 0.19;	ChP = 35.6	14, df =	6 (P < 0.)	00001);	P = 83%							
Test for overall effect: Z = 2.	11 (P = 0.0	3)										
fotal (95% CI)		550		1700	100.0%	1.63 [1.37, 1.95]				•		
fotal events	349		655					- 22	2		10	
leterogeneity: Tau ^a = 0.09; lest for overall effect: Z = 5.	ChP = 56.7 48 (P < 0.0	16, df =	18 (P < 0	00001); 1" = 687	6	0.1	0.2	0.5	1 2	5	10
Cost for subcome differences	e: Chill = 0	SE df	1 /P = 0	45) P	- 0%				ASA (-) ASA (+)		

Figure 3. Results of the meta-analysis for the SCMPT positive rate

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	ASA/+		ASA	i a		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% Cl	M-H. Random, 95% Cl
1.5.1 male SCMPT							
11 Morgan 1977 (1)	9	32	9	12	3.2%	0.38 [0.20, 0.71]	
11 Morgan 1977 (2)	10	32	11	12	3.8%	0.34 [0.20, 0.59]	
13 Almoida 1986	1	35	23	32	0.6%	0.04 [0.01, 0.28]	
15 Fjalbrant 1968 (1)	5	16	19	20	2.8%	0.33 [0.16, 0.69]	
15 Fjalbrant 1968 (2)	6	16	18	20	3.2%	0.42 [0.22, 0.80]	
15 Fjalbrant 1968 (4)	6	16	18	20	3.2%	0.42 [0.22, 0.80]	
15 Fjalbrant 1968 (5)	5	16	19	20	2.8%	0.33 [0.16, 0.69]	
3 Menge 1982 (2)	39	139	141	354	5.5%	0.70 [0.52, 0.95]	-
3 Menge 1982 (3)	50	103	375	419	6.1%	0.54 [0.44, 0.66]	-
7 Eggert-Kruse 1991 (3)	13	24	78	139	4.8%	0.97 [0.66, 1.43]	+
7 Eggert-Kruse 1991 (4)	13	24	85	139	4.8%	0.89 [0.60, 1.31]	+
7 Eggert-Kruse 1991 (5)	4	14	87	149	2.4%	0.49 [0.21, 1.13]	
7 Eggerl-Kruse 1991 (6)	4	14	94	149	2.4%	0.45 [0.20, 1.05]	
9 Eggert-Kruse 1989 (11)	34	50	89	138	5.9%	1.05 [0.84, 1.32]	Ť
9 Eggert-Kruse 1989 (3)	16	34	110	199	4.9%	0.85 [0.58, 1.24]	-
9 Eggert-Kruse 1989 (5)	19	34	116	199	5.3%	0.96 [0.70, 1.32]	+
9 Eggert-Kruse 1989 (9)	29	50	87	138	5.7%	0.92 [0.70, 1.20]	
Subtotal (95% CI)		649		2159	67.3%	0.61 [0.49, 0.75]	•
Total events	263		1379				
Heterogeneity: Tau ^e = 0.13; Chi	^p = 68.05,	df = 16	5 (P < 0.0	00001);	P = 76%		
Test for overall effect: Z = 4.54	(P < 0.000	01)					
1.5.2 female SCMPT							
16 Elstein 1970	11	16	2	3	2.3%	1.03 [0.43, 2.45]	
3 Menge 1982 (1)	35	136	190	323	5.4%	0.44 [0.32, 0.59]	-
8 inpensiev 1980 (1)	1	2	12	19	1.1%	0,79 (0,19, 3,30)	
8 ingerslev 1980 (2)	8	14	5	7	3.2%	0.80 [0.42, 1.54]	
9 Eggert-Kruse 1989 (10)	19	42	80	154	5.0%	0.87 [0.60, 1.26]	-+
9 Eggert-Kruse 1989 (12)	16	42	89	154	4.7%	0.66 [0.44, 0.99]	-
9 Eggent-Kruse 1989 (4)	24	42	125	193	5.6%	0.88 [0.67, 1.17]	+
9 Eggert-Kruse 1989 (6)	23	42	139	193	5.5%	0.78 [0.57, 1.01]	-
Subtotal (95% Cl)		336		1048	32.7%	0.72 [0.58, 0.91]	•
Total events	137		642				
Heterogeneity: Tau ^a = 0.05; Ch	P = 15.93,	df = 7	(P = 0.03	N; I* = 5	56%		
Test for overall effect: Z = 2.76	(P = 0.000	10					
Total (95% CI)		985		3205	100.0%	0.65 [0.56, 0.77]	•
Total events	400		2021				
Heterogeneity: Tau ² = 0.10; Chi	P = 83.96	df = 2	4 (P < 0.0	(10000	P = 71%		
Test for overall effect: Z = 5.19	(P < 0.000	(100					0.01 0.1 1 10 100
Test for subgroup differences: (Ch# = 1.21	. df = 1	1 (P = 0.2	27). If =	17.6%		Aan (+) Aan (+)

Figure 4. Results of the meta-analysis for the SCMPT semi-quantitative analysis

ASA(+)		ASA(-)		Std. Mean Difference		Std. Mean Difference	
Mean 50	Total Mean	SD Total	Weight.	IV, Random, 95% Ci		N. Random, 95% Cl	
0.38 0.62	18 1.38	0.59 20	10.0%	-1.87 [-2.33, -0.81]		-	
0.5 0.73	14 1.6	0.88 8	9.9%	-1.48 [2.48, -0.49]		-	
0.5 0.73	16 1.25	0.64 20	10.0%	-1.08 [-1.78, -0.37]		-	
0.36 0.62	16 1.7	0.57 3	9.7%	-2.05 [-3.49, -0.62]			
2.4 0.51	142 3.5	0.03 707	10.1%	-5.24 5.54, -4.93		•	
2.1 0.51	63 3.4	0.03 786	10.1%	-9.21 [-9.72, -8.70]	*		
1.67 0.92	24 1.71	0.96 139	10.1%	-0.04 [-0.47, 0.39]		*	
1.63 0.88	24 1.81	0.82 139	10.1%	-0.20 [-0.63, 0.24]		-	
1.14 0.86	14 1.76	0.94 149	10.1%	-0.66 [-1.21, -0.11]		-	
1.14 0.66	14 1.84	0.91 149	10.1%	-0.78 [-1.34, -0.23]		-	
	343	2120	100.0%	-2.24 [-4.28, -0.19]		•	
Chi? = 1294.0	6. # = 9 (P < 1	100001); P =	N9%		+		
4 (P = 0.03)					-10	ASA (+) ASA (-)	10
	ASA(+) Mean 50 0.58 0.52 0.5 0.73 0.58 0.52 2.4 0.51 1.67 0.02 1.67 0.02 1.63 0.68 1.14 0.66 ChP = 1294.0	ASA(+) / // Mean SD Total Mean 0.38 0.42 16 1.35 0.5 0.73 14 1.6 0.5 0.73 14 1.6 0.30 0.42 16 1.25 0.30 0.42 16 1.7 1.4 0.51 142 3.5 2.1 0.51 63 3.4 1.47 0.02 24 1.71 1.63 0.88 24 1.81 1.14 0.66 14 1.76 1.14 0.66 14 1.76 343 Ch ^o = 1294.05, d' = 9 (P < 0 4 (P = 0.03)	ASA(+) ASA(-) Mean 5D Total Mean 5D Total 0.38 0.42 16 1.36 0.48 8 0.5 0.73 14 1.40 0.68 8 0.5 0.73 14 1.40 0.68 8 0.5 0.73 16 1.25 0.44 20 0.36 0.42 16 1.70 0.57 3 2.4 0.51 142 3.5 0.03 707 2.1 0.51 632 3.4 0.03 707 2.1 0.51 632 3.4 0.03 707 2.1 0.51 632 24 1.71 0.81 199 1.63 0.88 24 1.81 0.82 139 1.63 0.68 24 1.84 0.81 149 1.14 0.66 14 1.84 0.81 149 1.44 0.66	ASA(+) ASA(-) Mean 50 Total Mean 50 Total Weight 0.38 0.42 16 1.56 0.59 20 10.0% 0.5 0.73 14 1.6 0.88 8 9.9% 0.5 0.73 16 1.25 0.44 20 10.0% 0.38 0.42 16 1.75 0.44 20 10.0% 0.36 0.42 16 1.7 0.57 3 9.7% 0.36 0.42 16 1.7 0.57 3 9.7% 1.47 0.51 142 3.5 0.03 707 10.1% 1.47 0.52 24 1.7 0.98 10.1% 1.45 0.82 139 10.1% 1.46 0.88 24 1.81 0.82 139 10.1% 1.46 0.46 14 1.76 0.84 149 10.7% 1.14 0.	$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	ASA(+) ASA(-) Std. Mean Difference Mean 50 Total Mean Std. Mean Difference 0.36 0.52 16 1.56 0.59 20 10.75% 1.75 1.75 0.36 0.57 16 1.56 0.59 20 10.75% 1.75 1.25 0.64 0.97% -1.48 1.24 0.48 0.97% -1.48 1.24 0.48 0.97% -1.48 1.24 0.44 0.97% -1.48 1.24 0.44 0.97% -1.48 1.24 0.44 0.97% -1.48 1.24 0.44 0.97% -1.48 1.24 0.44 0.97% -1.48 1.24 0.44 0.97% -1.48 1.24 0.46 1.45 0.87 3 77% -2.26 1.67 3 9.7% -2.20 1.64 1.45 0.82 1.97% -0.26 1.45 0.82 1.45 0.82 1.97% 0.20 1.0.60 1.0.7% -0.20 1.0.76 <t< td=""><td>ASA(+) ASA(-) Still. Mean Difference Still. Mean Dif</td></t<>	ASA(+) ASA(-) Still. Mean Difference Still. Mean Dif

Figure 5. Results of the source of ASA samples subgroup analysis for the PCT negative rate

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	ASA(+	•)	ASA(-)		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% C	M-H. Random, 95% (a
1.2.1 serum ASA								
15 Fjalbrant 1968 (3)	11	14	4	8	3.4%	1.57 [0.75, 3.31]		
15 Fjalbrant 1968 (6)	11	13	4	9	3.3%	1.90 [0.88, 4.10]		
1 Shibahara 2007 (1)	24	31	28	137	6.1%	3.79 [2.59, 5.55]	-	
Shibahara 2007 (2)	10	10	14	21	6.6%	1.45 [1.04, 2.01]	-	
Eggert-Kruse 1989 (1)	18	34	87	199	6.4%	1.21 [0.85, 1.73]	+	
Eggert-Kruse 1989 (2)	24	42	82	193	6.8%	1.34 [0.99, 1.83]	-	
Eggert-Kruse 1989 (7)	25	50	58	138	6.5%	1.19 [0.85, 1.67]		
Eggert-Kruse 1989 (8)	21	42	66	154	6.4%	1.17 [0.82, 1.66]	+-	
Subtotal (95% CI)		236		859	45.4%	1.54 [1.16, 2.06]	•	
Total events	144		343					
Heterogeneity: Tau ⁴ = 0.12;	Ch# = 28.8	1. ef =	7 (P = 0.0	0002); 1	- 76%			
Test for overall effect: Z = 2.	96 (P = 0.0	03)						
2.2 semen ASA								
0 Korlvama 2013 (1)	6	11	29	140	4.1%	2.63 [1.40, 4.94]		
0 Korivama 2013 (2)	4		31	143	3.3%	2.31 [1.08, 4.93]		
2 Wal 1974	26	45	25	70	5.9%	1.62 [1.08, 2.42]		
Gilbert 1985	20	22	17	37	6.2%	1.98 [1.36, 2.87]		
Barbonetti 2019	55	103	3	17	2.1%	3.03 [1.07, 8.58]		-
Check 1991	9	13	6	48	2.9%	5 31 [2.32, 12, 17]		_
Ecoert-Kruse 1991 (1)	22	28	79	162	7.3%	1.61 (1.26, 2.07)	-	
Eccert-Kruse 1991 (2)	13	17	88	173	6.9%	1.50 [1.11, 2.03]		
Subtotal (95% CI)		247		788	38.8%	1.94 [1.55, 2.42]	•	
Total events	155		278					
Heteroceneity: Tau* = 0.04;	ChP = 12.8	4. et =	7 (P = 0.0	8): P -	45%			
Test for overall effect: Z = 5.	82 (P < 0.0	0001)						
1.2.3 CM ASA								
4 Wong 1978 (1)	22	26	6	14	4.1%	1.97 [1.06, 3.69]		
4 Woog 1978 (2)	13	20	15	20	5.9%	0.87 10.58, 1.301	+	
4 Wong 1978 (3)	15	21	13	19	5.9%	1.04 (0.69, 1.57)	+	
Subtotal (95% CI)		67		53	15.8%	1.15 [0.75, 1.77]	•	
Total events	50		34					
isterogeneity: Tau* = 0.09;	Chi# = 5.04	df = 2	(P = 0.08	1); P=1	60%			
Test for overall effect: Z = 0.	62 (P = 0.5	3)						
Total (95% CI)		550		1700	100.0%	1.63 [1.37, 1.95]	•	
Total events	349		655					
Heterogeneity: Tau* = 0.09:	Chi# = 56.7	8. ef =	18 (P < 0	00001); P = 68%			
lest for overall effect Z = 5.	48 (P < 0.0	0001)					0.01 0.1 1	10 10
Test for subarroup difference	* Ch? = 4	01. df	2 (P = 0	09) P	- 59.3%		ASA (-) ASA (+)	

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Figure 6. Results of the source of ASA samples subgroup analysis for the SCMPT positive rate

	ASA(+)	ASA(-)		Risk Ratio	Risk Ratio
Study or Subgroup	Events Tota	Events Total	Weight	M-H, Random, 95% C	M-H. Random. 95% Cl
1.6.1 serum SCMPT					
11 Morgan 1977 (1)	9 32	9 12	3.2%	0.38 [0.20, 0.71]	
11 Morgan 1977 (2)	10 32	11 12	3.8%	0.34 [0.20, 0.59]	
15 Fjalbrant 1968 (1)	5 16	19 20	2.8%	0.33 [0.16, 0.69]	
15 Fjallbrant 1968 (2)	6 16	18 20	3.2%	0.42 [0.22, 0.80]	
15 Fjallbrant 1968 (4)	6 16	18 20	3.2%	0.42 [0.22, 0.80]	
15 Fjallbrant 1968 (5)	5 16	19 20	2.8%	0.33 [0.18, 0.69]	
3 Menge 1982 (2)	39 139	141 354	5.5%	0.70 [0.52, 0.95]	-
3 Mongo 1982 (3)	50 103	375 419	6.1%	0.54 [0.44, 0.66]	*
8 Ingenslev 1980 (2)	8 14	5 7	3.2%	0.80 [0.42, 1.54]	-
9 Eggert-Kruse 1989 (10)	19 42	80 154	5.0%	0.87 [0.60, 1.26]	-
9 Eggert-Kruse 1989 (11)	34 50	89 138	5.9%	1.05 [0.84, 1.32]	t
9 Eggert-Kruse 1989 (12)	16 42	89 154	4.7%	0.66 [0.44, 0.99]	-
9 Eggert-Kruse 1989 (3)	16 34	110 199	4.9%	0.85 [0.58, 1.24]	-
9 Eggert-Kruse 1989 (4)	24 43	125 193	5.6%	0.88 [0.67, 1.17]	+
9 Eggert-Kruse 1989 (5)	19 34	116 199	5.3%	0.96 [0.70, 1.32]	+
9 Eggert-Kruse 1989 (6)	23 42	139 193	5.5%	0.78 [0.57, 1.01]	-
9 Eggert-Kruse 1989 (9)	29 50	87 138	5.7%	0.92 [0.70, 1.20]	.†
Subtotal (95% Cl)	720	2252	76.3%	0.67 [0.56, 0.79]	•
Total events	318	1450			
Heterogeneity: Tau* = 0.08; Ch	i² = 55.14, df =	16 (P < 0.00001)	; P = 71%		
Test for overall effect: Z = 4.63	(P < 0.00001)				
1.6.2 semen SCMPT					
13 Almeida 1986	1 35	23 32	0.6%	0.04 [0.01, 0.28]	
7 Eggert-Kruse 1991 (3)	13 24	78 139	4.8%	0.97 [0.65, 1.43]	+
7 Eggert-Kruse 1991 (4)	13 24	85 139	4.8%	0.89 [0.60, 1.31]	-
7 Eggert-Kruse 1991 (5)	4 14	87 149	2.4%	0.49 [0.21, 1.13]	
7 Eggert-Kruse 1991 (6)	4 14	94 149	2.4%	0.45 [0.20, 1.05]	-
Subtotal (95% CI)	111	608	14.9%	0.55 [0.29, 1.05]	-
Total events	35	367			
Heterogeneity: Tau ^a = 0.38; Ch	i ² = 18.58, df =	4 (P = 0.0010); P	= 78%		
Test for overall effect: Z = 1.81	(P = 0.07)				
1.6.3 CM SCMPT					
16 Elstein 1970	11 16	2 3	2.3%	1.03 [0.43, 2.45]	
3 Menge 1982 (1)	35 136	190 323	5.4%	0.44 [0.32, 0.59]	
8 Ingerslev 1980 (1)	1 2	12 19	1.1%	0.79 [0.19, 3.30]	
Subtotal (95% CI)	154	345	8.8%	0.61 [0.33, 1.15]	—
Total events	47	204			
Heterogeneity: Tau* = 0.16; Ch	i ^a = 3.99, df = 2	(P = 0.14); P = 5	0%		
Test for overall effect: Z = 1.53	(P = 0.13)				
Total /05W, CD	001	0044	100.05	0.05 20 50 0 771	•
Total (95% CI)	980	3205	100.0%	0.00 [0.96, 0.77]	•
I outil events	400	2021			
Hererogeneity: Tau* = 0.10; Ch	r = 83.96, df =	24 (P < 0.00001)	; 1* = 71%		0.01 0.1 1 10 100
Test for overall effect: Z = 5.19	(P < 0.00001)				ASA (+) ASA (-)

Test for overall effect: Z = 5.19 (P < 0.00001) Test for suborouo differences: Ch^p = 0.38. df = 2 (P = 0.83). I^a = 0%

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	ASA(•)	ASA(•)		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl
1.3.1 TAT							
14 Wong 1978 (2)	13	20	15	20	6.2%	0.87 [0.58, 1.30]	-
15 Fjallbrant 1968 (3)	11	14	4		3.6%	1.57 [0.75, 3.31]	
9 Eggert-Kruse 1989 (1)	18	34	87	199	6.8%	1.21 [0.85, 1.73]	+
9 Eggert-Kruse 1989 (2)	24	42	82	193	7.2%	1.34 [0.99, 1.83]	-
Subtotal (95% CI)		110		420	23.8%	1.19 [0.96, 1.47]	•
Total events	66		188				
Heterogeneity: Tau# = 0.01; Cl	h# = 3.51	df = 3	(P = 0.32	t; P=1	14%		
Test for overall effect: Z = 1.58	5 (P = 0.1	2)					
1.3.2 SIT							
14 Wong 1978 (1)	22	26	6	14	4.4%	1.97 [1.06, 3.69]	
15 Fjøllbrønt 1968 (6)	11	13	4		3.5%	1.90 [0.88, 4.10]	
1 Shibahara 2007 (1)	24	31	28	137	6.5%	3.79 [2.59, 5.55]	
1 Shibahara 2007 (2)	10	10	14	21	7.0%	1.45 [1.04, 2.01]	-
Subtotal (95% CI)		89		181	21.0%	2.15 [1.25, 3.71]	-
Total events	67		52				
Heterogeneity: Tau ^a = 0.24; C	h ^p = 15.2	7, et =	3 (P = 0.0	(C2); P	= 80%		
Test for overall effect: Z = 2.75	5 (P = 0.0	06)					
11110							
5 Decksonti 2010		100			0.94	9 69 11 67 9 680	
5 Derborweis 2019	00	103		1/	2.3%	3.03 [1.07, 8.56]	-
7 Eggen-Kruse 1991 (1)	22	20	19	102	7.7%	1.61 [1.26, 2.07]	-
7 Eggen-Kruse 1991 (2) Robbelel (BSE CD	13		86	1/3	1.3%	1.50 [1.11, 2.03]	A
Sublocal (MON City		190	470	304	17.476	101 [1:30, 2:00]	•
Total events	90	4-3	1/0				
Technogenety: Tau* = 0.01; Cr	P = 2.32	, ar = 2	(P = 0.31	K P = 1	476		
LOPE for overall europ: 7 = 4.95	()- < 0.0	001)					
1.3.4 IBT							
10 Korivema 2013 (1)	6	11	29	140	4.4%	2.63 [1.40, 4.94]	
10 Korivama 2013 (2)	Ā		31	143	3.6%	2.31 [1.08, 4.93]	
6 Chack 1991	9	13	6	45	3.2%	5 31 (2.32, 12, 17)	
Subtotal (95% Ci)		32		329	11.2%	3.05 [1.90, 4.91]	•
Total eventa	19		66				-
Heterogeneity: Tau ^a = 0.04; Cl	h# = 2.53	df = 2	(P = 0.28	1); I ^a = 2	21%		
Test for overall effect: Z = 4.61	(P<0.0	0001)					
	*						
1.3.5 Immunolabelling							
12 Wall 1974	26	45	25	70	6.3%	1.62 [1.08, 2.42]	
14 Wong 1978 (3)	15	21	13	19	6.3%	1.04 [0.69, 1.57]	-
9 Eggert-Kruse 1989 (7)	25	50	58	138	6.9%	1.19 (0.85, 1.67)	-
9 Eggert-Kruse 1989 (8)	21	42	66	154	6.8%	1.17 [0.82, 1.66]	-
Subtotal (95% CI)		158		381	26.2%	1.23 [1.02, 1.48]	•
Total events	87		162				
Heterogeneity: Tau* = 0.00; Ci	h ^a = 2.57	df = 3	(P = 0.46	i); P=(2%		
Test for overall effect: Z = 2.18	8 (P = 0.0	3)					
TOTHI (89% CI)		528		1663	100.0%	1.62 [1.34, 1.94]	•
Total events	329		638		_		
Heterogeneity: Tau ^a = 0.10; Cl	h ² = 54.9	5, df =	17 (P < 0	00001); P = 69%	•	0.02 0.1 1 10 50
Test for overall effect; Z = 5.10	(P < 0.0	0001)					ASA (-) ASA (+)
Test for suboroup differences:	CN*=18	142. df	= 4 (P = (0.0011.	P = 78.31	6	

Figure 7. Results of the ASA detection methods subgroup analysis for the PCT negative rate

3.5 Publication bias

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The funnel plot showed that the graph is symmetrical, which indicated that there was no publication bias in our meta-analysis (Figure 9 A-B). The quality scores of included cohort studies ranged from 6 to 9.

	ASA(•)	ASA(-)		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% C	M-H, Random, 95% Cl
1.7.1 TAT							
15 Fjallbrant 1968 (1)	5	16	19	20	3.3%	0.33 [0.16, 0.69]	
15 Fjallbrant 1968 (2)	6	16	18	20	3.8%	0.42 [0.22, 0.80]	
8 Ingerslev 1980 (1)	1	2	12	19	1.2%	0.79 [0.19, 3.30]	
8 Ingenslev 1980 (2)	8	14	5	7	3.8%	0.80 [0.42, 1.54]	
9 Eggert-Kruse 1989 (3)	16	34	110	199	6.3%	0.85 [0.58, 1.24]	-
9 Eggert-Kruse 1989 (4)	24	42	125	193	7.4%	0.88 [0.67, 1.17]	-
9 Eggert-Kruse 1989 (5)	19	34	116	199	6.9%	0.96 [0.70, 1.32]	+
9 Eggert-Kruse 1989 (6)	23	42	139	193	7.3%	0.76 [0.57, 1.01]	
Subtotal (95% CI)		200		850	40.0%	0.76 [0.62, 0.93]	•
Total events	102		544				
Heterogeneity: Tau ^a = 0.03; Ch	P = 11.53,	df = 7	(P = 0.12	B): P = 3	39%		
Test for overall effect: Z = 2.66	(P = 0.004	8)					
1.7.2 SIT							
15 Fjallbrant 1968 (4)	6	16	18	20	3.8%	0.42 [0.22, 0.80]	
15 Fjellbrant 1968 (5)	5	16	19	20	3.3%	0.33 [0.18, 0.69]	
3 Menge 1982 (1)	35	138	190	323	7.2%	0.44 [0.32, 0.59]	T
Subtotal (95% CI)		168		363	14.3%	0.42 [0.33, 0.54]	•
Total events	46		227				
Heterogeneity: Tau* = 0.00; Ch	* = 0.50, ·	df = 2 ()	P = 0.78)	: P = 0	%		
Test for overall effect: Z = 6.67	(P < 0.00	001)					
1.7.3 MAR							
7 Eggert-Kruse 1991 (3)	13	24	78	139	6.1%	0.97 [0.65, 1.43]	T
7 Eggerl-Kruse 1991 (4)	13	24	85	139	6.2%	0.89 [0.60, 1.31]	
7 Eggert-Nruse 1991 (5)	4	14	87	149	2.8%	0.49 [0.21, 1.13]	-
7 Eggert-Rruse 1991 (6)	4	14	94	149	2.8%	0.45 [0.20, 1.05]	
Subtotal (95% CI)		76		576	17.8%	0.77 [0.55, 1.09]	•
Total events	34		344				
Heterogeneity: Tau* = 0.04; Ch	$t^{2} = 4.71, t$	df = 3 (P = 0.19)	; P = 34	576		
Test for overall effect: Z = 1.49	(P = 0.14))					
1.7.4 Immunolabelling							_
9 Eggen-R/use 1989 (10)	19	42	80	104	6.4%	0.87 [0.60, 1.26]	1
9 Eggert-Kruse 1989 (11)	34	50	89	138	8.0%	1.05 [0.84, 1.32]	
9 Eggert-Kruse 1989 (12)	16	42	89	154	6.0%	0.66 [0.44, 0.99]	
9 Eggen-Aruse 1989 (9)	29	50	87	138	7.5%	0.92 [0.70, 1.20]	1
Subtotal (95% CI)		104		204	21.9%	0.91 [0.76, 1.09]	1
Total events	98		345				
Heterogeneny: Tau* = 0.01; Ch	r = 4.32, (on = 3 ()	P = 0.23)	: P = 3	176		
rest for overall effect: Z = 1.06	(P = 0.29)	,					
Total /95% CD		628		2373	100.0%	0.71 10.60 0.841	•
Total questa	280		5460	2010	100.036	which the proof of a set	•
Historogeneity Tauf = 0.08: Ch	200	dt = 1	-400 8/12 < 0.0	0011-1	- 65%		
Test for everal effect 7 = 4.09	(P < 0.00)	011	0.0- 4.0.0	~~ (), (- 00%		0.005 0.1 1 10 200
Test for substrain differences:	Chill = 23.1	82 /18 -	3/2<0	00013	P = 87.43	6	ASA (+) ASA (-)
real for accounted of the ender.		- ur -				-	

Figure 8. Results of the ASA detection methods subgroup analysis for the SCMPT positive rate





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(Table 2). The only case-control study scored 7 points (Supplementary Table 1). Analysis of the methodological quality of the studies performed using NOS indicated moderate to high quality, which is expected in observational studies. All studies received ethical approval, and there was no conflict of interest between the authors.

Table 2: The quality of included cohort studies performed using NOS

	Selection					Outcome			
Study	Representa- tiveness of the exposed cohort	Selection of the non- exposed cohort	Ascertain- ment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assess- ment of outcome	Was follow up long enough for outcomes to occur	Adequate of follow up of cohorts	Scores
Shibahara	•	•	•	•	**	•	•	•	q
et al.	~	-	-	~	~ ~	-	-	~	
Menge	•	•	+		**	+	•	•	8
et al.	~	~	-		~ ~	~	~	~	
Menge	*	*	*	*	**	*	*	*	9
et al.									
Gilbert	*	*	*	*	**	*	*	*	9
Check									
et al.	*	*	*	*	*	*	*	*	8
Eggert-									
Kruse	*	*	*		**	*	*	*	8
et al.									
Ingerslev			•	•		•			0
et al.	Ħ	Ħ	Ħ	Ħ	ππ	Ħ	Ħ	Ħ	9
Eggert-									
Kruse	*	*	*	*	**	*	*	*	9
et al.									
Koriyama	•	•	•	•	•	•	•	•	8
et al.	~	~	-	~	-	-	~	~	0
Morgan	*	*	*	*	**	*	*	*	9
et al.									
Wall et al.	*	*	*		*	*	*	*	7
Almeida	•	•	•	•	•	_	•	•	0
et al.	-	-	~	~	~	-	-	-	0
Wong	*	*	*	*		*	*	*	7
Fjallbrant	•	•	•	•	**	•	•	•	9
et al.	-	-	~	A		-	-	-	5
Elstein	*	*	*			*	*	*	6
et al.									

4 Discussion

This systematic review is the first to assess sperm penetration in ASApositive couples using PCT and SCMPT as outcome variables. Although ASA antibodies and their effects on infertility are not novel, most of the available studies have conflicting results, and methods to assess sperm penetration are not uniform, prompting us to conduct this systematic review. The results of the meta-analysis confirmed that ASA positivity was associated with a decrease in sperm penetration rate, both in vivo

and in vitro.

Our findings are of great value and can provide new clinical ideas for professionals dealing with reproductive health. There are several theories on the mechanisms driving the decline in cervical mucus permeability, some of which we list here. Antibodies directed against sperm components have shown to exert detrimental effects on different preand post-fertilization events[34]. Anti-sperm antibodies can affect sperm concentration, liquefaction, transport, sperm motility and viability, gamete

interaction and also early embryonic development, implantation and fetal development[35-38]. Moreover, ASA may alter sperm plasma membrane functional integrity, sperm capacitation, sperm binding and penetration of the zona pellucida (ZP)[39-42]. Other ASA may act as opsonins, facilitating the recognition and destruction of sperm by phagocytes or may evoke the complement cascade that leads to sperm lysis [43]. We focused primarily on the reduced capacity of sperm to penetrate cervical mucus in individuals who are ASA positive in the body, which may result in a reduction in the rate of conception. Sperm agglutination or fixation in cervical mucus may result from ASA in female cervical mucus [44]. The ASA will bond to the sperm in the male body, giving rise to what appears to be a normal sperm count, but the sperm may not function as intended. Moreover, the combination sticks to the protein network of the cervical mucus, making it challenging to pass through the cervix's mucus [33]. There have also been studies that found more ASA in men with decreased sperm forward motility [45], which may affect sperm passing through cervical mucus [32]. We think that ASA-positive patients may have compromised fertility due to reduced ability to pass cervical mucus.

We used subgroup analysis and sensitivity analysis to explore the source of heterogeneity, different detection methods of ASA may be one source of heterogeneity, and we noticed that even for the same assay, different cutoff values for antibody titers lead to differences in results, suggesting that more prospective studies may be needed in the future to control for the confounding variables of ASA detection method and titer threshold to further validate the experimental results. The 16 controlled studies we included were performed in different regions, 15 from developed countries and 1 from developing country. The sample sizes of different studies varied greatly, with the most [22] contained 522 samples and the least [13] were only 19 samples. Besides, the heterogeneity between studies may come from factors such as regional and cultural differences, age of participants, and the sample size. This study has some limitations. First, due to the limited number of controlled studies on sperm penetration in ASA-positive patients, this analysis did not include a sufficient number of studies and included studies at earlier times. Second, some studies did not have complete data information. Third, differences in the control group may not be representative of the general population. The last limitation was the high heterogeneity of research. We recommend further research based on the relevant criteria of region, sample size, rigorous statistical analysis and research design. In addition, future studies should consider gender differences in the source of ASA antibodies and differences in detection methods when interpreting the results.

An important feature of this review was the inclusion of articles using PCT and SCMPT as outcome variables. To protect patient privacy, sperm penetration was assessed by observational studies; therefore, we attempted to obtain a variety of relevant case-control, cohort, and cross-sectional studies. The lack of data and diversity of studies requires careful and differentiated examination. Data were carefully examined to minimize risk of bias. Two validated methods were used to assess risk of bias and quality, namely funnel plots and NOS scales. Compared with the control group, the sperm penetration rate was lower in the ASA-positive

group. Clinicians working in reproductive health and infertility should be aware of this issue in order to assess and treat patients to improve patient pregnancy rates. Routine ASA antibody testing is recommended for infertile couples. Semen anti-sperm antibodies are not related to pregnancy rates after IVF or ICSI, suggesting that both forms of ART remain viable options for infertile couples with semen ASA[47-48]. For ASA-positive patients, artificial insemination and assisted reproduction can get past the problem of sperm traveling through cervical mucus, allowing more sperm to reach the oocyte and increasing the likelihood of fertilization. Also, since partners who test positive for ASA in male blood and semen are more likely to have the substance in cervical mucus, which is comparable to raising the amount of ASA exposed to sperm, assisted reproductive technology can prevent this negative effect. Therefore, providing couples with ASA screening and suggesting treatment strategies can help improve the success rate of reproductive therapy. In conclusion, both in vivo and in vitro experiments reflected decreased sperm penetration through the cervical mucus in ASA-positive patients, so it is advised that ASA screening for couples be added to the routine exam.

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